ClinicalTrials.gov PRS
Protocol Registration and Results System

ID: EP-101-03 Study to Investigate the Dose Response, Safety and Efficacy of Nebulized EP-101(SUN101) in Patients With Chronic Obstructive Pulmonary Disease (COPD): GOLDEN-1 Study NCT01426009

Protocol Registration and Results Preview

Study to Investigate the Dose Response, Safety and Efficacy of Nebulized EP-101(SUN101) in Patients With Chronic Obstructive Pulmonary Disease (COPD): GOLDEN-1 Study

This study has been completed.

Sponsor:
Sunovion Respiratory Development Inc.

Information provided by (Responsible Party):
Sunovion Respiratory Development Inc.

ClinicalTrials.gov Identifier:
NCT01426009

First received: August 29, 2011
Last updated: May 3, 2017
Last verified: June 2016

Purpose

The purpose of this study is to determine steady-state efficacy and dose response profile and to assess safety and pharmacokinetic profile of nebulized EP-101(SUN101) after 7-day dosing using an investigational high efficiency nebulizer (eFlow®) compared with placebo and two active comparators in patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD).

Condition	Intervention	Phase
Chronic Obstructive Pulmonary Disease	Drug: EP-101 via nebulizer (eFlow®) Drug: Placebo EP-101 Drug: Tiotropium bromide via (Spiriva® Handihaler®) Drug: Ipratropium bromide Inhalation Solution via Handihaler® DPI	Phase 2

Study Type: Interventional
Study Design: Primary Purpose: Treatment
Study Phase: Phase 2
Interventional Study Model: Crossover Assignment
Masking: Participant, Care Provider, Investigator, Outcomes Assessor
Allocation: Randomized

Official Title: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Seven Arm, Four-Period Cross-over, Incomplete Block Design, 7-Day Dosing Study to Assess the Dose-Response, Safety, and Efficacy of EP-101 (SUN101) in Subjects With Moderate to Severe COPD

Further study details as provided by Sunovion Respiratory Development Inc.:

Primary Outcome Measure:

- Mean Change in 24 Post Dose Trough Forced Expiratory Volume in 1 Second (FEV1) [Time Frame: Day 1 through Day 7]
  Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines. Trough FEV1 was defined as the mean of the spirometry values collected at 23 hours 30 minutes and 24 hours post dose within each Treatment Period.

- Standardized Change in FEV1 Area Under the Curve (AUC) (0-12hr , 12-24hr, 0-24hr) on Day 1 and Day 7 [Time Frame: Day 1 through Day 7]
  Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines.

Secondary Outcome Measures:

- Peak FEV1 (Maximum FEV1 During the First 4 Hours Post-dose on Day 1 and Day 7) [Time Frame: Day 1 and Day 7]
  Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines

- Treatment Responders (Number of Subjects With Clinically Meaningful Change From Pre-dose in Trough FEV1 on Day 1 and Day 7) [Time Frame: Day 1 and Day 7]
  Number of subjects with clinically meaningful change from pre-dose in trough FEV1 on Day 1 and Day 7 Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines.

- Safety and Tolerability of EP-101: Adverse Events, Vital Signs, ECG, and Clinical Laboratory Tests [Time Frame: Day 1 through Day 7]
  AEs are defined as existing conditions which worsen or events which occur during the course of the clinical trial after treatment. Vital signs were performed during the screening period to confirm study eligibility and at the final study visit. ECGs were performed during the screening period to confirm study eligibility. Vital signs and ECG were additionally collected within 30 minutes pre-dose; and 30 minutes, and 1, 2, 4, 6, 12 hours, and 23 hours 45 minutes post-dose within each treatment period. Clinical laboratory assessments were conducted during the screening period, at each study visit during each treatment period, and at the final study visit.

- Rescue Medication Use [Time Frame: Day 1 through Day 7]
  Mean number of puffs of daily rescue medication

- Treatment Responders (Percentage of Subjects With Clinically Meaningful Change From Pre-dose in Trough FEV1 on Day 1 and Day 7) [Time Frame: Day 1 and Day 7]
  percentage of subjects with clinically meaningful change from pre-dose in trough FEV1 on Day 1 and Day 7 Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines.

Enrollment: 275
Study Start Date: August 2011
Study Completion Date: December 2011
Primary Completion Date: December 2011

Arms	Assigned Interventions
Experimental: EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®)	Drug: EP-101 via nebulizer (eFlow®) EP-101 Dose 1 administered once daily for 7 days Other Names: • SUN101 Drug: EP-101 via nebulizer (eFlow®) EP-101 administered once daily for 7 days Other Names: • SUN101 Drug: EP-101 via nebulizer (eFlow®) EP-101 administered once daily for 7 days Other Names: • SUN101 Drug: EP-101 via nebulizer (eFlow®) EP-101 administered once daily for 7 days Other Names: • SUN101
Active Comparator: Tiotropium bromide via (Spiriva® Handihaler®) Tiotropium bromide via (Spiriva® Handihaler®)	Drug: Tiotropium bromide via (Spiriva® Handihaler®) Tiotropium 18 µg administered once daily for 7 days using Handihaler® DPI Other Names: • Tiotropium bromide
Active Comparator: Ipratropium bromide Inhalation Solution Ipratropium bromide Inhalation Solution via Handihaler® DPI	Drug: Ipratropium bromide Inhalation Solution via Handihaler® DPI Ipratropium 500 µg administered three times daily for 7 days using general purpose nebulizer Other Names: • Ipratropium bromide
Placebo Comparator: Placebo EP-101 Placebo	Drug: Placebo EP-101 Placebo EP-101 administered once daily for 7 days Other Names: • Placebo

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, four-period, incomplete block design cross-over study using EP-101(SUN101) and open-label active controls (tiotropium bromide and ipratropium bromide). The study population will consist of subjects of 40-75 years of age with moderate to severe COPD. Approximately 133 subjects diagnosed with moderate to severe COPD will be enrolled in order to achieve minimum 105 subjects completing the study.

