ClinicalTrials.gov PRS
Protocol Registration and Results System

ID: EP-101-02 Assessment of the Safety and Ability of a Once-a-day Dose of an Orally Inhaled Medicine [i.e., Glycopyrrolate Inhalation Solution = GIS] to Improve Airflow in the Lungs When Delivered Using an eFlow Nebulizer in Patients With Chronic Obstructive Pulmonary Disease (COPD) NCT02948582

Protocol Registration and Results Preview

Assessment of the Safety and Ability of a Once-a-day Dose of an Orally Inhaled Medicine [i.e., Glycopyrrolate Inhalation Solution = GIS] to Improve Airflow in the Lungs When Delivered Using an eFlow Nebulizer in Patients With Chronic Obstructive Pulmonary Disease (COPD)

This study has been completed.

Sponsor:
Sunovion Respiratory Development Inc.

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

ClinicalTrials.gov Identifier:
NCT02948582

First received: October 26, 2016
Last updated: May 9, 2017
Last verified: January 2017

Purpose

The study assessed the safety and ability of an orally inhaled medicine [i.e., Glycopyrrolate Inhalation Solution = GIS] to improve airflow in the lungs when delivered using an eFlow nebulizer in 42 patients with Chronic Obstructive Pulmonary Disease (COPD). Each patient randomly received several, single doses of GIS, or placebo, separated by approximately 1 to 2 weeks. After the dose was given, lung airflow was measured over 24 hours and blood was collected to measure how much GIS was in the bloodstream. The study was conducted to find the once-a- day GIS dose that produced the highest improvement in lung airflow using the eFlow nebulizer.

Condition	Intervention	Phase
Chronic Obstructive Pulmonary Disease	Drug: Glycopyrrolate Inhalation Solution12.5µg Drug: Glycopyrrolate Inhalation Solution 50µg Drug: Glycopyrrolate Inhalation Solution 100µg Drug: Glycopyrrolate Inhalation Solution 200µg Drug: Glycopyrrolate Inhalation Solution 400µg Drug: Placebo 0.5mL	Phase 2

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

Official Title: Randomized, Placebo-Controlled, Double-Blind, Dose Ranging, Single-Dose, 6-Way Crossover Study to Assess Safety, Efficacy and Pharmacokinetics of EP-101 Using eFlow Nebuliser in Patients With COPD

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

Primary Outcome Measure:

- Trough FEV1 (Change From Baseline) [Time Frame: 24hr post dose]
  Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines. Trough FEV1 was defined as the mean of FEV1 values obtained at 23 hours 30 minutes and 24 hours post-dose of each Treatment Visit.

- Standardized FEV1AUC0-12 Area Under the FEV1 Curve From 0 to 12 Hours Post-dose (Actual and Change From Baseline). [Time Frame: 0-12h post dose]
  Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines

- Standardized FEV1AUC12-24 Area Under the FEV1 Curve From 12 to 24 Hours Post- Dose (Actual and Change From Baseline). [Time Frame: 12-24h post dose]
  Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines

- Standardized FEV1 AUC0-24 Area Under the FEV1 Curve From 0 to 24 Hours Post-dose (Actual and Change Baseline) [Time Frame: 0 to 24h]
  Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines

- Peak FEV1 (Change From Baseline and Percent Change) [Time Frame: 0-4h post dose]
  spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines

Secondary Outcome Measures:

- Cmax; Maximum Observed Plasma Concentration [Time Frame: 0 to 12 hour]
  Pk parameters are calculated from glycopyrrolate plasma concentration analysed from serial blood samples collected between 0 and 12 hr

- Tmax; Time to Maximum Observed Plasma Concentration [Time Frame: 0 to 12 hours]

Pk parameters are calculated from glycopyrrolate plasma concentration analysed from serial blood samples collected between 0 and 12 hr

- t1/2; Plasma Half-life [Time Frame: 0 to 12 hour]
  Pk parameters are calculated from glycopyrrolate plasma concentration analysed from serial blood samples collected between 0 and 12 hr

- AUC0-t; Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Measurable Drug Concentration. [Time Frame: 0 to 12 hour]
  Pk parameters are calculated from glycopyrrolate plasma concentration analysed from serial blood samples collected between 0 and 12 hr

- AUC0-inf Area Under the Plasma Concentration-time Curve From Time Zero to Infinity [Time Frame: 0 to 12 hour]
  Pk parameters are calculated from glycopyrrolate plasma concentration analysed from serial blood samples collected between 0 and 12 hr

- Number of Subjects Who Died, Number of Subjects With Treatment Emergent SAEs, Number of Subjects Who Discontinued Due to AE, Percentage of Subjects With Treatment Emergent AEs [Time Frame: Day 69 (includes dosing Day 1, washout Day 12, safety follow up Day 69)]
  AE's are defined as existing conditions which worsen or events which occur during the course of the clinical trial after treatment

- Number of Subjects With Clinically Significant Abnormal Vital Signs Reported During the Study [Time Frame: 0-24 h]
  Vital signs were measured at screening and at each Treatment Visit pre-dose (within 30 minutes prior to dose); post-dose at 30 minutes and 1, 2, 4, 8, 12 and 24 hours; and then at the post study assessment.

