Protocol Registration Receipt
04/17/2014

A Study to Look at Day to Day Changes in Lung Function in COPD Subjects Taking Albuterol/Salbutamol and Ipratropium

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01691482

Purpose

The objective of this study is to assess the daily variation in bronchodilator response to an inhaled short acting beta2-agonist (albuterol/salbutamol) and an inhaled short acting anticholinergic (ipratropium) individually and when used in combination in subjects with COPD.

Condition	Intervention	Phase
Pulmonary Disease, Chronic Obstructive	Drug: Albuterol/salbutamol Drug: Ipratropium	Phase 4

Study Type: Interventional

Study Design: Treatment, Crossover Assignment, Open Label, Randomized, Efficacy Study

Official Title: A 4-Week Randomized Cross-Over Study to Evaluate Daily Lung Function Following the Administration of Albuterol/Salbutamol and Ipratropium in Subjects With Chronic Obstructive Pulmonary Disease

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Variability in Daily FEV1, Estimated by Coefficient of Variation [Time Frame: up to 10 days] [Designated as safety issue: No]

  FEV1 is the maximal amount of air that can be forcefully exhaled in one second. During each study period, pre- and post-bronchodilator spirometry for evaluation of FEV1 was performed at study visits as follows: prior to administration of the first short-acting bronchodilator, approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second short-acting bronchodilator (2 hours). Variability in daily FEV1 was measured as the fluctuation around the mean FEV1 data collected from Day 1 to Day 10. Variability was measured by the coefficient of variation (CV) and the half range. The CV is the dispersion of the data around the mean, whereas the half range method is the difference between the maximum and minimum FEV1 values.

- Variability in Daily FEV1, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum Values) [Time Frame: up to 10 days] [Designated as safety issue: No]

  FEV1 is the maximal amount of air that can be forcefully exhaled in one second. During each study period, pre- and post-bronchodilator spirometry for evaluation of FEV1 was performed at study visits as follows: prior to administration of the first short-acting bronchodilator, approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second short-acting bronchodilator (2 hours). Variability in daily FEV1 was measured as the fluctuation around the mean FEV1 data collected from Day 1 to Day 10. Variability was measured by the coefficient of variation (CV) and the half range. The CV is the dispersion of the data around the mean, whereas the half range method is half the difference between the maximum and minimum FEV1 values.

Secondary Outcome Measures:

- The Maximal Bronchodilator Response for the First Administered Agent [Time Frame: up to 10 days] [Designated as safety issue: No]

  The maximal bronchodilator response for the first administered agent is defined as the FEV1 (the maximal amount of air that can be forcefully exhaled in one second) 1 hour post-dose of the first bronchodilator minus the pre-dose. The maximal bronchodilator response for the second agent is defined as the FEV1 1 hour post-dose of the second bronchodilator minus the FEV1 at 1 hour post-dose of the first bronchodilator. The maximal bronchodilator response for the combination is defined as the FEV1 (the maximal amount of air that can be forcefully exhaled in one second) at 1 hour post-administration of the second bronchodilator minus the corresponding pre-dose FEV1. Derived FEV1 response is FEV1 change from 0 hours (0H) for the first agent assessment (at 1 hour [1H]); change from 1H for the second agent assessment (at 2 hours [2H]); and change from 0H for the combination assessment (at 2H). Data were adjusted for FEV1, smoking status, and center.

- Percentage of Days for Which Participants Achieved a >=12% and 200 Milliliter (mL) Increase From Baseline in FEV1 [Time Frame: up to 35 days] [Designated as safety issue: No]

  FEV1 is the maximal amount of air that can be forcefully exhaled in one second. During each study period, pre- and post-bronchodilator spirometry for

evaluation of FEV1 was performed at study visits as follows: approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second short-acting bronchodilator (2 hours).

- Percentage of Days for Which Participants Achieved a Threshold Increase From Baseline in FEV1 of 100 mL, 200 mL, and 250 mL [Time Frame: up to 35 days] [Designated as safety issue: No]

  FEV1 is the maximal amount of air that can be forcefully exhaled in one second. During each study period, pre- and post-bronchodilator spirometry for evaluation of FEV1 was performed at study visits as follows: approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second short-acting bronchodilator (2 hours).

- Variability in Daily Inspiratory Capacity (IC), Estimated by Coefficient of Variation [Time Frame: up to 10 days] [Designated as safety issue: No]

  IC is the the total amount of air that can be drawn into the lungs after normal expiration. During each study period, pre- and post-bronchodilator spirometry for evaluation of IC was performed at study visits as follows: prior to administration of the first short-acting bronchodilator, approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second short-acting bronchodilator (2 hours). Variability in daily IC was measured as the fluctuation around the mean IC data collected from Day 1 to Day 10. Variability was measured by the coefficent of variation (CV) and the half range. The CV is the dispersion of the data around the mean, whereas the half range method is the difference between the maximum and minimum IC values.