Following a run-in phase, each subject will be randomly assigned to one of 7 treatment sequences, with each sequence comprised of four 7-day Treatment Periods. There will be a washout period of 7 days between each Treatment Period. Study visits will be conducted on Days 1 and 7 of each Treatment Period, with an overnight stay required in the clinic during these visits. A Final Study Visit will be conducted 7 days following the last study treatment.

During each Treatment Period, study treatments will be administered once daily (QD), except for ipratropium inhalation solution, which will be administered three times daily (TID). EP-101 (SUN101)active and placebo treatments will be administered using an investigational high-efficiency eFlow® nebulizer. Tiotropium bromide (Spiriva®) will be administered in an open-label manner via Handihaler® dry-powder inhaler (DPI). Ipratropium bromide inhalation solution will be administered in an open-label manner via general purpose nebulizer.

This study was previously posted by Elevation Pharmaceuticals, Inc. On September 5, 2012, Elevation was acquired by merger with Sunovion Pharmaceuticals Inc. ("Sunovion"), which resulted in Elevation becoming a direct wholly-owned subsidiary of Sunovion. In conjunction with this acquisition, the name of Elevation has been changed to Sunovion Respiratory Development Inc.

Eligibility

Ages Eligible for Study: 40 Years to 75 Years

Sexes Eligible for Study: All

Inclusion Criteria:

- 40-75 years of age
- Clinical diagnosis of moderate to severe COPD
- Current/ex-smokers with at least 10 pack-year smoking history
- Post-bronchodilator FEV1 ≥ 30% and ≤ 70% predicted normal values
- Post-bronchodilator FEV1/FVC ratio of ≤ 0.70
- Post-bronchodilator improvement in FEV1 ≥ 12% and ≤ 30%, and a minimum of 100 mL
- Willing and able to remain at the study site for at least 24 hours at each study visit
- Signed written informed consent

Exclusion Criteria:

- Current evidence or recent history of any clinically significant and unstable disease or abnormality (e.g., myocardial infarction, cardiac failure, uncontrolled hypertension, life-threatening arrhythmias, uncontrolled diabetes)

- Primary diagnosis of asthma
- History of malignancy within the past 5 years
- History of COPD exacerbation within 6 weeks of Screening
- Daily oxygen therapy > 10 hours per day
- Systemic steroids use within 6 weeks of Screening
- Respiratory tract infection within 6 weeks of Screening
- History of tuberculosis, bronchiectasis
- History of urinary retention or bladder neck obstruction type symptoms
- History of glaucoma
- Prolonged QTc interval (>460msec) or history of long QT syndrome
- Recent history of alcohol or drug abuse
- Females who are pregnant or breastfeeding, or if of child-bearing potential unwilling to practice acceptable birth control methods
- History of hypersensitivity or intolerance to aerosol medications
- Participation in another investigational drug study within 30 days of Screening

Contacts and Locations

Locations

United States, Arizona
Elevation Investigational Site
Phoenix, Arizona, United States, 85006

United States, California
Elevation Investigational Site
Los Angeles, California, United States, 90048

United States, Florida
Elevation Investigational Site
DeLand, Florida, United States, 32720

United States, Kentucky
Elevation Investigational SIte
Madisonville, Kentucky, United States, 42431

United States, Massachusetts
Elevation Investigational Site
North Dartmouth, Massachusetts, United States, 02747

United States, North Carolina
Elevation Investigational Site
Charlotte, North Carolina, United States, 28207
Elevation Investigational Site
Raleigh, North Carolina, United States, 27607

United States, Oregon
Elevation Investigational Site
Medford, Oregon, United States, 97504

United States, South Carolina
Elevation Investigational Site
Spartanburg, South Carolina, United States, 29303

United States, Washington
Elevation Investigational Site
Tacoma, Washington, United States, 98418

United Kingdom
Elevation Investigational Site
Manchester, United Kingdom, M21 8AD

Investigators

Study Director: Ahmet Tutuncu, M.D., Ph.D. Chief Medical Officer / Elevation Pharmaceuticals, Inc.

More Information

ClinicalTrials.gov Identifier: NCT01426009
Responsible Party: Sunovion Respiratory Development Inc.
Other Study ID Numbers: EP-101-03
Human Subjects Protection Review Board Status: Approved

Study Results

Participant Flow

Recruitment Details	
Pre-Assignment Details	

Arm/Group Title	EP-101 Via Nebulizer (eFlow®) 25 mcg	EP-101 Via Nebulizer (eFlow®) 50 mcg	EP-101 Via Nebulizer (eFlow®)100 mcg	EP-101 Via Nebulizer (eFlow®) 200 mcg	Ipr In
▼ Arm/Group Description	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	Iprat Inha Han Iprat Inha Han Iprat adm time usin nebu

Period Title: **Period**

Started	74	78	76	76	
Completed	72	76	75	73	
Not Completed	2	2	1	3	
<u>Reason Not Completed</u>					
Adverse Event	1	1	1	2	
Personal Reasons	1	1	0	0	
never received study medication	0	0	0	1	
(Not Public)	Not Completed =2 Total from all reasons =2	Not Completed =2 Total from all reasons =2	Not Completed =1 Total from all reasons =1	Not Completed =3 Total from all reasons =3	

Period Title: **Washout**

Started	72	76	75	73	
Completed	69	76	74	72	
Not Completed	3	0	1	1	
<u>Reason Not Completed</u>					
Lost to Follow-up	1	0	0	0	
Personal Reasons	1	0	1	0	
elective surgery	0	0	0	1	
Withdrawal by Subject	1	0	0	0	
(Not Public)	Not Completed =3 Total from all reasons =3	Not Completed =0 Total from all reasons =0	Not Completed =1 Total from all reasons =1	Not Completed =1 Total from all reasons =1	