- Number of Clinically Significant Abnormal Laboratory Results Reported During the Study [Time Frame: Day -14, Day 69]
  Clinical safety lab parameters were collected at screening and at the post study assessment. Any laboratory values that were out of range of normal reference values were evaluated by the Investigators.

- Number of Subjects With Clinically Significant ECG Parameters Reported During the Study [Time Frame: 0 to 24h]
  ECGs were recorded at screening and at each study treatment visit pre-dose (within 30 minutes prior to dose); post-dose at 30 minutes and 1, 2, 4, 8, 12 and 24 hours; and then at the post study assessment.

Enrollment: 42
Study Start Date: July 2010
Study Completion Date: November 2010
Primary Completion Date: November 2010

Arms	Assigned Interventions
Experimental: Glycopyrrolate Inhalation Solution12.5µg Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily	Drug: Glycopyrrolate Inhalation Solution12.5µg Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily Other Names: • GIS
Experimental: Glycopyrrolate Inhalation Solution 50µg Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily	Drug: Glycopyrrolate Inhalation Solution 50µg Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily Other Names: • GIS
Experimental: Glycopyrrolate Inhalation Solution 100µg Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily	Drug: Glycopyrrolate Inhalation Solution 100µg Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily Other Names: • GIS
Experimental: Glycopyrrolate Inhalation Solution 200µg Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily	Drug: Glycopyrrolate Inhalation Solution 200µg Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily Other Names: • GIS
Experimental: Glycopyrrolate Inhalation Solution 400µg Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily	Drug: Glycopyrrolate Inhalation Solution 400µg Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily Other Names: • GIS
Placebo Comparator: Placebo 0.5mL Placebo 0.5mL via e-flow nebulizer, once daily	Drug: Placebo 0.5mL Placebo 0.5mL via eFlow, once daily Other Names: • Placebo

Eligibility

Ages Eligible for Study: 40 Years to 75 Years

Inclusion Criteria:

1. Male and female patients aged 40 through 75 years, inclusive
2. A clinical diagnosis of COPD according to the GOLD guidelines
3. Current smokers or ex-smokers with at least 10 pack-year smoking history (e.g., at least 1 pack/day for 10
4. Post-bronchodilator FEV1 30-70% of predicted normal at the Screening Visit
5. Post-bronchodilator FEV1/FVC ratio < 0.70 at the Screening Visit
6. Improvement in FEV1 >12% and 150 mL following inhalation of ipratropium bromide at the Screening Visit
7. Ability to perform reproducible spirometry according to the ATS/ERS guidelines
8. Willing to stay at the study site for approximately 30 hours on each treatment visit
9. Willing and able to provide written informed consent

Exclusion Criteria:

1. Females who are pregnant or lactating at the Screening Visit, or if of childbearing potential not using one of the following acceptable means of birth control throughout the study:
   - Abstinence
   - Post-menopausal for at least two years
   - Surgically sterile (i.e., tubal ligation, hysterectomy)
   - Oral contraceptives (taken for at least one month prior to the Screening Visit)
   - Approved implantable or injectable contraceptives (e.g., Norplant®, Depo-Provera® or equivalent)
   - Barrier methods (e.g., condoms with spermicide)
   - Intrauterine device (i.e., IUD)
   - Vasectomy of male partner
   - Non-heterosexual life style
2. Current evidence or recent history of any clinically significant disease (other than COPD) or abnormality in the opinion of the Investigator that would put the subject at risk or which would compromise the quality of the study data; including but not limited to cardiovascular disease, myocardial infarction, cardiac failure, uncontrolled hypertension, life-threatening arrhythmias, uncontrolled diabetes, neurologic or neuromuscular disease, liver disease, gastrointestinal disease or electrolyte abnormalities
3. Recent history of hospitalization due to an exacerbation of airway disease within 3 months or need for increased treatments for COPD within 6 weeks prior to the Screening Visit
4. Primary diagnosis of asthma
5. Prior lung volume reduction surgery or history of chest/lung irradiation
6. Regular use of daily oxygen therapy
7. Use of systemic (eg, intramuscular or intravenous) steroids within 3 months prior to the Screening Visit
8. Respiratory tract infection within 6 weeks prior to the Screening Visit
9. History of tuberculosis, bronchiectasis or other non- specific pulmonary disease
10. History of urinary retention or bladder neck obstruction type symptoms
11. History of narrow-angle glaucoma
12. Clinically significant abnormal ECG
13. Positive Hepatitis B surface antigen or positive Hepatitis C antibody
14. Positive screening test for HIV antibodies
15. Current or recent history (previous 12 months) of excessive use or abuse of alcohol
16. Current evidence or history of abusing legal drugs or use of illegal drugs or substances
17. Donation of 450 mL of blood within 8 weeks of the Screening Visit
18. History of hypersensitivity or intolerance to aerosol medications
19. Participation in another investigational drug study was received within 30 days prior to the Screening Visit