- Variability in Daily IC, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum) [Time Frame: up to 10 days] [Designated as safety issue: No]

  IC is the the total amount of air that can be drawn into the lungs after normal expiration. During each study period, pre- and post-bronchodilator spirometry for evaluation of IC was performed at study visits as follows: prior to administration of the first short-acting bronchodilator, approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second short-acting bronchodilator (2 hours). Variability in daily IC was measured as the fluctuation around the mean IC data collected from Day 1 to Day 10. Variability was measured by the coefficent of variation (CV) and the half range. The CV is the dispersion of the data around the mean, whereas the half range method is half the difference between the maximum and minimum IC values.

Enrollment: 56
Study Start Date: July 2012
Study Completion Date: February 2013
Primary Completion Date: February 2013

Arms	Assigned Interventions
Active Comparator: Albuterol/salbutamol followed by ipratropium Subjects will recieve daily albuterol/salbutamol followed by ipratropium which will be adminstered one	Drug: Albuterol/salbutamol Albuterol/salbutamol (daily)

Arms	Assigned Interventions
hour after adminstration of albuterol/salbutamol	
Active Comparator: Ipratropium followed by albuterol/salbutamol Subjects will recieve daily ipratropium followed by albuterol/salbutamol which will be adminstered one hour after adminstration of ipratropium	Drug: Ipratropium Ipratropium (daily)

Beta2-agonist and anticholinergics are a principle component of the pharmacologic management of chronic obstructive pulmonary disease COPD. It has been demonstrated that the combination of a short acting beta2-agonist and a short acting anticholinergic yields greater efficacy as measured by FEV1 when compared with the response to the individual short acting bronchodilators. However, daily bronchial response to these agents is poorly understood. It is also poorly understood how the variation in magnitude of the response to the individual agents and how the variation in response for one agent coincides with the variation in response to the other agent. This study will seek to define the pattern of response of each individual agent and the relationship between them. The study will also explore if the combination of the two agents leads to less variation in response compared to the individual agents. This is a randomized, open label, two period cross-over study. Eligible subjects will be randomized to a sequence of either albuterol/salbutamol via metered-dose inhaler (MDI) followed by ipratropium via MDI or the same dose of each bronchodilator given in the opposite order. Each study period will consist of 10 clinic visits to be conducted over 10 to 14 days.

Eligibility

Ages Eligible for Study: 40 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- Subjects must give their signed and dated written informed consent to participate.
- Subjects 40 years of age or older at Visit 1.
- Male or female subjects .
- An established clinical history of COPD.
- Current or former cigarette smokers with a history of cigarette smoking of >=10 pack-years at Visit 1.
- A post-albuterol/salbutamol FEV1/FVC ratio of <0.70 and a post-albuterol/salbutamol FEV1 of >=30 and <= 70% of predicted normal values at Visit 1

calculated using NHANES III reference equations .

Exclusion Criteria:

- A current diagnosis of asthma
- Women who are pregnant of lactating or are planning on becoming pregnant during the study.
- Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1.
- Participation in pulmonary rehabilitation

Contacts and Locations

Locations

United States, South Carolina

GSK Investigational Site

Spartanburg, South Carolina, United States, 29303

United Kingdom

GSK Investigational Site

Manchester, United Kingdom, M23 9LT

Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Responsible Party:	GlaxoSmithKline
Study ID Numbers:	114956
Health Authority:	United States: Institutional Review Board United Kingdom: Medicines and Healthcare Products Regulatory Agency United States: Food and Drug Administration

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Study Results

Participant Flow

Pre-Assignment Details

This was a randomized, open-label, two-period cross-over study to evaluate the daily bronchodilator response to albuterol/salbutamol and ipratropium individually and in combination in participants with chronic obstructive pulmonary disease.

Reporting Groups

	Description
A/S Then Ipratropium in TP1; Ipratropium Then A/S in TP2	Participants received albuterol (4 puffs; 90 micrograms [µg] per puff)/salbutamol (A/S) (4 puffs; 100 µg per puff) followed by ipratropium (4 puffs; 20 µg per puff) via a metered-dose inhaler (MDI) during treatment period 1 (TP1) then, ipratropium followed by A/S at the same doses via an MDI in treatment period 2 (TP2).
Ipratropium Then A/S in TP1; A/S Then Ipratropium in TP2	Participants received Ipratropium (4 puffs; 20 µg per puff) followed by albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) (A/S) via a MDI in TP1, then A/S followed by ipratropium at the same doses via an MDI in TP2.