Baseline Characteristics

		Arm/Group Title	Total Particiants	
		▼ Arm/Group Description	total of all participants in the study	
		Overall Number of Baseline Participants	139	
		▼ Baseline Analysis Population Description	modified Intent to Treat population for analysis set	
Age, Categorical Measure Type: Count of Participants Unit of measure: participants	Number Analyzed		139 participants	
		<=18 years	0	0%
		Between 18 and 65 years	88	63.31%
		>=65 years	51	36.69%
Age, Continuous Mean (Standard Deviation) Unit of measure: years	Number Analyzed		139 participants	
			61.4 (8.11)	
Sex: Female, Male Measure Type: Count of Participants Unit of measure: participants	Number Analyzed		139 participants	
		Female	78	56.12%
		Male	61	43.88%
Ethnicity (NIH/OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed		139 participants	
		Hispanic or Latino	1	0.72%
		Not Hispanic or Latino	138	99.28%
		Unknown or Not Reported	0	0%
Race (NIH/OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed		139 participants	
		American Indian or Alaska Native	1	0.72%
		Asian	0	0%
		Native Hawaiian or Other Pacific Islander	0	0%
		Black or African American	4	2.88%
		White	134	96.4%
		More than one race	0	0%
		Unknown or Not Reported	0	0%

Region of Enrollment Measure Type: Number Unit of measure: participants	Number Analyzed	139 participants
United States		120
United Kingdom		19

Outcome Measures

1. Primary Outcome

Title:	Mean Change in 24 Post Dose Trough Forced Expiratory Volume in 1 Second (FEV1)
Description:	Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines. Trough FEV1 was defined as the mean of the spirometry values collected at 23 hours 30 minutes and 24 hours post dose within each Treatment Period.
Time Frame:	Day 1 through Day 7

Outcome Measure Data

Analysis Population Description

All subjects who received at least one dose of study medication and who had Day 1 pre-dose and Day 7 trough FEV1 values were included in the modified intent to treat analysis set

Arm/Group Title		EP-101 Via Nebulizer (eFlow®) 25 mcg	EP-101 Via Nebulizer (eFlow®) 50 mcg	EP-101 Via Nebulizer (eFlow®) 100 mcg	EP-101 Via Nebulizer (eFlow®) 200 mcg	Ipratropium Bromide Inhalation Solution	Tiotropium Bromide Via (Spiriva® Handihaler®)	Placebo
Arm/Group Description:		EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	Ipratropium bromide Inhalation Solution via Handihaler® DPI Ipratropium bromide Inhalation Solution via Handihaler® DPI: Ipratropium 500 µg administered three times daily for 7 days using general purpose nebulizer	Tiotropium bromide via (Spiriva® Handihaler®) Tiotropium bromide via (Spiriva® Handihaler®): Tiotropium 18 µg administered once daily for 7 days using Handihaler® DPI	Placebo Placebo : Placebo administered once daily for 7 days
Overall Number of Participants Analyzed		72	75	75	75	72	76	77
Mean (Standard Deviation) Unit of Measure: liters								
Row Title								
Trough FEV1 - day 1	Number Analyzed	72 participants	75 participants	75 participants	75 participants	72 participants	76 participants	77 participants
		0.0477 (0.16359)	0.1009 (0.13261)	0.0648 (0.14239)	0.0632 (0.14965)	0.0933 (0.18980)	0.0740 (0.144441)	0.0301 (0.14394)
Trough FEV1 - day 7	Number Analyzed	72 participants	75 participants	73 participants	72 participants	72 participants	76 participants	77 participants
		0.0478 (0.18965)	0.0699 (0.16909)	0.0666 (0.15132)	0.0840 (0.13842)	0.0292 (0.16507)	0.0564 (0.16356)	-0.155 (0.17934)

Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 25 mcg, Placebo
	Comments	An ANCOVA was used with change from baseline in trough FEV1 as the response,with factors for treatment, period, sequence, baseline as a covariate and a random effect for subject nested within sequence. A sample size of 30 subjects per comparison(133 total with dropouts) provides 90% power to detect a 0.12L difference in mean change trough FEV1 between active and placebo at an alpha of 0.05 using a 2-tailed t-test and assuming a within-subject standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority

	Comments	Day 7 analysis
Statistical Test of Hypothesis	P-Value	0.0003
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean]
	Estimated Value	0.0723
	Confidence Interval	(2-Sided) 95% 0.0347 to 0.1099
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0188
	Estimation Comments	[Not specified]

▼ Statistical Analysis 2 ✔

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 50 mcg, Placebo
	Comments	An ANCOVA was used with change from baseline in trough FEV1 as the response,with factors for treatment, period, sequence, baseline as a covariate and a random effect for subject nested within sequence.A sample size of 30 subjects per comparison(133 total with dropouts) provides 90% power to detect a 0.12L difference in mean change trough FEV1 between active and placebo at an alpha of 0.05 using a 2-tailed t-test and assuming a within-subject standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	Day 7 analysis
Statistical Test of Hypothesis	P-Value	0.0006
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean]
	Estimated Value	0.0676
	Confidence Interval	(2-Sided) 95% 0.0307 to 0.1046
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0184
	Estimation Comments	[Not specified]

▼ Statistical Analysis 3 ✔

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®)100 mcg, Placebo
	Comments	An ANCOVA was used with change from baseline in trough FEV1 as the response, with factors for treatment, period, sequence, baseline as a covariate and a random effect for subject nested within sequence.A sample size of 30 subjects per comparison(133 total with dropouts) provides 90% power to detect a 0.12L difference in mean change trough FEV1 between active and placebo at an alpha of 0.05 using a 2-tailed t-test and assuming a within-subject standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	Day 7 analysis
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANCOVA

	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean]
	Estimated Value	0.1021
	Confidence Interval	(2-Sided) 95% 0.0644 to 0.1398
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0188
	Estimation Comments	[Not specified]

▼ Statistical Analysis 4 ✔

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 200 mcg, Placebo
	Comments	An ANCOVA was used with change from baseline in trough FEV1 as the response, with factors for treatment, period, sequence, baseline as a covariate and a random effect for subject nested within sequence.A sample size of 30 subjects per comparison(133 total with dropouts) provides 90% power to detect a 0.12L difference in mean change trough FEV1 between active and placebo at an alpha of 0.05 using a 2-tailed t-test and assuming a within-subject standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	Day 7 analysis
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean]
	Estimated Value	0.1299
	Confidence Interval	(2-Sided) 95% 0.0918 to 00.1681
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0190
	Estimation Comments	[Not specified]