Contacts and Locations

Investigators

Study Chair: Ahmet Tutuncu, MD, PhD Elevation Pharmaceuticals, Inc., (now known as Sunovion Respriatory Developement Inc.)

More Information

ClinicalTrials.gov Identifier: NCT02948582

Responsible Party: Sunovion Respiratory Development Inc.

Other Study ID Numbers: EP-101-02
2010-018987-17

Human Subjects Protection Review Board Status: Approved

Study Results

Participant Flow

Recruitment Details	
Pre-Assignment Details	All enrolled subjects were randomized. all randomized subjects received at least one dose of study medication

Arm/Group Title	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Treatment Grou
Arm/Group Description	subjects received placebo, glycopyrrolate	subjects received glycopyrrolate 12.5	subjects received glycopyrrolate 50 mcg,	subjects received glycopyrrolate 100 mcg,	subjects received glycopyrrolate 200

	400mcg, glycopyrrolate 50 mcg, glycopyrrolate 12.5 mcg, glycoyrrolate 200mcg, or glycopryrrolate 100mcg	mcg, glycopyrrolate 50 mcg, glycopryrrolate 100mcg, placebo, glycopyrrolate 200mcg, glycoyrrolate 400mcg, or placebo	Placebo, glycopyrrolate 200 mcg, glycopryrrolate 100mcg, glycopyrrolate 12.5mcg, or glycoyrrolate 400mcg	glycopyrrolate 200 mcg, glycopryrrolate 400mcg, placebo, glycopyrrolate 50mcg, or glycoyrrolate 12.5mcg	glycopyrrolate 12. mcg, placebo, glycopryrrolate 40 placebo, glycopyr 100mcg, or glycoyrrolate 50m
Period Title: **Treatment Period 1**					
Started	7	7	7	7	7
Completed	7	7	7	7	7
Not Completed	0	0	0	0	0
Period Title: **Washout Period 1**					
Started	7	7	7	7	7
Completed	7	5	7	7	7
Not Completed	0	2	0	0	0
Reason Not Completed					
Adverse Event	0	2	0	0	0
Protocol Violation	0	0	0	0	0
(Not Public)	Not Completed =0 Total from all reasons =0	Not Completed =2 Total from all reasons =2	Not Completed =0 Total from all reasons =0	Not Completed =0 Total from all reasons =0	Not Comp Total from all rea
Period Title: **Treatment Period 2**					
Started	7	5	7	7	7
Completed	7	5	7	7	7
Not Completed	0	0	0	0	0
Period Title: **Washout Period 2**					
Started	7	5	7	7	7
Completed	7	4	7	6	7
Not Completed	0	1	0	1	0
Reason Not Completed					
Adverse Event	0	1	0	0	0
personal reasons	0	0	0	1	0
(Not Public)	Not Completed =0 Total from all reasons =0	Not Completed =1 Total from all reasons =1	Not Completed =0 Total from all reasons =0	Not Completed =1 Total from all reasons =1	Not Comp Total from all rea
Period Title: **Treatment Period 3**					
Started	7	4	7	6	7
Completed	7	4	7	6	7
Not Completed	0	0	0	0	0
Period Title: **Washout Period 3**					
Started	7	4	7	6	7
Completed	7	4	7	6	7
Not Completed	0	0	0	0	0
Period Title: **Treatment Period 4**					
Started	7	4	7	6	7
Completed	7	4	7	6	7
Not Completed	0	0	0	0	0
Period Title: **Washout Period 4**					
Started	7	4	7	6	7
Completed	6	4	6	6	7
Not Completed	1	0	1	0	0
Reason Not Completed					
Adverse Event	1	0	1	0	0
(Not Public)	Not Completed =1 Total from all reasons =1	Not Completed =0 Total from all reasons =0	Not Completed =1 Total from all reasons =1	Not Completed =0 Total from all reasons =0	Not Comp Total from all rea