Treatment Period 1

	A/S Then Ipratropium in TP1; Ipratropium Then A/S in TP2	Ipratropium Then A/S in TP1; A/S Then Ipratropium in TP2
Started	28	28
Completed	28	28
Not Completed	0	0

Treatment Period 2

	A/S Then Ipratropium in TP1; Ipratropium Then A/S in TP2	Ipratropium Then A/S in TP1; A/S Then Ipratropium in TP2
Started	28	28
Completed	27	26
Not Completed	1	2
Adverse Event	0	1
Protocol Violation	1	1

Baseline Characteristics

Reporting Groups

	Description
All Randomized Participants	All participants randomized to receive a sequence of either salbutamol (4 puffs; 100 µg per puff) via an MDI and albuterol (4 puffs; 90 µg per puff) followed by ipratropium (4 puffs; 20 µg per puff) via an MDI in TP1 and the same dose of each bronchodilator given in the opposite order in TP2, or ipratropium followed by albuterol/salbutamol in TP1 and the same dose of each bronchodilator given in the opposite order in TP2

Baseline Measures

	All Randomized Participants
Number of Participants	56
Age, Continuous [units: Years] Mean (Standard Deviation)	60.3 (7.42)
Gender, Male/Female [units: Participants]	
Female	35
Male	21
Race/Ethnicity, Customized [units: participants]	
African American/African Heritage	4
White	52

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Variability in Daily FEV1, Estimated by Coefficient of Variation
Measure Description	FEV1 is the maximal amount of air that can be forcefully exhaled in one second. During each study period, pre- and post-bronchodilator spirometry for evaluation of FEV1 was performed at study visits as follows: prior to administration of the first short-acting bronchodilator, approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second

	short-acting bronchodilator (2 hours). Variability in daily FEV1 was measured as the fluctuation around the mean FEV1 data collected from Day 1 to Day 10. Variability was measured by the coefficient of variation (CV) and the half range. The CV is the dispersion of the data around the mean, whereas the half range method is the difference between the maximum and minimum FEV1 values.
Time Frame	up to 10 days
Safety Issue?	No

Analysis Population Description

Efficacy Population: participants in the Intent-to-Treat Population (all participants who were randomized and received at least one bronchodilator in the treatment period) who completed pre- and post- bronchodilator assessments for at least 17 visits, with no more than 3 consecutive missing days

Reporting Groups

	Description
Albuterol/Salbutamol Followed by Ipratropium	All participants randomized to receive a sequence of albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI followed by ipratropium (4 puffs; 20 µg per puff) via an MDI in either TP1 or TP2.
Ipratropium Followed by Albuterol/Salbutamol	All participants randomized to receive a sequence of ipratropium (4 puffs; 20 µg per puff) via an MDI followed by albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI in either TP1 or TP2

Measured Values

	Albuterol/Salbutamol Followed by Ipratropium	Ipratropium Followed by Albuterol/Salbutamol
Number of Participants Analyzed	55	55

	Albuterol/Salbutamol Followed by Ipratropium	Ipratropium Followed by Albuterol/Salbutamol
Variability in Daily FEV1, Estimated by Coefficient of Variation [units: Liters] Mean (Standard Error)		
Pre-dose/non-bronchodilator	0.081 (0.0394)	0.079 (0.0372)
Albuterol/Salbutamol (A/S) alone, 1 hour	0.059 (0.0276)	NA (NA) [1]
A/S followed by ipratropium, 2 hours	0.054 (0.0232)	NA (NA) [2]
Ipratropium alone, 1 hour	NA (NA) [3]	0.072 (0.0406)
Ipratropium followed by A/S, 2 hours	NA (NA) [4]	0.063 (0.0327)

[1] Participants in this treatment arm received ipratropium as the first bronchodilator; thus, data were not collected for albuterol/salbutamol (A/S) at this time point.

[2] Participants in this treatment arm received ipratropium followed by A/S; thus, data were not collected for A/S followed by ipratropium.

[3] Participants in this treatment arm received A/S as the first bronchodilator; thus, data were not collected for ipratropium at this time point.

[4] Participants in this treatment arm received A/S followed by ipratropium; thus, data were not collected for ipratropium followed by A/S.