▼ Statistical Analysis 5 ✔

Statistical Analysis Overview	Comparison Group Selection	Ipratropium Bromide Inhalation Solution, Placebo
	Comments	An ANCOVA was used with change from baseline in trough FEV1 as the response, with factors for treatment, period, sequence, baseline as a covariate and a random effect for subject nested within sequence.A sample size of 30 subjects per comparison(133 total with dropouts) provides 90% power to detect a 0.12L difference in mean change trough FEV1 between active and placebo at an alpha of 0.05 using a 2-tailed t-test and assuming a within-subject standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	Day 7 analysis
Statistical Test of Hypothesis	P-Value	0.0200
	Comments	[Not specified]
	Method	Mantel Haenszel
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean]
	Estimated Value	0.0446

	Confidence Interval	(2-Sided) 95% 0.0073 to 0.0820
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0186
	Estimation Comments	[Not specified]

▼ Statistical Analysis 6 ✔

Statistical Analysis Overview	Comparison Group Selection	Tiotropium Bromide Via (Spiriva® Handihaler®), Placebo
	Comments	An ANCOVA was used with change from baseline in trough FEV1 as the response, with factors for treatment, period, sequence, baseline as a covariate and a random effect for subject nested within sequence.A sample size of 30 subjects per comparison(133 total with dropouts) provides 90% power to detect a 0.12L difference in mean change trough FEV1 between active and placebo at an alpha of 0.05 using a 2-tailed t-test and assuming a within-subject standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	Day 7 analysis
Statistical Test of Hypothesis	P-Value	0.0060
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean]
	Estimated Value	0.0813
	Confidence Interval	(2-Sided) 95% 0.0243 to 0.1382
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0284
	Estimation Comments	[Not specified]

▼ Statistical Analysis 7 ✔

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 25 mcg, Placebo
	Comments	An ANCOVA was used with change from baseline in trough FEV1 as the response, with factors for treatment, period, sequence, baseline as a covariate and a random effect for subject nested within sequence.A sample size of 30 subjects per comparison(133 total with dropouts) provides 90% power to detect a 0.12L difference in mean change trough FEV1 between active and placebo at an alpha of 0.05 using a 2-tailed t-test and assuming a within-subject standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	Day 1 analysis
Statistical Test of Hypothesis	P-Value	0.0402
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean]
	Estimated Value	0.0385
	Confidence Interval	(2-Sided) 95% 0.0018 to 0.0752
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0183
	Estimation Comments	[Not specified]

▼ Statistical Analysis 8

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 50 mcg, Placebo
	Comments	An ANCOVA was used with change from baseline in trough FEV1 as the response, with factors for treatment, period, sequence, baseline as a covariate and a random effect for subject nested within sequence.A sample size of 30 subjects per comparison(133 total with dropouts) provides 90% power to detect a 0.12L difference in mean change trough FEV1 between active and placebo at an alpha of 0.05 using a 2-tailed t-test and assuming a within-subject standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	Day 1 analysis
Statistical Test of Hypothesis	P-Value	0.0003
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean]
	Estimated Value	0.0696
	Confidence Interval	(2-Sided) 95% 0.0337 to 0.1055
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0179
	Estimation Comments	[Not specified]

▼ Statistical Analysis 9

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®)100 mcg, Placebo
	Comments	An ANCOVA was used with change from baseline in trough FEV1 as the response, with factors for treatment, period, sequence, baseline as a covariate and a random effect for subject nested within sequence.A sample size of 30 subjects per comparison(133 total with dropouts) provides 90% power to detect a 0.12L difference in mean change trough FEV1 between active and placebo at an alpha of 0.05 using a 2-tailed t-test and assuming a within-subject standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	Day 1 analysis
Statistical Test of Hypothesis	P-Value	0.0074
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean]
	Estimated Value	0.0501
	Confidence Interval	(2-Sided) 95% 0.0140 to 0.0861
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0180
	Estimation Comments	[Not specified]

2. Primary Outcome

Title:	Standardized Change in FEV1 Area Under the Curve (AUC) (0-12hr , 12-24hr, 0-24hr) on Day 1 and Day 7
▼ Description:	Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines. NOTE : Outcome Measure Description is shorter than the Outcome Measure Title.

Time Frame:	Day 1 through Day 7

Outcome Measure Data

Analysis Population Description

All subjects who received at least one dose of study medication and who had Day 1 pre-dose and Day 7 trough FEV1 values were included in the modified intent-to-treat (mITT) analysis set

Arm/Group Title	EP-101 Via Nebulizer (eFlow®) 25 mcg	EP-101 Via Nebulizer (eFlow®) 50 mcg	EP-101 Via Nebulizer (eFlow®)100 mcg	EP-101 Via Nebulizer (eFlow®) 200 mcg	Ipratropium Bromide Inhalation Solution	Tiotropium Bromide Via (Spiriva® Handihaler®)	Placebo
Arm/Group Description:	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	Ipratropium bromide Inhalation Solution via Handihaler® DPI Ipratropium bromide Inhalation Solution via Handihaler® DPI: Ipratropium 500 µg administered three times daily for 7 days using general purpose nebulizer	Tiotropium bromide via (Spiriva® Handihaler®) Tiotropium bromide via (Spiriva® Handihaler®): Tiotropium 18 µg administered once daily for 7 days using Handihaler® DPI	Placebo Placebo : Placebo administered once daily for 7 days
Overall Number of Participants Analyzed	72	76	75	71	74	75	76
Mean (Standard Deviation) Unit of Measure: liters							
Row Title							
AUC 0-12 on Day 1	0.1001 (0.15704)	0.1520 (0.13646)	0.1414 (0.11045)	0.1720 (0.12644)	0.1990 (0.13740)	0.1213 (0.12548)	0.0130 (0.11486)
AUC 12-24 on Day 1	0.0039 (0.17104)	0.0681 (0.12835)	0.0413 (0.14032)	0.0645 (0.13275)	0.0987 (0.16958)	0.0499 (0.14532)	-0.0245 (0.12151)
AUC 0-24 on Day 1	0.0525 (0.15495)	0.1107 (0.12207)	0.0919 (0.11554)	0.1194 (0.11905)	0.1496 (0.14425)	0.0872 (0.12638)	-0.0073 (0.11377)
AUC 0-12 on Day 7	0.1034 (0.19035)	0.1411 (0.16343)	0.1329 (0.13416)	0.1438 (0.14833)	0.1603 (0.16420)	0.1256 (0.15197)	-0.0098 (0.15537)
AUC 12-24 on Day 7	0.0112 (0.18136)	0.0540 (0.16633)	0.0278 (0.15187)	0.0614 (0.13450)	0.0357 (0.17382)	0.0283 (0.15596)	0.0698 (0.16584)
AUC 0-24 on Day 7	0.0579 (0.17822)	0.0980 (0.15651)	0.0812 (0.13293)	0.1030 (0.13162)	0.1009 (0.15882)	0.0776 (0.14702)	-0.0395 (0.15415)

Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 25 mcg, Placebo
	Comments	ACU 0-24 on Day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.0767
	Confidence Interval	(2-Sided) 95% 0.0505 to 0.1028
	Parameter Dispersion	Type: Standard Error of the Mean

		Value: 0.0131
	Estimation Comments	[Not specified]

▼ Statistical Analysis 2 ✔

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 50 mcg, Placebo
	Comments	ACU 0-24 Day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1220
	Confidence Interval	(2-Sided) 95% 0.0965 to 0.1475
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0127
	Estimation Comments	[Not specified]

▼ Statistical Analysis 3 ✔

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®)100 mcg, Placebo
	Comments	AUC 0-24 Day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1222
	Confidence Interval	(2-Sided) 95% 0.0965 to 0.1479
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0128
	Estimation Comments	[Not specified]

▼ Statistical Analysis 4 ✔

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 200 mcg, Placebo
	Comments	AUC 0-24 day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]

	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1625
	Confidence Interval	(2-Sided) 95% 0.1362 to 0.1888
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0131
	Estimation Comments	[Not specified]

▼ Statistical Analysis 5 ✔

Statistical Analysis Overview	Comparison Group Selection	Ipratropium Bromide Inhalation Solution, Placebo
	Comments	AUC 0-24 day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1690
	Confidence Interval	(2-Sided) 95% 0.1434 to 0.1946
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0128
	Estimation Comments	[Not specified]

▼ Statistical Analysis 6 ✔

Statistical Analysis Overview	Comparison Group Selection	Tiotropium Bromide Via (Spiriva® Handihaler®), Placebo
	Comments	AUC 0-24 day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1095
	Confidence Interval	(2-Sided) 95% 0.0716 to 0.1473
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0189
	Estimation Comments	[Not specified]

▼ Statistical Analysis 7 ✔

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 25 mcg, Placebo
	Comments	AUC 0-24 on Day 7

	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1095
	Confidence Interval	(2-Sided) 95% 0.0812 to 0.1379
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0141
	Estimation Comments	[Not specified]

▼ Statistical Analysis 8 ✔

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 50 mcg, Placebo
	Comments	AUC0-24 on Day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1271
	Confidence Interval	(2-Sided) 95% 0.0993 to 0.1548
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0139
	Estimation Comments	[Not specified]

▼ Statistical Analysis 9 ✔

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®)100 mcg, Placebo
	Comments	AUC 0-24 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1450
	Confidence Interval	(2-Sided) 95% 0.1169 to 0.1730
	Parameter Dispersion	Type: Standard Error of the Mean

		Value: 0.0140
	Estimation Comments	[Not specified]

▼ Statistical Analysis 10 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 200 mcg, Placebo
	Comments	AUC 0-24 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1688
	Confidence Interval	(2-Sided) 95% 0.1403 to 0.1972
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0142
	Estimation Comments	[Not specified]

▼ Statistical Analysis 11 ✓

Statistical Analysis Overview	Comparison Group Selection	Ipratropium Bromide Inhalation Solution, Placebo
	Comments	AUC 0-24 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1396
	Confidence Interval	(2-Sided) 95% 0.1117 to 0.1730
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0139
	Estimation Comments	[Not specified]

▼ Statistical Analysis 12 ✓

Statistical Analysis Overview	Comparison Group Selection	Tiotropium Bromide Via (Spiriva® Handihaler®), Placebo
	Comments	AUC 0-24 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]

	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1183
	Confidence Interval	(2-Sided) 95% 0.0795 to 0.1972
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0194
	Estimation Comments	[Not specified]

▼ Statistical Analysis 13 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 25 mcg, Placebo
	Comments	AUC 0-12 on day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1038
	Confidence Interval	(2-Sided) 95% 0.0776 to 0.1301
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0131
	Estimation Comments	[Not specified]

▼ Statistical Analysis 14 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 50 mcg, Placebo
	Comments	AUC 0-12 on day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1468
	Confidence Interval	(2-Sided) 95% 0.1212 to 0.1724
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0128
	Estimation Comments	[Not specified]

▼ Statistical Analysis 15 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®)100 mcg, Placebo
	Comments	AUC 0-12 on day 1

	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1579
	Confidence Interval	(2-Sided) 95% 0.1322 to 0.1837
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0128
	Estimation Comments	[Not specified]

▼ Statistical Analysis 16 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 200 mcg, Placebo
	Comments	AUC 0-12 on day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1919
	Confidence Interval	(2-Sided) 95% 0.1655 to 0.2184
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0132
	Estimation Comments	[Not specified]

▼ Statistical Analysis 17 ✓

Statistical Analysis Overview	Comparison Group Selection	Ipratropium Bromide Inhalation Solution, Placebo
	Comments	AUC 0-12 on day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1994
	Confidence Interval	(2-Sided) 95% 0.1738 to 0.2251
	Parameter Dispersion	Type: Standard Error of the Mean

		Value: 0.0128
	Estimation Comments	[Not specified]

▼ Statistical Analysis 18 ✓

Statistical Analysis Overview	Comparison Group Selection	Tiotropium Bromide Via (Spiriva® Handihaler®), Placebo
	Comments	AUC 0-12 on day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1248
	Confidence Interval	(2-Sided) 95% 0.0872 to 0.1625
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0188
	Estimation Comments	[Not specified]