Period Title: **Treatment Period 5**					
Started	6	4	6	6	7
Completed	6	4	6	6	7
Not Completed	0	0	0	0	0
Period Title: **Washout Period 5**					
Started	6	4	6	6	7
Completed	6	4	6	6	7
Not Completed	0	0	0	0	0
Period Title: **Treatment Period 6**					
Started	6	4	6	6	7
Completed	6	4	6	6	7
Not Completed	0	0	0	0	0
Period Title: **Wshout Period 6**					
Started	6	4	6	6	7
Completed	6	4	6	6	7
Not Completed	0	0	0	0	0

Baseline Characteristics

		Arm/Group Title	Total Participants	
		▼ Arm/Group Description	Intent to treat population same as safety population -not full analysis set	
		Overall Number of Baseline Participants	42	
		▼ Baseline Analysis Population Description	Intent to treat population same as safety population -not full analysis set	
Age, Categorical Measure Type: Count of Participants Unit of measure: participants	Number Analyzed		42 participants	
	<=18 years		0	0%
	Between 18 and 65 years		29	69.05%
	>=65 years		13	30.95%
Age, Continuous Mean (Standard Deviation) Unit of measure: years	Number Analyzed		42 participants	
			62.0 (6.99)	
Sex: Female, Male Measure Type: Count of Participants Unit of measure: participants	Number Analyzed		42 participants	
	Female		15	35.71%
	Male		27	64.29%
Ethnicity (NIH/OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed		42 participants	
	Hispanic or Latino		0	0%
	Not Hispanic or Latino		42	100%
	Unknown or Not Reported		0	0%
Race (NIH/OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed		42 participants	
	American Indian or Alaska Native		0	0%
	Asian		0	0%
	Native Hawaiian or Other Pacific Islander		0	0%
	Black or African American		0	0%
	White		41	97.62%
	More than one race		1	2.38%
	Unknown or Not Reported		0	0%
Region of Enrollment Measure Type: Number Unit of measure: participants	Number Analyzed		42 participants	
United Kingdom			42	

Outcome Measures

1. Primary Outcome

Title:	Trough FEV1 (Change From Baseline)

Description:	Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines. Trough FEV1 was defined as the mean of FEV1 values obtained at 23 hours 30 minutes and 24 hours post-dose of each Treatment Visit.
Time Frame:	24hr post dose

Outcome Measure Data

Analysis Population Description

All subjects who received at least one dose of study medication and had at least one postbaseline efficacy measurement (FEV1) were included in the intent-to-treat analysis.

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg	Placebo 0.5mL
Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily	Placebo 0.5mL via e-flow nebulizer, once daily Placebo 0.5mL: Placebo 0.5mL via eFlow, once daily
Overall Number of Participants Analyzed	38	38	37	37	37	37
Mean (Standard Deviation) Unit of Measure: liters	-0.093 (0.1189)	0.0114 (0.1308)	0.0447 (0.1548)	0.0542 (0.1779)	0.0292 (0.1468)	-0.0612 (0.1233)

Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution12.5µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in trough FEV1 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence. A sample size of 34 subjects (42 with dropouts) provides 80% power to detect a 0.14L difference in mean change trough FEV1 between 2 groups at an alpha of 0.05 using a 2-tailed t-test and assuming a common standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.1257
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.033
	Confidence Interval	(2-Sided) 95% -0.009 to 0.075
	Estimation Comments	[Not specified]

Statistical Analysis 2

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution 50µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in trough FEV1 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence. A sample size of 34 subjects (42 with dropouts) provides 80% power to detect a 0.14L difference in mean change trough FEV1 between 2

		groups at an alpha of 0.05 using a 2-tailed t-test and assuming a common standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0008
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.072
	Confidence Interval	(2-Sided) 95% 0.030 to 0.113
	Estimation Comments	[Not specified]

▼ Statistical Analysis 3 ✔

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution 100µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in trough FEV1 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence. A sample size of 34 subjects (42 with dropouts) provides 80% power to detect a 0.14L difference in mean change trough FEV1 between 2 groups at an alpha of 0.05 using a 2-tailed t-test and assuming a common standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.102
	Confidence Interval	(2-Sided) 95% 0.061 to 0.144
	Estimation Comments	[Not specified]

▼ Statistical Analysis 4 ✔

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution 200µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in trough FEV1 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence. A sample size of 34 subjects (42 with dropouts) provides 80% power to detect a 0.14L difference in mean change trough FEV1 between 2 groups at an alpha of 0.05 using a 2-tailed t-test and assuming a common standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mean]

	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.108
	Confidence Interval	(2-Sided) 95% 0.066 to 0.150
	Estimation Comments	[Not specified]