Statistical Analysis 1 for Variability in Daily FEV1, Estimated by Coefficient of Variation

Groups	Albuterol/Salbutamol Followed by Ipratropium
Method	

Other Estimated Parameter [Adjusted Mean]	0.058
Standard Error of the mean	± 0.0046
95% Confidence Interval	0.049 to 0.067

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: A/S alone. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), FEV1 Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 2 for Variability in Daily FEV1, Estimated by Coefficient of Variation

Groups	Ipratropium Followed by Albuterol/Salbutamol
Method	
Other Estimated Parameter [Adjusted Mean]	0.071
Standard Error of the mean	± 0.0046
95% Confidence Interval	0.062 to 0.080

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: ipratropium alone. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), FEV1 Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 3 for Variability in Daily FEV1, Estimated by Coefficient of Variation

Groups	Albuterol/Salbutamol Followed by Ipratropium
Method	

Other Estimated Parameter [Adjusted Mean]	0.053
Standard Error of the mean	± 0.0046
95% Confidence Interval	0.044 to 0.062

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: A+I. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), FEV1 Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 4 for Variability in Daily FEV1, Estimated by Coefficient of Variation

Groups	Ipratropium Followed by Albuterol/Salbutamol
Method	
Slope	0.062
Standard Error of the mean	± 0.0046
95% Confidence Interval	0.053 to 0.071

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: I+A. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), FEV1 Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

2. Primary Outcome Measure:

Measure Title	Variability in Daily FEV1, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum Values)

Measure Description	FEV1 is the maximal amount of air that can be forcefully exhaled in one second. During each study period, pre- and post-bronchodilator spirometry for evaluation of FEV1 was performed at study visits as follows: prior to administration of the first short-acting bronchodilator, approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second short-acting bronchodilator (2 hours). Variability in daily FEV1 was measured as the fluctuation around the mean FEV1 data collected from Day 1 to Day 10. Variability was measured by the coefficient of variation (CV) and the half range. The CV is the dispersion of the data around the mean, whereas the half range method is half the difference between the maximum and minimum FEV1 values.
Time Frame	up to 10 days
Safety Issue?	No

Analysis Population Description

Efficacy Population

Reporting Groups

	Description
Albuterol/Salbutamol Followed by Ipratropium	All participants randomized to receive a sequence of albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI followed by ipratropium (4 puffs; 20 µg per puff) via an MDI in either TP1 or TP2.
Ipratropium Followed by Albuterol/Salbutamol	All participants randomized to receive a sequence of ipratropium (4 puffs; 20 µg per puff) via an MDI followed by albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI in either TP1 or TP2

Measured Values

	Albuterol/Salbutamol Followed by Ipratropium	Ipratropium Followed by Albuterol/Salbutamol
Number of Participants Analyzed	55	55
Variability in Daily FEV1, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum Values) [units: Liters] Mean (Standard Error)		
Pre-dose/non-bronchodilator	0.136 (0.0627)	0.135 (0.0780)
Albuterol/Salbutamol (A/S) alone, 1 hour	0.125 (0.0525)	NA (NA) [1]
A/S followed by ipratropium, 2 hours	0.122 (0.0542)	NA (NA) [2]
Ipratropium alone, 1 hour	NA (NA) [3]	0.145 (0.0805)
Ipratropium followed by A/S, 2 hours	NA (NA) [4]	0.137 (0.0726)

[1] Participants in this treatment arm received ipratropium as the first bronchodilator; thus, data were not collected for albuterol/salbutamol (A/S) at this time point.

[2] Participants in this treatment arm received ipratropium followed by A/S; thus, data were not collected for A/S followed by ipratropium.

[3] Participants in this treatment arm received A/S as the first bronchodilator; thus, data were not collected for ipratropium at this time point.

[4] Participants in this treatment arm received A/S followed by ipratropium; thus, data were not collected for ipratropium followed by A/S.

Statistical Analysis 1 for Variability in Daily FEV1, Estimated by Half Range (i.e., Half the Difference Between Maximum and

Minimum Values)

Groups	Albuterol/Salbutamol Followed by Ipratropium
Method	
Other Estimated Parameter [Adjusted Mean]	0.058
Standard Error of the mean	± 0.0046
95% Confidence Interval	0.049 to 0.067

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: A/S alone. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), FEV1 Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 2 for Variability in Daily FEV1, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum Values)

Groups	Ipratropium Followed by Albuterol/Salbutamol
Method	
Other Estimated Parameter [Adjusted Mean]	0.071
Standard Error of the mean	± 0.0046
95% Confidence Interval	0.062 to 0.080

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: ipratropium alone. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), FEV1 Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 3 for Variability in Daily FEV1, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum Values)

Groups	Albuterol/Salbutamol Followed by Ipratropium
Method	
Other Estimated Parameter [Adjusted Mean]	0.053
Standard Error of the mean	± 0.0046
95% Confidence Interval	0.044 to 0.062

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: A+I. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), FEV1 Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 4 for Variability in Daily FEV1, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum Values)

Groups	Ipratropium Followed by Albuterol/Salbutamol
Method	
Other Estimated Parameter [Adjusted Mean]	0.062
95% Confidence Interval	0.053 to 0.071

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: I+A. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), FEV1 Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