▼ Statistical Analysis 19 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 25 mcg, Placebo
	Comments	AUC 0-12 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1279
	Confidence Interval	(2-Sided) 95% 0.0970 to 0.1587
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0154
	Estimation Comments	[Not specified]

▼ Statistical Analysis 20 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 50 mcg, Placebo
	Comments	AUC 0-12 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]

	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1454
	Confidence Interval	(2-Sided) 95% 0.1151 to 0.1756
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0151
	Estimation Comments	[Not specified]

▼ Statistical Analysis 21 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®)100 mcg, Placebo
	Comments	AUC 0-12 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1699
	Confidence Interval	(2-Sided) 95% 0.1393 to 0.2004
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0152
	Estimation Comments	[Not specified]

▼ Statistical Analysis 22 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 200 mcg, Placebo
	Comments	AUC 0-12 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1814
	Confidence Interval	(2-Sided) 95% 0.1503 to 0.2125
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0155
	Estimation Comments	[Not specified]

▼ Statistical Analysis 23 ✓

Statistical Analysis Overview	Comparison Group Selection	Ipratropium Bromide Inhalation Solution, Placebo
	Comments	AUC 0-12 on day 7

	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1697
	Confidence Interval	(2-Sided) 95% 0.1393 to 0.201
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0152
	Estimation Comments	[Not specified]

▼ Statistical Analysis 24 ✓

Statistical Analysis Overview	Comparison Group Selection	Tiotropium Bromide Via (Spiriva® Handihaler®), Placebo
	Comments	AUC 0-12 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1384
	Confidence Interval	(2-Sided) 95% 0.0951 to 0.1817
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0216
	Estimation Comments	[Not specified]

▼ Statistical Analysis 25 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 25 mcg, Placebo
	Comments	AUC 12-24 on day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.0471
	Confidence Interval	(2-Sided) 95% 0.0155 to 0.0786
	Parameter Dispersion	Type: Standard Error of the Mean

		Value: 0.0157
	Estimation Comments	[Not specified]

▼ Statistical Analysis 26 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 50 mcg, Placebo
	Comments	AUC 12-24 on day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.0918
	Confidence Interval	(2-Sided) 95% 0.0611 to 0.1226
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0154
	Estimation Comments	[Not specified]

▼ Statistical Analysis 27 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®)100 mcg, Placebo
	Comments	AUC 12-24 on day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.0829
	Confidence Interval	(2-Sided) 95% 0.0519 to 0.1139
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0155
	Estimation Comments	[Not specified]

▼ Statistical Analysis 28 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 200 mcg, Placebo
	Comments	AUC 12-24 o day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]

	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1299
	Confidence Interval	(2-Sided) 95% 0.0982 to 0.1617
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0158
	Estimation Comments	[Not specified]

▼ Statistical Analysis 29 ✓

Statistical Analysis Overview	Comparison Group Selection	Ipratropium Bromide Inhalation Solution, Placebo
	Comments	AUC 12-24 on day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1369
	Confidence Interval	(2-Sided) 95% 0.1061 to 0.1678
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0154
	Estimation Comments	[Not specified]

▼ Statistical Analysis 30 ✓

Statistical Analysis Overview	Comparison Group Selection	Tiotropium Bromide Via (Spiriva® Handihaler®), Placebo
	Comments	AUC 12-24 on day 1
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.0934
	Confidence Interval	(2-Sided) 95% 0.0490 to 0.1377
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0221
	Estimation Comments	[Not specified]

▼ Statistical Analysis 31 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 25 mcg, Placebo
	Comments	AUC 12-24 on day 7

	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.0879
	Confidence Interval	(2-Sided) 95% 0.0573 to 0.1186
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0153
	Estimation Comments	[Not specified]

▼ Statistical Analysis 32 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 50 mcg, Placebo
	Comments	AUC 12-24 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1088
	Confidence Interval	(2-Sided) 95% 0.0788 to 0.1388
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0150
	Estimation Comments	[Not specified]

▼ Statistical Analysis 33 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®)100 mcg, Placebo
	Comments	AUC 12-24 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1175
	Confidence Interval	(2-Sided) 95% 0.0872 to 0.1478
	Parameter Dispersion	Type: Standard Error of the Mean

		Value: 0.0151
	Estimation Comments	[Not specified]

▼ Statistical Analysis 34 ✓

Statistical Analysis Overview	Comparison Group Selection	EP-101 Via Nebulizer (eFlow®) 200 mcg, Placebo
	Comments	[Not specified]
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1532
	Confidence Interval	(2-Sided) 95% 0.1226 to 0.1838
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0153
	Estimation Comments	[Not specified]

▼ Statistical Analysis 35 ✓

Statistical Analysis Overview	Comparison Group Selection	Ipratropium Bromide Inhalation Solution, Placebo
	Comments	[Not specified]
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.1048
	Confidence Interval	(2-Sided) 95% 0.0747 to 0.1350
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0150
	Estimation Comments	[Not specified]

▼ Statistical Analysis 36 ✓

Statistical Analysis Overview	Comparison Group Selection	Tiotropium Bromide Via (Spiriva® Handihaler®), Placebo
	Comments	AUC 12-24 on day 7
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Least squares mean (SE)]

	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Least Squares Mean (SE)]
	Estimated Value	0.0993
	Confidence Interval	(2-Sided) 95% 0.0589 to 0.1398
	Parameter Dispersion	Type: Standard Error of the Mean Value: 0.0202
	Estimation Comments	[Not specified]

3. Secondary Outcome

Title:	Peak FEV1 (Maximum FEV1 During the First 4 Hours Post-dose on Day 1 and Day 7)
Description:	Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines
Time Frame:	Day 1 and Day 7

Outcome Measure Data

Analysis Population Description

All subjects who received at least one dose of study medication and who had Day 1 pre-dose and Day 7 trough FEV1 values were included in the modified intent-to-treat (mITT) analysis set