▼ Statistical Analysis 5 ✔

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution 400µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in trough FEV1 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence. A sample size of 34 subjects (42 with dropouts) provides 80% power to detect a 0.14L difference in mean change trough FEV1 between 2 groups at an alpha of 0.05 using a 2-tailed t-test and assuming a common standard deviation for change in trough FEV1 of 0.2.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.098
	Confidence Interval	(2-Sided) 95% 0.056 to 0.140
	Estimation Comments	[Not specified]

2. Primary Outcome

Title:	Standardized FEV1AUC0-12 Area Under the FEV1 Curve From 0 to 12 Hours Post-dose (Actual and Change From Baseline).
▼ 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:	0-12h post dose

▼ Outcome Measure Data ✔

▼ Analysis Population Description

All subjects who received at least one dose of study medication and had at least one postbaseline efficacy measurement (FEV1) were included in the intent to treat analysis

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg	Placebo 0.5mL
▼ Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily	Placebo 0.5mL via e-flow nebulizer, once daily Placebo 0.5mL: Placebo 0.5mL via eFlow, once daily
Overall Number of Participants Analyzed	39	38	37	37	37	37

Mean (Standard Deviation) Unit of Measure: liters						
Row Title						
actual standardized FEV1 AUC0_12	1.259 (0.409)	1.311 (0.422)	1.335 (0.394)	1.374 (0.391)	1.390 (0.423)	1.180 (0.427)
change from baseline standardized FEV1 AUC0_12	0.055 (0.113)	0.126 (0.112)	0.136 (0.134)	0.184 (0.134)	0.170 (0.110)	-0.024 (0.095)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution12.5µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in standardized FEV1 AUC0_12 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.086
	Confidence Interval	(2-Sided) 95% 0.050 to 0.123
	Estimation Comments	[Not specified]

▼ Statistical Analysis 2 ✔

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution 50µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in standardized FEV1 AUC0_12 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.151
	Confidence Interval	(2-Sided) 95% 0.114 to 0.187
	Estimation Comments	[Not specified]

▼ Statistical Analysis 3 ✔

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution 100µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in standardized FEV1 AUC0_12 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence.

	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.156
	Confidence Interval	(2-Sided) 95% 0.120 to 0.193
	Estimation Comments	[Not specified]

▼ Statistical Analysis 4 ✔

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution 200µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in standardized FEV1 AUC0_12 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.202
	Confidence Interval	(2-Sided) 95% 0.165 to 0.239
	Estimation Comments	[Not specified]

▼ Statistical Analysis 5 ✔

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution 400µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in standardized FEV1 AUC0_12 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.199
	Confidence Interval	(2-Sided) 95% 0.162 to 0.235
	Estimation Comments	[Not specified]

3. Primary Outcome

Title:	Standardized FEV1AUC12-24 Area Under the FEV1 Curve From 12 to 24 Hours Post- Dose (Actual and Change From Baseline).
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:	12-24h post dose

Outcome Measure Data

Analysis Population Description

All subjects who received at least one dose of study medication and had at least one postbaseline efficacy measurement (FEV1) were included in the intent to treat analysis

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg	Placebo 0.5mL
Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily	Placebo 0.5mL via e-flow nebulizer, once daily Placebo 0.5mL: Placebo 0.5mL via eFlow, once daily
Overall Number of Participants Analyzed	39	38	37	37	37	37
Mean (Standard Deviation) Unit of Measure: liters						
Row Title						
acutal standardized FEV1 AUC0_12	1.165 (0.377)	1.203 (0.404)	1.227 (0.369)	1.253 (0.346)	1.259 (0.396)	1.123 (0.392)
change from baseline standardized FEV1 AUC0_12	-0.038 (0.132)	0.018 (0.135)	0.028 (0.138)	0.063 (0.178)	0.039 (0.135)	-0.082 (0.120)

Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution12.5µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in standardized FEV1 AUC12_24 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0028
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.058
	Confidence Interval	(2-Sided) 95% 0.021 to 0.095
	Estimation Comments	[Not specified]

Statistical Analysis 2

	Comparison Group Selection	Placebo 0.5mL

Statistical Analysis Overview	Comments	An analysis of covariance was used with change from baseline in standardized FEV1 AUC12_24 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mena]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.100
	Confidence Interval	(2-Sided) 95% 0.063 to 0.137
	Estimation Comments	[Not specified]

▼ Statistical Analysis 3 ✔

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution 100µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in standardized FEV1 AUC12_24 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.105
	Confidence Interval	(2-Sided) 95% 0.068 to 0.142
	Estimation Comments	[Not specified]

▼ Statistical Analysis 4 ✔

Statistical Analysis Overview	Comparison Group Selection	Glycopyrrolate Inhalation Solution 200µg, Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in standardized FEV1 AUC12_24 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.135

	Confidence Interval	(2-Sided) 95% 0.098 to 0.173
	Estimation Comments	[Not specified]

▼ Statistical Analysis 5 ✔

Statistical Analysis Overview	Comparison Group Selection	Placebo 0.5mL
	Comments	An analysis of covariance was used with change from baseline in standardized FEV1 AUC12_24 as the response, with factors for center, treatment, period, sequence, baseline FEV1 as a covariate and a random effect for subject nested within sequence.
	Type of Statistical Test	Superiority
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [least squares mean]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[least squares mean]
	Estimated Value	0.128
	Confidence Interval	(2-Sided) 95% 0.091 to 0.166
	Estimation Comments	[Not specified]

4. Primary Outcome

Title:	Standardized FEV1 AUC0-24 Area Under the FEV1 Curve From 0 to 24 Hours Post-dose (Actual and Change Baseline)
▼ 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:	0 to 24h

▼ Outcome Measure Data ✔

▼ Analysis Population Description

all subjects who received at least one dose of study medication and had at least one postbaseline efficacy measurement (FEV1) were included in the intent to treat analysis

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg	Placebo 0.5mL
▼ Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily	Placebo 0.5mL via e-flow nebulizer, once daily Placebo 0.5mL: Placebo 0.5mL via eFlow, once daily
Overall Number of Participants Analyzed	39	38	37	37	37	37
Mean (Standard Deviation) Unit of Measure: liters						
Row Title						
Actual standardized FEV1 AUC0_12	1.212 (0.391)	1.257 (0.411)	1.281 (0.379)	1.313 (0.364)	1.325 (0.407)	1.151 (0.408)
change from baseline standardized FEV1 AUC0_12	0.009 (0.114)	0.072 (0.115)	0.082 (0.128)	0.123 (0.146)	0.105 (0.113)	-0.053 (0.102)

5. Primary Outcome

Title:	Peak FEV1 (Change From Baseline and Percent Change)
Description:	spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines
Time Frame:	0-4h post dose

Outcome Measure Data

Analysis Population Description

all subjects who received at least one dose of study medication and have at least one post baseline efficacy measurement were included in the efficacy population

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg	Placebo 0.5mL
Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily	Placebo 0.5mL via e-flow nebulizer, once daily Placebo 0.5mL: Placebo 0.5mL via eFlow, once daily
Overall Number of Participants Analyzed	39	38	37	37	37	37
Mean (Standard Deviation) Unit of Measure: liters						
Row Title						
Change from baseline	0.165 (0.113)	0.229 (0.113)	0.260 (0.151)	0.292 (0.120)	0.272 (0.125)	0.061 (0.102)
percent change from baseline	15.30 (11.37)	21.05 (11.87)	24.14 (20.69)	26.73 (12.56)	25.44 (15.10)	5.24 (8275)

6. Secondary Outcome

Title:	Cmax; Maximum Observed Plasma Concentration
Description:	Pk parameters are calculated from glycopyrrolate plasma concentration analysed from serial blood samples collected between 0 and 12 hr
Time Frame:	0 to 12 hour

Outcome Measure Data

Analysis Population Description

All subjects who received at least one dose of EP-101 and who have sufficient blood samples taken to obtain a plasma concentration by time profile and have no major protocol violations were included in the PK analysis.

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg
Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily
Overall Number of Participants Analyzed	2	13	12	12	13
Geometric Mean (Geometric Coefficient of Variation) Unit of Measure: pg/mL	59.25 (78.49%)	74.48 (62.24%)	144.58 (52.53%)	316.05 (48.35%)	504.93 (55.67%)

7. Secondary Outcome

Title:	Tmax; Time to Maximum Observed Plasma Concentration

Description:	Pk parameters are calculated from glycopyrrolate plasma concentration analysed from serial blood samples collected between 0 and 12 hr
Time Frame:	0 to 12 hours

Outcome Measure Data

Analysis Population Description

All subjects who received at least one dose of EP-101 and who have sufficient blood samples taken to obtain a plasma concentration by time profile and have no major protocol violations were included in the PK analysis.

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg
Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily
Overall Number of Participants Analyzed	2	13	12	12	12
Median (Full Range) Unit of Measure: hours	0.165 (0.150 to 0.180)	0.320 (.0150 to 0.350)	0.260 (0.150 to 0.330)	0.275 (0.150 to 0.380)	0.180 (0.150 to 0.320)

8. Secondary Outcome

Title:	t1/2; Plasma Half-life
Description:	Pk parameters are calculated from glycopyrrolate plasma concentration analysed from serial blood samples collected between 0 and 12 hr
Time Frame:	0 to 12 hour

Outcome Measure Data

Analysis Population Description

All subjects who received at least one dose of EP-101 and who have sufficient blood samples taken to obtain a plasma concentration by time profile and have no major protocol violations were included in the PK analysis.

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg
Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily
Overall Number of Participants Analyzed	0	2	4	7	6
Geometric Mean (Geometric Coefficient of Variation) Unit of Measure: hours	---	0.8949 (2.3707%)	3.0137 (50.7557%)	3.1663 (45.4839%)	4.1238 (63.5353%)

9. Secondary Outcome

Title:	AUC0-t; Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last Measurable Drug Concentration.
Description:	Pk parameters are calculated from glycopyrrolate plasma concentration analysed from serial blood samples collected between 0 and 12 hr
Time Frame:	0 to 12 hour

Outcome Measure Data

▼ Analysis Population Description

All subjects who received at least one dose of EP-101 and who have sufficient blood samples taken to obtain a plasma concentration by time profile and have no major protocol violations were included in the PK analysis.

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg
▼ Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily
Overall Number of Participants Analyzed	2	13	12	12	13
Geometric Mean (Geometric Coefficient of Variation) Unit of Measure: pg.h/ml	135.87 (209.27%)	67.18 (143.22%)	237.80 (98.45%)	677.24 (66.34%)	1481.36 (82.17%)

10. Secondary Outcome

Title:	AUC0-inf Area Under the Plasma Concentration-time Curve From Time Zero to Infinity
▼ Description:	Pk parameters are calculated from glycopyrrolate plasma concentration analysed from serial blood samples collected between 0 and 12 hr
Time Frame:	0 to 12 hour

▼ Outcome Measure Data ✔

▼ Analysis Population Description

All subjects who received at least one dose of EP-101 and who have sufficient blood samples taken to obtain a plasma concentration by time profile and have no major protocol violations were included in the PK analysis.

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg
▼ Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily
Overall Number of Participants Analyzed	0	2	4	7	6
Geometric Mean (Geometric Coefficient of Variation) Unit of Measure: pg.h/ml	---	246.84 (37.49%)	634.65 (34.28%)	772.59 (26.30%)	1367.76 (76.70%)

11. Secondary Outcome

Title:	Number of Subjects Who Died, Number of Subjects With Treatment Emergent SAEs, Number of Subjects Who Discontinued Due to AE, Percentage of Subjects With Treatment Emergent AEs
▼ Description:	AE's are defined as existing conditions which worsen or events which occur during the course of the clinical trial after treatment NOTE : Outcome Measure Description is shorter than the Outcome Measure Title.
Time Frame:	Day 69 (includes dosing Day 1, washout Day 12, safety follow up Day 69)

▼ Outcome Measure Data ✔

▼ Analysis Population Description

all subjects who received at least one dose of study drug were included in the safety analysis

Arm/Group Title						Placebo 0.5mL

	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg	
▼ Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily	Placebo 0.5mL via e-flow nebulizer, once daily Placebo 0.5mL: Placebo 0.5mL via eFlow, once daily
Overall Number of Participants Analyzed	39	38	37	37	37	37
Measure Type: Number Unit of Measure: pg.h/ml						
Row Title						
subjects who died	0	0	0	0	0	0
subjects with treatment emergent SAEs	0	0	1	0	0	0
Subjects whodiscontinued due to an AE	2	2	2	0	0	0
subjects with treatment emergent AEs	16	14	17	15	13	14
percentage of subjects with treatment emergent AEs	41.0	36.8	45.9	40.5	35.1	37.8

12. Secondary Outcome

Title:	Number of Subjects With Clinically Significant Abnormal Vital Signs Reported During the Study
▼ Description:	Vital signs were measured at screening and at each Treatment Visit pre-dose (within 30 minutes prior to dose); post-dose at 30 minutes and 1, 2, 4, 8, 12 and 24 hours; and then at the post study assessment.
Time Frame:	0-24 h

▼ Outcome Measure Data ✔

▼ Analysis Population Description

all subjects who received at least one does of study drug were included in the safety analysis

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg	Placebo 0.5mL
▼ Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily	Placebo 0.5mL via e-flow nebulizer, once daily Placebo 0.5mL: Placebo 0.5mL via eFlow, once daily
Overall Number of Participants Analyzed	39	38	37	37	37	37
Measure Type: Number Unit of Measure: number of events	0	0	0	0	0	0

13. Secondary Outcome

Title:	Number of Clinically Significant Abnormal Laboratory Results Reported During the Study
▼ Description:	Clinical safety lab parameters were collected at screening and at the post study assessment. Any laboratory values that were out of range of normal reference values were evaluated by the Investigators.
Time Frame:	Day -14, Day 69

Outcome Measure Data

Analysis Population Description
all subjects who received at least one dose of study drug were included in the safety analysis

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg	Placebo 0.5mL
Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily	Placebo 0.5mL via e-flow nebulizer, once daily Placebo 0.5mL: Placebo 0.5mL via eFlow, once daily
Overall Number of Participants Analyzed	39	38	37	37	37	37
Measure Type: Number Unit of Measure: number of events	0	0	0	0	0	0

14. Secondary Outcome

Title:	Number of Subjects With Clinically Significant ECG Parameters Reported During the Study
Description:	ECGs were recorded at screening and at each study treatment visit pre-dose (within 30 minutes prior to dose); post-dose at 30 minutes and 1, 2, 4, 8, 12 and 24 hours; and then at the post study assessment.
Time Frame:	0 to 24h

Outcome Measure Data

Analysis Population Description
all subjects who received at least one dose of study drug were included in the safety analysis

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg	Placebo 0.5mL
Arm/Group Description:	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily	Placebo 0.5mL via e-flow nebulizer, once daily Placebo 0.5mL: Placebo 0.5mL via eFlow, once daily
Overall Number of Participants Analyzed	39	38	37	37	37	37
Measure Type: Number Unit of Measure: number of events	0	0	0	0	0	0

Adverse Events

Time Frame	0-69 days
Adverse Event Reporting Description	AEs are defined as existing conditions which worsen or events which occur during the course of the clinical trial after treatment
Source Vocabulary	MedDRA 13.0

Name for Table Default	
Collection Approach for Table Default	Systematic Assessment

Arm/Group Title	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg
Arm/Group Description	Glycopyrrolate Inhalation Solution12.5µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution12.5µg: Glycopyrrolate Inhalation Solution12.5µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 50mg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 50µg: Glycopyrrolate Inhalation Solution 50µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 100µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 100µg: Glycopyrrolate Inhalation Solution 100µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 200µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 200µg: Glycopyrrolate Inhalation Solution 200µg via eFlow, once daily	Glycopyrrolate Inhalation Solution 400µg via e-flow nebulizer, once daily Glycopyrrolate Inhalation Solution 400µg: Glycopyrrolate Inhalation Solution 400µg via eFlow, once daily

All-Cause Mortality

	Glycopyrrolate Inhalation Solution12.5µg	Glycopyrrolate Inhalation Solution 50µg	Glycopyrrolate Inhalation Solution 100µg	Glycopyrrolate Inhalation Solution 200µg	Glycopyrrolate Inhalation Solution 400µg
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	--- /---	--- /---	--- /---	--- /---	--- /---

Serious Adverse Events

	Glycopyrrolate Inhalation Solution12.5µg		Glycopyrrolate Inhalation Solution 50µg		Glycopyrrolate Inhalation Solution 100µg		Glycopyrrolate Inhalation Solution 200µg		Glycopyrrolate Inhalation Solution 400µg	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	0/39 (0%)		0/38 (0%)		1/37 (2.7%)		0/37 (0%)		0/37 (0%)	
General disorders										
groin pain †A	0/39 (0%)	0	0/38 (0%)	0	1/37 (2.7%)	2	0/37 (0%)	0	0/37 (0%)	0

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.0

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	5%

	Glycopyrrolate Inhalation Solution12.5µg		Glycopyrrolate Inhalation Solution 50µg		Glycopyrrolate Inhalation Solution 100µg		Glycopyrrolate Inhalation Solution 200µg		Glycopyrrolate Inhalation Solution 400µg	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	13/39 (33.33%)		9/38 (23.68%)		10/37 (27.03%)		10/37 (27.03%)		10/37 (27.03%)	
Injury, poisoning and procedural complications										
skin injury †A	0/39 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	0/37 (0%)	0	0/37 (0%)	0
Nervous system disorders										
headache †A	6/39 (15.38%)	7	5/38 (13.16%)	6	5/37 (13.51%)	8	7/37 (18.92%)	9	6/37 (16.22%)	8
Respiratory, thoracic and mediastinal disorders										

chronic obstructive pulmonary disease †A	2/39 (5.13%)	2	1/38 (2.63%)	1	0/37 (0%)	0	0/37 (0%)	0	0/37 (0%)	0
cough †A	3/39 (7.69%)	3	2/38 (5.26%)	2	5/37 (13.51%)	5	3/37 (8.11%)	3	3/37 (8.11%)	4
dyspnoea †A	3/39 (7.69%)	3	2/38 (5.26%)	2	1/37 (2.7%)	1	1/37 (2.7%)	2	1/37 (2.7%)	1

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.0

Limitations and Caveats

None

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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