3. Secondary Outcome Measure:

Measure Title	The Maximal Bronchodilator Response for the First Administered Agent
Measure Description	The maximal bronchodilator response for the first administered agent is defined as the FEV1 (the maximal amount of air that can be forcefully exhaled in one second) 1 hour post-dose of the first bronchodilator minus the pre-dose. The maximal bronchodilator response for the second agent is defined as the FEV1 1 hour post-dose of the second bronchodilator minus the FEV1 at 1 hour post-dose of the first bronchodilator. The maximal bronchodilator response for the combination is defined as the FEV1 (the maximal amount of air that can be forcefully exhaled in one second) at 1 hour post-administration of the second bronchodilator minus the corresponding pre-dose FEV1. Derived FEV1 response is FEV1 change from 0 hours (0H) for the first agent assessment (at 1 hour [1H]); change from 1H for the second agent assessment (at 2 hours [2H]); and change from 0H for the combination assessment (at 2H). Data were adjusted for FEV1, smoking status, and center.
Time Frame	up to 10 days
Safety Issue?	No

Analysis Population Description

Efficacy Population

Reporting Groups

	Description
All Randomized Participants	All participants randomized to receive a sequence of either salbutamol (4 puffs; 100 µg per puff) via an MDI and albuterol (4 puffs; 90 µg per puff) followed by ipratropium (4 puffs; 20 µg per puff) via an MDI in TP1 and the same dose of each bronchodilator given in the opposite order

	Description
	in TP2, or ipratropium followed by albuterol/salbutamol in TP1 and the same dose of each bronchodilator given in the opposite order in TP2

Measured Values

	All Randomized Participants
Number of Participants Analyzed	55
The Maximal Bronchodilator Response for the First Administered Agent [units: Liters] Least Squares Mean (Standard Error)	
First agent, albuterol/salbutamol (A/S)	0.269 (0.0174)
First agent, ipratropium	0.243 (0.0174)
Second agent, A/S	0.094 (0.0123)
Second agent, ipratropium	0.094 (0.0123)
A/S followed by ipratropium	0.363 (0.0200)
Ipratropium followed by A/S	0.337 (0.0200)

4. Secondary Outcome Measure:

Measure Title	Percentage of Days for Which Participants Achieved a >=12% and 200 Milliliter (mL) Increase From Baseline in FEV1
Measure Description	FEV1 is the maximal amount of air that can be forcefully exhaled in one second. During each study period, pre- and post-bronchodilator spirometry for evaluation of FEV1 was performed at study visits as follows: approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second short-acting bronchodilator (2 hours).
Time Frame	up to 35 days
Safety Issue?	No

Analysis Population Description

Efficacy Population

Reporting Groups

	Description
Albuterol/Salbutamol Followed by Ipratropium	All participants randomized to receive a sequence of albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI followed by ipratropium (4 puffs; 20 µg per puff) via an MDI in either TP1 or TP2.
Ipratropium Follwed by Albuterol/Salbutamol	All participants randomized to receive a sequence of ipratropium (4 puffs; 20 µg per puff) via an MDI followed by albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI in either TP1 or TP2

Measured Values

	Albuterol/Salbutamol Followed by Ipratropium	Ipratropium Follwed by Albuterol/Salbutamol
Number of Participants Analyzed	55	55
Percentage of Days for Which Participants Achieved a >=12% and 200 Milliliter (mL) Increase From Baseline in FEV1 [units: percentage of days] Mean (Standard Deviation)		
Albuterol/Salbutamol (A/S) alone, 1 hour	58.4 (38.26)	NA (NA) [1]
A/S followed by ipratropium, 2 hours	71.7 (35.51)	NA (NA) [2]
Ipratropium alone, 1 hour	NA (NA) [3]	55.4 (39.34)
Ipratropium followed by A/S, 2 hours	NA (NA) [4]	69.1 (36.82)

[1] Participants in this treatment arm received ipratropium as the first bronchodilator; thus, data were not collected for albuterol/salbutamol (A/S) at this time point.

[2] Participants in this treatment arm received ipratropium followed by A/S; thus, data were not collected for A/S followed by ipratropium.

[3] Participants in this treatment arm received A/S as the first bronchodilator; thus, data were not collected for ipratropium at this time point.

[4] Participants in this treatment arm received A/S followed by ipratropium; thus, data were not collected for ipratropium followed by A/S.