Arm/Group Title	EP-101 Via Nebulizer (eFlow®) 25 mcg	EP-101 Via Nebulizer (eFlow®) 50 mcg	EP-101 Via Nebulizer (eFlow®)100 mcg	EP-101 Via Nebulizer (eFlow®) 200 mcg	Ipratropium Bromide Inhalation Solution	Tiotropium Bromide Via (Spiriva® Handihaler®)	Placebo
Arm/Group Description:	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	Ipratropium bromide Inhalation Solution via Handihaler® DPI Ipratropium bromide Inhalation Solution via Handihaler® DPI: Ipratropium 500 µg administered three times daily for 7 days using general purpose nebulizer	Tiotropium bromide via (Spiriva® Handihaler®) Tiotropium bromide via (Spiriva® Handihaler®): Tiotropium 18 µg administered once daily for 7 days using Handihaler® DPI	Placebo Placebo : Placebo administered once daily for 7 days
Overall Number of Participants Analyzed	72	76	75	72	74	76	77
Mean (Standard Deviation) Unit of Measure: liters							
Row Title							
Day 1	1.469 (0.5049)	1.498 (0.4857)	1.443 (0.4431)	1.455 (0.4355)	1.601 (0.4665)	1.434 (0.4774)	1.356 (0.4471)
Day 7	1.482 (0.4993)	1.496 (0.4694)	1.462 (0.4300)	1.453 (0.4476)	1.594 (0.4943)	1.475 (0.4556)	1.348 (0.4465)

4. Secondary Outcome

Title:	Treatment Responders (Number of Subjects With Clinically Meaningful Change From Pre-dose in Trough FEV1 on Day 1 and Day 7)
Description:	Number of subjects with clinically meaningful change from pre-dose in trough FEV1 on Day 1 and Day 7 Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines.
Time Frame:	Day 1 and Day 7

Outcome Measure Data

Analysis Population Description

All subjects who received at least one dose of study medication and who had Day 1 pre-dose and Day 7 through FEV1 values were included in the modified intent-to-treat (mITT) analysis set

Arm/Group Title							

	EP-101 Via Nebulizer (eFlow®) 25 mcg	EP-101 Via Nebulizer (eFlow®) 50 mcg	EP-101 Via Nebulizer (eFlow®)100 mcg	EP-101 Via Nebulizer (eFlow®) 200 mcg	Ipratropium Bromide Inhalation Solution	Tiotropium Bromide Via (Spiriva® Handihaler®)
Arm/Group Description:	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	Ipratropium bromide Inhalation Solution via Handihaler® DPI Ipratropium bromide Inhalation Solution via Handihaler® DPI: Ipratropium 500 µg administered three times daily for 7 days using general purpose nebulizer	Tiotropium bromide via (Spiriva® Handihaler®) Tiotropium bromide via (Spiriva® Handihaler®): Tiotropium 18 µg administered once daily for 7 days using Handihaler® DPI
Overall Number of Participants Analyzed	72	76	75	72	74	76
Measure Type: Number Unit of Measure: number of participants						
Row Title						
Day 1	18	29	24	24	24	26
Day 7	29	30	34	37	27	37

5. Secondary Outcome

Title:	Safety and Tolerability of EP-101: Adverse Events, Vital Signs, ECG, and Clinical Laboratory Tests
Description:	AEs are defined as existing conditions which worsen or events which occur during the course of the clinical trial after treatment. Vital signs were performed during the screening period to confirm study eligibility and at the final study visit. ECGs were performed during the screening period to confirm study eligibility. Vital signs and ECG were additionally collected within 30 minutes pre-dose; and 30 minutes, and 1, 2, 4, 6, 12 hours, and 23 hours 45 minutes post-dose within each treatment period. Clinical laboratory assessments were conducted during the screening period, at each study visit during each treatment period, and at the final study visit.
Time Frame:	Day 1 through Day 7

Outcome Measure Data ✓

Analysis Population Description

All subjects who received at least one dose of study medication were included in the safety analysis.

Arm/Group Title	EP-101 Via Nebulizer (eFlow®) 25 mcg	EP-101 Via Nebulizer (eFlow®) 50 mcg	EP-101 Via Nebulizer (eFlow®)100 mcg	EP-101 Via Nebulizer (eFlow®) 200 mcg	Ipratropium Bromide Inhalation Solution	Tiotropium Bromide Via (Spiriva® Handihaler®)	Placebo
Arm/Group Description:	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	Ipratropium bromide Inhalation Solution via Handihaler® DPI Ipratropium bromide Inhalation Solution via Handihaler® DPI: Ipratropium 500 µg administered three times daily for 7 days using general purpose nebulizer	Tiotropium bromide via (Spiriva® Handihaler®) Tiotropium bromide via (Spiriva® Handihaler®): Tiotropium 18 µg administered once daily for 7 days using Handihaler® DPI	Placebo Placebo : Placebo administered once daily for 7 days
Overall Number of Participants Analyzed	74	78	76	75	75	76	77
Measure Type: Number Unit of Measure: number of participants							

Row Title							
Treatment emergent AEs	23	23	28	26	19	12	25
Clinical signicant abnormal vital signs	0	0	2	0	1	0	1
Clinically significant abnormal ECG values Day 1	10	7	13	11	5	8	6
Clinically significant abnormal ECG values Day 7	7	5	8	11	3	8	7
Clinicall significant abnormal lab valuesday1-day7	1	0	2	2	1	0	3

6. Secondary Outcome

Title:	Rescue Medication Use
Description:	Mean number of puffs of daily rescue medication
Time Frame:	Day 1 through Day 7

Outcome Measure Data

Analysis Population Description
All subjects who received at least one dose of study medication and who had Day 1 pre-dose and Day 7 through FEV1 values were included in the modified intent-to-treat (mITT) analysis set