5. Secondary Outcome Measure:

Measure Title	Percentage of Days for Which Participants Achieved a Threshold Increase From Baseline in FEV1 of 100 mL, 200 mL, and 250 mL

Measure Description	FEV1 is the maximal amount of air that can be forcefully exhaled in one second. During each study period, pre- and post-bronchodilator spirometry for evaluation of FEV1 was performed at study visits as follows: approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second short-acting bronchodilator (2 hours).
Time Frame	up to 35 days
Safety Issue?	No

Analysis Population Description

Efficacy Population

Reporting Groups

	Description
Albuterol/Salbutamol Followed by Ipratropium	All participants randomized to receive a sequence of albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI followed by ipratropium (4 puffs; 20 µg per puff) via an MDI in either TP1 or TP2.
Ipratropium Follwed by Albuterol/Salbutamol	All participants randomized to receive a sequence of ipratropium (4 puffs; 20 µg per puff) via an MDI followed by albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI in either TP1 or TP2

Measured Values

	Albuterol/Salbutamol Followed by Ipratropium	Ipratropium Follwed by Albuterol/Salbutamol
Number of Participants Analyzed	55	55
Percentage of Days for Which Participants		

	Albuterol/Salbutam Followed by Ipratropium	Ipratropium Follwed by Albuterol/Salbutamol
Achieved a Threshold Increase From Baseline in FEV1 of 100 mL, 200 mL, and 250 mL [units: percentage of days] Mean (Standard Deviation)		
A/S alone, 1 hour, 100 mL	81.6 (31.35)	NA (NA) [1]
A/S followed by ipratropium, 2 hours, 100 mL	85.2 (29.92)	NA (NA) [2]
Ipratropium alone, 1 hour, 100 mL	NA (NA) [3]	72.9 (38.06)
Ipratropium followed by A/S, 2 hours, 100 mL	NA (NA) [4]	81.2 (33.46)
A/S alone, 1 hour, 200 mL	59.2 (38.20)	NA (NA) [5]
A/S followed by ipratropium, 2 hours, 200 mL	72.7 (35.25)	NA (NA) [6]
Ipratropium alone, 1 hour, 200 mL	NA (NA) [7]	56.0 (39.54)
Ipratropium followed by A/S, 2 hours, 200 mL	NA (NA) [8]	70.5 (36.23)
A/S alone, 1 hour, 250 mL	45.9 (38.85)	NA (NA) [9]
A/S followed by ipratropium, 2 hours, 250 mL	64.0 (39.08)	NA (NA) [10]
Ipratropium alone, 1 hour, 250 mL	NA (NA) [11]	45.8 (36.94)
Ipratropium followed by A/S, 2 hours, 250 mL	NA (NA) [12]	59.6 (38.19)

[1] Participants in this treatment arm received ipratropium as the first bronchodilator; thus, data were not collected for albuterol/salbutamol (A/S) at this time point.
[2] Participants in this treatment arm received ipratropium followed by A/S; thus, data were not collected for A/S followed by ipratropium.
[3] Participants in this treatment arm received A/S as the first bronchodilator; thus, data were not collected for ipratropium at this time point.
[4] Participants in this treatment arm received A/S followed by ipratropium; thus, data were not collected for ipratropium followed by A/S.
[5] Participants in this treatment arm received ipratropium as the first bronchodilator; thus, data were not collected for albuterol/salbutamol (A/S) at this time point.
[6] Participants in this treatment arm received ipratropium followed by A/S; thus, data were not collected for A/S followed by ipratropium.
[7] Participants in this treatment arm received A/S as the first bronchodilator; thus, data were not collected for ipratropium at this time point.
[8] Participants in this treatment arm received A/S followed by ipratropium; thus, data were not collected for ipratropium followed by A/S.
[9] Participants in this treatment arm received ipratropium as the first bronchodilator; thus, data were not collected for albuterol/salbutamol (A/S) at this time point.
[10] Participants in this treatment arm received ipratropium followed by A/S; thus, data were not collected for A/S followed by ipratropium.
[11] Participants in this treatment arm received A/S as the first bronchodilator; thus, data were not collected for ipratropium at this time point.
[12] Participants in this treatment arm received A/S followed by ipratropium; thus, data were not collected for ipratropium followed by A/S.

6. Secondary Outcome Measure:

Measure Title	Variability in Daily Inspiratory Capacity (IC), Estimated by Coefficient of Variation

Measure Description	IC is the the total amount of air that can be drawn into the lungs after normal expiration. During each study period, pre- and post-bronchodilator spirometry for evaluation of IC was performed at study visits as follows: prior to administration of the first short-acting bronchodilator, approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second short-acting bronchodilator (2 hours). Variability in daily IC was measured as the fluctuation around the mean IC data collected from Day 1 to Day 10. Variability was measured by the coefficent of variation (CV) and the half range. The CV is the dispersion of the data around the mean, whereas the half range method is the difference between the maximum and minimum IC values.
Time Frame	up to 10 days
Safety Issue?	No

Analysis Population Description

Efficacy Population

Reporting Groups

	Description
Albuterol/Salbutamol Followed by Ipratropium	All participants randomized to receive a sequence of albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI followed by ipratropium (4 puffs; 20 µg per puff) via an MDI in either TP1 or TP2.
Ipratropium Followed by Albuterol/Salbutamol	All participants randomized to receive a sequence of ipratropium (4 puffs; 20 µg per puff) via an MDI followed by albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI in either TP1 or TP2