Arm/Group Title	EP-101 Via Nebulizer (eFlow®) 25 mcg	EP-101 Via Nebulizer (eFlow®) 50 mcg	EP-101 Via Nebulizer (eFlow®)100 mcg	EP-101 Via Nebulizer (eFlow®) 200 mcg	Ipratropium Bromide Inhalation Solution	Tiotropium Bromide Via (Spiriva® Handihaler®)	Placebo
Arm/Group Description:	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	Ipratropium bromide Inhalation Solution via Handihaler® DPI Ipratropium bromide Inhalation Solution via Handihaler® DPI: Ipratropium 500 µg administered three times daily for 7 days using general purpose nebulizer	Tiotropium bromide via (Spiriva® Handihaler®) Tiotropium bromide via (Spiriva® Handihaler®): Tiotropium 18 µg administered once daily for 7 days using Handihaler® DPI	Placebo Placebo : Placebo administered once daily for 7 days
Overall Number of Participants Analyzed	72	76	75	72	74	76	77
Mean (Standard Deviation) Unit of Measure: average daily number of puffs	1.34 (2.72)	1.11 (1.89)	1.48 (2.43)	1.29 (2.70)	1.42 (2.91)	1.33 (3.01)	1.59 (2.16)

7. Secondary Outcome

Title:	Treatment Responders (Percentage of Subjects With Clinically Meaningful Change From Pre-dose in Trough FEV1 on Day 1 and Day 7)
Description:	percentage of subjects with clinically meaningful change from pre-dose in trough FEV1 on Day 1 and Day 7 Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines.
Time Frame:	Day 1 and Day 7

Outcome Measure Data

Analysis Population Description
All subjects who received at least one dose of study medication and who had Day 1 pre-dose and Day 7 through FEV1 values were included in the modified intent-to-treat (mITT) analysis set

Arm/Group Title	EP-101 Via Nebulizer	EP-101 Via Nebulizer	EP-101 Via Nebulizer	EP-101 Via Nebulizer	Ipratropium Bromide	Tiotropium Bromide Via

	(eFlow®) 25 mcg	(eFlow®) 50 mcg	(eFlow®)100 mcg	(eFlow®) 200 mcg	Inhalation Solution	(Spiriva® Handihaler®)
Arm/Group Description:	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	Ipratropium bromide Inhalation Solution via Handihaler® DPI Ipratropium bromide Inhalation Solution via Handihaler® DPI: Ipratropium 500 µg administered three times daily for 7 days using general purpose nebulizer	Tiotropium bromide via (Spiriva® Handihaler®) Tiotropium bromide via (Spiriva® Handihaler®): Tiotropium 18 µg administered once daily for 7 days using Handihaler® DPI
Overall Number of Participants Analyzed	72	76	75	72	74	76
Measure Type: Number Unit of Measure: percentage of participants						
Row Title						
Day 1	25.0	38.7	32.0	35.3	33.8	34.7
Day 7	40.3	40.0	46.6	51.4	37.5	48.7

Adverse Events

Time Frame	day 1 through day 7
Adverse Event Reporting Description	existing conditions which worsen or events which occur during the course of the clinical trial after treatment with randomized study dr
Source Vocabulary Name for Table Default	MedDRA (14.0)
Collection Approach for Table Default	Systematic Assessment

Arm/Group Title	EP-101 Via Nebulizer (eFlow®) 25 mcg	EP-101 Via Nebulizer (eFlow®) 50 mcg	EP-101 Via Nebulizer (eFlow®)100 mcg	EP-101 Via Nebulizer (eFlow®) 200 mcg	Ipratropium Bromide Inhalation Solution	Tic
Arm/Group Description	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	EP-101 via nebulizer (eFlow®) EP-101 via nebulizer (eFlow®): EP-101 Dose 1 administered once daily for 7 days EP-101 via nebulizer (eFlow®): EP-101 administered once daily for 7 days	Ipratropium bromide Inhalation Solution via Handihaler® DPI Ipratropium bromide Inhalation Solution via Handihaler® DPI: Ipratropium 500 µg administered three times daily for 7 days using general purpose nebulizer	Tiot via Har Tiot via Har Tiot adm dail Har

All-Cause Mortality

	EP-101 Via Nebulizer (eFlow®) 25 mcg	EP-101 Via Nebulizer (eFlow®) 50 mcg	EP-101 Via Nebulizer (eFlow®)100 mcg	EP-101 Via Nebulizer (eFlow®) 200 mcg	Ipratropium Bromide Inhalation Solution	Tiot
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)	Aff F
Total	0/74 (0%)	0/78 (0%)	0/76 (0%)	0/75 (0%)	0/75 (0%)	0/

Serious Adverse Events

	EP-101 Via Nebulizer (eFlow®) 25 mcg		EP-101 Via Nebulizer (eFlow®) 50 mcg		EP-101 Via Nebulizer (eFlow®)100 mcg		EP-101 Via Nebulizer (eFlow®) 200 mcg		Ipratropium Bromide Inhalation Solution		Tiot
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Aff R
Total	8/74 (10.81%)		13/78 (16.67%)		14/76 (18.42%)		13/75 (17.33%)		5/75 (6.67%)		2/76
Nervous system disorders											
headache †A	3/74 (4.05%)	4	3/78 (3.85%)	5	5/76 (6.58%)	5	4/75 (5.33%)	7	0/75 (0%)	0	2/76
Respiratory, thoracic and mediastinal disorders											
cough †A	5/74 (6.76%)	9	10/78 (12.82%)	13	9/76 (11.84%)	15	9/75 (12%)	14	5/75 (6.67%)	5	1/76

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (14.0)

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	5%

	EP-101 Via Nebulizer (eFlow®) 25 mcg		EP-101 Via Nebulizer (eFlow®) 50 mcg		EP-101 Via Nebulizer (eFlow®)100 mcg		EP-101 Via Nebulizer (eFlow®) 200 mcg		Ipratropium Bromide Inhalation Solution		Tiot
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Aff R
Total	0/74 (0%)		0/78 (0%)		0/76 (0%)		0/75 (0%)		0/75 (0%)		0/

Limitations and Caveats

[Not Specified]

More Information

Certain Agreements

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

In the event the study is part of a multi-center study. The first publication of the results of the Study shall be made in conjunction with the results of other participating study sites as a multi-center publication; provided however, if a multi-center publication is not forthcoming within twenty-four (24) months following completion of the Study at all sites, Institution and Investigator shall be free to publish.

Results Point of Contact

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