Measured Values

	Albuterol/Salbutamol Followed by Ipratropium	Ipratropium Followed by Albuterol/Salbutamol
Number of Participants Analyzed	55	55
Variability in Daily Inspiratory Capacity (IC), Estimated by Coefficient of Variation [units: Liters] Mean (Standard Deviation)		
Pre-dose/non-bronchodilator	0.078 (0.0305)	0.083 (0.0374)
Albuterol/Salbutamol (A/S) alone, 1 hour	0.069 (0.0310)	NA (NA) [1]
A/S followed by ipratropium (A+I), 2 hours	0.070 (0.0373)	NA (NA) [2]
Ipratropium alone, 1 hour	NA (NA) [3]	0.072 (0.0353)
Ipratropium followed by A/S (I+A), 2 hours	NA (NA) [4]	0.066 (0.0307)

[1] Participants in this treatment arm received ipratropium as the first bronchodilator; thus, data were not collected for albuterol/salbutamol (A/S) at this time point.

[2] Participants in this treatment arm received ipratropium followed by A/S; thus, data were not collected for A/S followed by ipratropium.

[3] Participants in this treatment arm received A/S as the first bronchodilator; thus, data were not collected for ipratropium at this time point.

[4] Participants in this treatment arm received A/S followed by ipratropium; thus, data were not collected for ipratropium followed by A/S.

Statistical Analysis 1 for Variability in Daily Inspiratory Capacity (IC), Estimated by Coefficient of Variation

Groups	Albuterol/Salbutamol Followed by Ipratropium
Method	
Other Estimated Parameter [Adjusted Mean]	0.067
Standard Error of the mean	± 0.0045
95% Confidence Interval	0.058 to 0.076

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: A/S alone. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), IC Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 2 for Variability in Daily Inspiratory Capacity (IC), Estimated by Coefficient of Variation

Groups	Ipratropium Followed by Albuterol/Salbutamol
Method	
Other Estimated Parameter [Adjusted Mean]	0.070
Standard Error of the mean	± 0.0045
95% Confidence Interval	0.061 to 0.079

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: ipratropium alone. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), IC Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 3 for Variability in Daily Inspiratory Capacity (IC), Estimated by Coefficient of Variation

Groups	Albuterol/Salbutamol Followed by Ipratropium
Method	
Other Estimated Parameter [Adjusted Mean]	0.069
Standard Error of the mean	± 0.0045
95% Confidence Interval	0.060 to 0.078

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: A+I. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), IC Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 4 for Variability in Daily Inspiratory Capacity (IC), Estimated by Coefficient of Variation

Groups	Ipratropium Followed by Albuterol/Salbutamol
Method	
Other Estimated Parameter [Adjusted Mean]	0.064
Standard Error of the mean	± 0.0045
95% Confidence Interval	0.055 to 0.073

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: I+A. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), IC Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

7. Secondary Outcome Measure:

Measure Title	Variability in Daily IC, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum)
Measure Description	IC is the the total amount of air that can be drawn into the lungs after normal expiration. During each study period, pre- and post-bronchodilator spirometry for evaluation of IC was performed at study visits as follows: prior to administration of the first short-acting bronchodilator, approximately 1 hour after administration of the first bronchodilator (1 hour), and approximately 1 hour after administration of the second short-acting bronchodilator (2 hours). Variability in daily IC was measured as the fluctuation around the mean IC data collected from Day 1 to Day 10. Variability was measured by the coefficent of variation (CV) and the half range. The CV is the dispersion of the data around the mean, whereas the half range method is half the difference between the maximum and minimum IC values.
Time Frame	up to 10 days
Safety Issue?	No

Analysis Population Description

Efficacy Population

Reporting Groups

	Description
Albuterol/Salbutamol Followed by Ipratropium	All participants randomized to receive a sequence of albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI followed by ipratropium (4 puffs; 20 µg per puff) via an MDI in either TP1 or TP2.
Ipratropium Followed by Albuterol/Salbutamol	All participants randomized to receive a sequence of ipratropium (4 puffs; 20 µg per puff) via an MDI followed by albuterol (4 puffs; 90 µg per puff)/salbutamol (4 puffs; 100 µg per puff) via an MDI in either TP1 or TP2

Measured Values

	Albuterol/Salbutamol Followed by Ipratropium	Ipratropium Followed by Albuterol/Salbutamol
Number of Participants Analyzed	55	55
Variability in Daily IC, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum) [units: Liters] Mean (Standard Deviation)		
Pre-dose/non-bronchodilator	0.225 (0.1017)	0.236 (0.1166)
Albuterol/Salbutamol (A/S) alone, 1 hour	0.229 (0.1004)	NA (NA) [1]
A/S followed by ipratropium, 2 hours	0.233 (0.1132)	NA (NA) [2]
Ipratropium alone, 1 hour	NA (NA) [3]	0.235 (0.1026)
Ipratropium followed by A/S, 2 hours	NA (NA) [4]	0.221 (0.1066)

[1] Participants in this treatment arm received ipratropium as the first bronchodilator; thus, data were not collected for albuterol/salbutamol (A/S) at this time point.

[2] Participants in this treatment arm received ipratropium followed by A/S; thus, data were not collected for A/S followed by ipratropium.

[3] Participants in this treatment arm received A/S as the first bronchodilator; thus, data were not collected for ipratropium at this time point.

[4] Participants in this treatment arm received A/S followed by ipratropium; thus, data were not collected for ipratropium followed by A/S.

Statistical Analysis 1 for Variability in Daily IC, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum)

Groups	Albuterol/Salbutamol Followed by Ipratropium
Method	
Other Estimated Parameter [Adjusted Mean]	0.228
Standard Error of the mean	± 0.0140
95% Confidence Interval	0.200 to 0.255

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: A/S alone. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), IC Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 2 for Variability in Daily IC, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum)

Groups	Ipratropium Followed by Albuterol/Salbutamol
Method	
Other Estimated Parameter [Adjusted Mean]	0.231
Standard Error of the mean	± 0.0140
95% Confidence Interval	0.203 to 0.258

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: ipratropium alone. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), IC Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 3 for Variability in Daily IC, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum)

Groups	Albuterol/Salbutamol Followed by Ipratropium
Method	
Other Estimated Parameter [Adjusted Mean]	0.232
Standard Error of the mean	± 0.0140
95% Confidence Interval	0.204 to 0.259

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: A+I. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), IC Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Statistical Analysis 4 for Variability in Daily IC, Estimated by Half Range (i.e., Half the Difference Between Maximum and Minimum)

Groups	Ipratropium Followed by Albuterol/Salbutamol
Method	
Other Estimated Parameter [Adjusted Mean]	0.217
Standard Error of the mean	± 0.0140
95% Confidence Interval	0.190 to 0.245

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Other relevant estimation information:

Treatment: I+A. A mixed model analysis, with period, treatment (A+I, I+A, Albuterol alone, Ipratropium alone), IC Baseline, smoking status at Screening, and center fitted as fixed effects and participant as a random effect was used.

Reported Adverse Events

Reporting Groups

	Description
All Randomized Participants	All participants randomized to receive a sequence of either salbutamol (4 puffs; 100 µg per puff) via an MDI and albuterol (4 puffs; 90 µg per puff) followed by ipratropium (4 puffs; 20 µg per puff) via an MDI in TP1 and the same dose of each bronchodilator given in the opposite order in TP2, or ipratropium followed by albuterol/salbutamol in TP1 and the same dose of each bronchodilator given in the opposite order in TP2

Serious Adverse Events

	All Randomized Participants
Total # participants affected/at risk	1/56 (1.79%)
General disorders	
Death † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	All Randomized Participants
Total # participants affected/at risk	16/56 (28.57%)
Gastrointestinal disorders	
Abdominal pain upper † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Diarrhoea † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Toothache † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Vomiting † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
General disorders	
Chest discomfort † [A]	

	All Randomized Participants
# participants affected/at risk	1/56 (1.79%)
# events	
Influenza like illness † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Oedema peripheral † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Infections and infestations	
Bacterial infection † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Herpes zoster † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Nasopharyngitis † [A]	

	All Randomized Participants
# participants affected/at risk	1/56 (1.79%)
# events	
Rhinitis † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Injury, poisoning and procedural complications	
Excoriation † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Fall † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Muscle strain † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Radius fracture † [A]	

	All Randomized Participants
# participants affected/at risk	1/56 (1.79%)
# events	
Tooth fracture † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Musculoskeletal and connective tissue disorders	
Back pain † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Joint swelling † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Muscle spasms † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	

	All Randomized Participants
Nervous system disorders	
Dizziness †[A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Dysgeusia †[A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Headache †[A]	
# participants affected/at risk	4/56 (7.14%)
# events	
Renal and urinary disorders	
Haematuria †[A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Respiratory, thoracic and mediastinal disorders	

	All Randomized Participants
Cough † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Epistaxis † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Increased upper airway secretion † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Painful respiration † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	
Sneezing † [A]	
# participants affected/at risk	1/56 (1.79%)
# events	

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

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.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Limitations and Caveats:

Results Point of Contact:

Name/Official Title: GSK Response Center
Organization: GlaxoSmithKline
Phone: 866-435-7343
Email: