Protocol Registration Receipt
03/13/2014

# Effects of Salmeterol on Autonomic Nervous System (ESAN)

This study has been completed.

| | |
|---|---|
| Sponsor: | GlaxoSmithKline |
| Collaborators: | |
| Information provided by (Responsible Party): | GlaxoSmithKline |
| ClinicalTrials.gov Identifier: | NCT01536587 |

## Purpose

This is a 4-week non-randomized, partially blinded, single-arm monocentre study in subjects with Chronic Obstructive Pulmonary Disease (COPD) Global Initiative for Chronic Obstructive Lung Disease (GOLD) class II or III with the aim to demonstrate that inhaled therapy with salmeterol reduces sympathetic activity as evaluated by microneurography. A maximum of 32 subjects is planned to be enrolled.

| Condition | Intervention | Phase |
|---|---|---|
| Pulmonary Disease, Chronic Obstructive | Drug: Salmeterol | Phase 4 |

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Single Blind (Subject), N/A, Efficacy Study
Official Title: Effects of Bronchodilatation With Salmeterol on the Autonomic Nervous System

## Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Change in Muscle Sympathetic Nerve Activity (MSNA) at 2 Hours (Week 0) [Time Frame: Baseline and 2 hours (Week 0)] [Designated as safety issue: No]

  Human MSNA is composed of vasoconstrictor impulses grouped in pulse synchronous bursts that usually occur in sequences, preferentially during transient reductions of blood pressure. Sympathetic activity was measured using microneurographic recordings of efferent in the peroneal nerve. MSNA reflects sympathetic discharge to the vascular bed of the skeletal muscle. The change in MSNA (bursts per 100 heart beats [bursts/100 heart beats]) was calculated as the difference in MSNA change from Baseline to after the inhalation of salmeterol (2 hours, Week 0, Visit 1) minus the MSNA change from Baseline to after the inhalation of placebo (1 hour, Week 0, Visit 1).

Secondary Outcome Measures:

- Change From Baseline in MSNA (Evaluated by Microneurography as Bursts/100 Heart Beats) at Week 4 [Time Frame: Baseline and Week 4] [Designated as safety issue: No]

  Human MSNA is composed of vasoconstrictor impulses grouped in pulse synchronous bursts that usually occur in sequences, preferentially during transient reductions of blood pressure. Sympathetic activity was measured using microneurographic recordings of efferent in the peroneal nerve. MSNA reflects sympathetic discharge to the vascular bed of the skeletal muscle. Change in MSNA is expressed in terms of bursts per 100 heart beats (bursts/100 heart beats). Change from Baseline was calculated as the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in MSNA (Evaluated by Microneurography as Bursts/Minute) at 2 Hours (Week 0) [Time Frame: Baseline and 2 hours (Week 0)] [Designated as safety issue: No]

  Human MSNA is composed of vasoconstrictor impulses grouped in pulse synchronous bursts that usually occur in sequences, preferentially during transient reductions of blood pressure. Sympathetic activity was measured using microneurographic recordings of efferent in the peroneal nerve. MSNA reflects sympathetic discharge to the vascular bed of the skeletal muscle. The change in MSNA (bursts per minute [bursts/minute]) was calculated as the difference in MSNA change from Baseline to after the inhalation of salmeterol (2 hours, Week 0, Visit 1) minus the MSNA change from Baseline to after the inhalation of placebo (1 hour, Week 0, Visit 1).
- Change From Baseline in MSNA (Evaluated by Microneurography as Bursts/Minute) at Week 4 [Time Frame: Baseline and Week 4] [Designated as safety issue: No]

  Human MSNA is composed of vasoconstrictor impulses grouped in pulse synchronous bursts that usually occur in sequences, preferentially during transient reductions of blood pressure. Sympathetic activity was measured using microneurographic recordings of efferent in the peroneal nerve. MSNA reflects sympathetic discharge to the vascular bed of the skeletal muscle. Change in MSNA is expressed in terms of bursts per minute (bursts/minute). Change from Baseline was calculated as the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).

- Change From Baseline in Heart Rate Variability (HRV): Standard Deviation of NN Intervals (SDNN) at 2 Hours (Week 0) and at Week 4 (ITT Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Heart rate variability (HRV) refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. SDNN reflects all the cyclic components responsible for variability in the period of recording; therefore, it represents total variability. Change in HRV (SDNN) after salmeterol inhalation is expressed in terms of milliseconds (ms). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Heart Rate Variability (HRV): Standard Deviation of NN Intervals (SDNN) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. SDNN reflects all the cyclic components responsible for variability in the period of recording; therefore, it represents total variability. Change in HRV (SDNN) after salmeterol inhalation is expressed in terms of milliseconds (ms). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Heart Rate Variability (HRV): Square Root of the Mean Squared Difference of Successive NNs (RMSSD) at 2 Hours (Week 0) and at Week 4 (ITT Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. Compared with SDNN, RMSSD is a short-term variation of heart rate. Change in HRV (RMSSD) after salmeterol inhalation is expressed in terms of milliseconds (ms). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Heart Rate Variability (HRV): Square Root of the Mean Squared Difference of Successive NNs (RMSSD) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. Compared with SDNN, RMSSD is a short-term variation of heart rate. Change in HRV (RMSSD) after salmeterol inhalation is expressed in terms of milliseconds (ms). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Heart Rate Variability (HRV): Absolute Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the LF component of the HRV spectrum reflects sympathetic activity. Change in HRV (absolute LF) after salmeterol inhalation is expressed in terms of milliseconds squared (ms^2). Change from Baseline were calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Heart Rate Variability (HRV): Absolute Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

HRV refers to the complex beat-to-beat (N-N) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: The LF component of the HRV spectrum reflects sympathetic activity. Change in HRV (absolute LF) after salmeterol inhalation is expressed in terms of milliseconds squared (ms2). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation), respectively.

- Change From Baseline in Heart Rate Variability (HRV): Absolute High Frequency (HF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the HF component of the HRV spectrum reflects parasympathetic activity. Change in HRV (absolute HF) after salmeterol inhalation is expressed in terms of milliseconds squared (ms^2). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Heart Rate Variability (HRV): Absolute High Frequency (HF) Power at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the HF component of the HRV spectrum reflects parasympathetic activity. Change in HRV (absolute HF) after salmeterol inhalation is expressed in terms of milliseconds squared (ms^2). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Heart Rate Variability (HRV): Normalized Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the LF component of the HRV spectrum reflects sympathetic activity. Change in HRV (normalized LF) after salmeterol inhalation is expressed in terms of normalized units that represent the relative value of LF power component in proportion to the total power minus the very LF (VLF) component (LF/(Total Power-VLF)*100). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Heart Rate Variability (HRV): Normalized Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: The LF component of the HRV spectrum reflects sympathetic activity. Change in HRV (normalized LF) after salmeterol inhalation is expressed in terms of normalized units that represent the relative value of LF power component in proportion to the total power minus the very LF (VLF) component (LF/(Total Power-VLF)*100). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).

- Change From Baseline in Heart Rate Variability (HRV): Normalized High Frequency (HF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the HF component of the HRV spectrum reflects parasympathetic activity. Change in HRV (normalized HF) after salmeterol inhalation is expressed in terms of normalized units that represent the relative value of HF power component in proportion to the total power minus the very LF (VLF) component (HF/(Total Power-VLF)*100). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Heart Rate Variability (HRV): Normalized High Frequency Power (HF) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the HF component of the HRV spectrum reflects parasympathetic activity. Change in HRV (normalized HF) after salmeterol inhalation is expressed in terms of normalized units that represent the relative value of HF power component in proportion to the total power minus the very LF (VLF) component (HF/(Total Power-VLF)*100). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Heart Rate Variability (HRV): Heart Rate at 2 Hours (Week 0) and at Week 4 (ITT Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Heart rate refers to the speed of the heartbeat, specifically the number of heartbeats per unit of time. Change in HRV (heart rate) after salmeterol inhalation is expressed in terms of the heart rate (beats) per minute (heart rate/min). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0 before any inhalation).
- Change From Baseline in Heart Rate Variability (HRV): Heart Rate at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Heart rate refers to the speed of the heartbeat, specifically the number of heartbeats per unit of time. Change in HRV (heart rate) after salmeterol inhalation is expressed in terms of the heart rate (beats) per minute (heart rate/min). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0 before any inhalation).
- Change From Baseline in Spontaneous Baroreflex Sensitivity (BRS) at 2 Hours (Week 0) and at Week 4 (ITT Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  BRS is an important characteristic of baroreflex control and is often noninvasively assessed by relating heart rate (HR) fluctuations to blood pressure (BP) fluctuations. Change in BRS after salmeterol inhalation is expressed in terms of milliseconds per millimeters of mercury (ms/mmHg). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0 before any inhalation).
- Change From Baseline in Spontaneous Baroreflex Sensitivity (BRS) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) [Time Frame: Baseline, 2

hours (Week 0), and Week 4] [Designated as safety issue: No]

BRS is an important characteristic of baroreflex control and is often noninvasively assessed by relating heart rate (HR) fluctuations to blood pressure (BP) fluctuations. Change in BRS after salmeterol inhalation is expressed in terms of milliseconds per millimeters of mercury (ms/mmHg). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0 before any inhalation).

- Change From Baseline in Forced Expiratory Volume in One Second (FEV1) at 2 Hours (Week 0) and at Week 4 (ITT Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Pulmonary function was measured by FEV1, defined as the volume of air that which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Change in FEV1 after salmeterol inhalation is expressed in terms of liters (L). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Forced Expiratory Volume in One Second (FEV1) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Pulmonary function was measured by FEV1, defined as the volume of air that which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Change in FEV1 after salmeterol inhalation is expressed in terms of liters (L). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Systolic and Diastolic Blood Pressure (BP) at 2 Hours (Week 0) and at Week 4 [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Systolic and diastolic BP was manually measured. Change in BP after salmeterol inhalation is expressed in terms of millimeters of mercury (mmHg). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Respiratory Rate at 2 Hours (Week 0) and at Week 4 [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Respiratory rate is defined as the number of breaths taken within a set amount of time (typically within 60 seconds). Change in respiratory rate after salmeterol inhalation is expressed in terms of respiratory rate (breaths) per minute (min). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Tidal Volume at 2 Hours (Week 0) and at Week 4 [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Tidal volume is defined as the lung volume representing the normal volume of air displaced between normal inspiration and expiration when extra effort is not applied (normal value is approximately 500 milliliters or 7 milliliters per kilogram of body weight). Change in tidal volume after salmeterol inhalation is expressed in terms of milliliters (mL). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Respiratory Minute Volume at 2 Hours (Week 0) and at Week 4 [Time Frame: Baseline, 2 hours (Week 0), and Week 4]

[Designated as safety issue: No]

Respiratory minute volume is defined as the volume of gas inhaled (inhaled minute volume) or exhaled (exhaled minute volume) from a person's lungs per minute. Change in respiratory minute volume after salmeterol inhalation is expressed in terms of milliliters per minute (mL/min). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).

- Change From Baseline in Catecholamines (Plasma Norepinephrine) at 2 Hours (Week 0) and at Week 4 [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Catecholamines are important neurotransmitters in the central nervous system and play a crucial role in the autonomic regulation of many homeostatic functions. Change in catecholamines (plasma norepinephrine) after salmeterol inhalation is expressed in terms of nanogramms per liter (ng/L). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Catecholamines (Plasma Epinephrine) at 2 Hours (Week 0) and at Week 4 [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Catecholamines are important neurotransmitters in the central nervous system and play a crucial role in the autonomic regulation of many homeostatic functions. Change in catecholamines (plasma epinephrine) after salmeterol inhalation is expressed in terms of nanograms per milliliter (ng/mL). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Catecholamines (Brain Natriuretic Peptide [BNP]) at 2 Hours (Week 0) and at Week 4 [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Catecholamines are important neurotransmitters in the central nervous system and play a crucial role in the autonomic regulation of many homeostatic functions. Change in catecholamines (BNP) after salmeterol inhalation is expressed in terms of picograms per milliliter (pg/mL). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Oxygen Saturation Measured Via Pulse Oxymetry (SpO2) at 2 Hours (Week 0) and at Week 4 [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Oxygen saturation measures the capacity of blood to transport oxygen to other parts of the body. Oxygen binds to hemoglobin in red blood cells when moving through the lungs. A pulse oximeter uses two frequencies of light (red and infrared) to determine the percentage of hemoglobin in the blood that is saturated with oxygen. The percentage is called blood oxygen saturation, or SpO2. Change in SpO2 after salmeterol inhalation is expressed in terms of percent. Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).
- Change From Baseline in Transcutaneous Carbon Dioxide (tCO2) at 2 Hours (Week 0) and at Week 4 [Time Frame: Baseline, 2 hours (Week 0), and Week 4] [Designated as safety issue: No]

  Transcutaneous carbon dioxide monitoring is a noninvasive way of continuously measuring the tension of these gases in the skin. This methodology provides a continuous noninvasive estimation of the arterial CO2 value. Change in tCO2 after salmeterol inhalation is expressed in terms of millimeters of mercury (mmHg). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4

(Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation).

- Lung Function (Forced Vital Capacity [FVC], Functional Residual Capacity [FRC; Body and Helium], Total Lung Capacity [TLC], and Residual Volume [RV]) at Baseline (Week 0) and at Week 4 [Time Frame: Baseline and Week 4] [Designated as safety issue: No]

  FVC is defined as the volume of air that can be forcibly blown out from the lungs after a full inspiration. FRC is defined as the volume of air present in the lungs, specifically the parenchyma tissues, at the end of a passive expiration. TLC is defined as the maximum volume to which the lungs can be expanded with the greatest possible inspiratory effort; it is equal to VC plus the RV and is approximately 5800 milliliters. RV is defined as the amount of gas remaining in the lungs at the end of a maximal exhalation. All parameters describing lung function are expressed in terms of liters (L). Lung function (FVC, FRC [body and helium], TLC, and RV) was evaluated at Baseline (Week 0, [Visit 1, before any inhalation]) and at Week 4 (Visit 2, after salmeterol inhalation).

- Number of Participants With Diastolic Dysfunction on Echocardiography at Baseline (Week 0) and at Week 4 [Time Frame: Baseline and Week 4] [Designated as safety issue: No]

  Diastolic dysfunction refers to the decline in performance of one (usually the left ventricle) or both (left and right) ventricles during diastole. The number of participants with diastolic dysfunction on echocardiography was evaluated at Baseline (Week 0, [Visit 1, before any inhalation]) and at Week 4 (Visit 2, after salmeterol inhalation).

- Arterial Stiffness at Baseline (Week 0) and at Week 4 [Time Frame: Baseline and Week 4] [Designated as safety issue: No]

  Arterial stiffness occurs as a consequence of age and arteriosclerosis. Carotid-femoral pulse wave velocity (PWV), a measure of arterial stiffness, is determined from the time taken for the arterial pulse to propagate from the carotid to the femoral artery. PWV was evaluated in terms of meters per second (m/s). PWV after salmeterol inhalation at Baseline (Week 0, [Visit 1, before any inhalation]) and at Week 4 (Visit 2, after inhalation of salmeterol) was assessed.

Enrollment: 32
Study Start Date: July 2012
Study Completion Date: November 2012
Primary Completion Date: November 2012

| Arms | Assigned Interventions |
|---|---|
| Single Arm<br>Inhalation of salmeterol 50 µg twice daily over 4 weeks | Drug: Salmeterol<br>At visit 1 the sympathetic activity will be registered using microneurographic recordings of efferent muscle sympathetic nerve activity (MSNA) in the peroneal nerve and respiration over 2 hours, after 20 minutes of recording, 1 dose of placebo will be administered and after a further recording period of 45 minutes a dose of salmeterol 50 µg will be |

| Arms | Assigned Interventions |
|---|---|
| | administered which will be followed by a further period of data registration. At visit 2 following 4 weeks of inhaled treatment with salmeterol the same procedures will be performed but a placebo inhalation will not be performed. |

This is a 4-week non-randomized, partially blinded, single-arm monocentre study in subjects with COPD GOLD class II or III with the aim to demonstrate that inhaled therapy with salmeterol reduces sympathetic activity as evaluated by microneurography. A maximum of 32 subjects is planned to be enrolled.

During a complex data registration period comprising the continuous recording of muscle sympathetic nerve activity (MSNA) and respiration and of various other measurements at Visit 1, placebo and 50 µg of salmeterol via Diskus™ inhaler will be administered in a sequential design. Following Visit 1, the subjects will be treated with salmeterol 50 µg twice daily via Diskus inhaler for 4 weeks. At the Final Visit (Visit 2) the data registration period of Visit 1 will be repeated with the only difference that no placebo will be administered.

Further endpoints, besides the evaluation of MSNA, include heart rate variability (HRV), spontaneous baroreflex sensitivity and lung function parameters.

Study enrolment will be stopped when valid MSNA data on the immediate effect of inhalation (manoeuvres at Visit 1) are available for 24 subjects.

## Eligibility

Ages Eligible for Study: 41 Years to 79 Years
Genders Eligible for Study: Both

Inclusion Criteria:

- COPD of GOLD Class II or III with a post-bronchodilator spirometry forced expiratory volume in one second (FEV1) <60% predicted and FEV1/vital capacity (VC) <70% in accordance with the GOLD executive summary
- Subject is ambulatory (outpatient)
- Subject is therapy-naive (defined as not receiving any previous regular COPD therapy)
- Subjects with a current or prior history of ≥10 pack-years of cigarette smoking at Screening Visit. Previous smokers are defined as those who have stopped smoking for at least 1 month prior to Visit 1
- Willing to participate in the study, must be able to inhale study medication

Exclusion Criteria:

- Women who are pregnant or lactating
- Subjects not willing or unable to sign the informed consent before study start
- diagnosis of asthma
- α-1 antitrypsin deficiency
- active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases
- Subjects with lung volume reduction surgery within the 12 months prior to Screening
- Subjects who have been hospitalized due to poorly controlled COPD within 6 weeks prior to the Screening Visit
- Subjects with poorly controlled COPD, defined as the occurrence of an exacerbation managed with systemic corticosteroids or antibiotics prescribed by a physician 6 weeks prior to the Screening Visit
- Frequent exacerbations necessitating the therapy with inhaled glucocorticosteroids according to the GOLD guideline
- COPD with nasal intermittent positive pressure ventilation (NIPPV)
- Treatment with drugs having direct sympathomimetic activity (e.g. theophylline, moxonidine, clonidine), Oral medication with beta2-sympathomimetics
- Inhaled therapy with anti-cholinergics, sodium cromoglycate or nedocromil sodium
- Treatment with systemic, oral or parenteral (intra-articular) corticosteroids
- Treatment with strong cytochrome P450 3A4 inhibitors
- Treatment with any other investigational drug
- Oxygen therapy: Subjects receiving treatment with long-term oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours a day
- Subjects who are medically unable to withhold their short-acting beta-agonist (SABA) for the 6-hour period required prior to spirometry testing at each study visit
- Subjects with clinically significant sleep apnoea that is uncontrolled
- Unstable angina pectoris or signs and history of left heart failure with a left ventricular ejection fraction <40%
- Arterial hypertension necessitating treatment with >1 antihypertensive drug
- Clinically evident polyneuropathy
- Diabetes mellitus necessitating any pharmacological therapy
- Severe concomitant disease (likely to reduce life expectancy to less than 3 years)
- Other diseases/abnormalities: Subjects with historical or current evidence of clinically significant neurological, psychiatric, renal, hepatic, immunological, endocrine or haematological abnormality that is uncontrolled

## Contacts and Locations

### Locations

#### Germany

GSK Investigational Site
Goettingen, Niedersachsen, Germany, 37075

### Investigators

| | | |
|---|---|---|
| Study Director: | GSK Clinical Trials | GlaxoSmithKline |

## More Information

| | |
|---|---|
| Responsible Party: | GlaxoSmithKline |
| Study ID Numbers: | 114520 |
| Health Authority: | Germany: Bundesinstitut für Arzneimittel und Medizinprodukte |

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# Study Results

## Participant Flow

### Pre-Assignment Details

At Visit 1, a complex data registration was performed during which placebo and 50 micrograms (µg) salmeterol via SEREVENT DISKUS inhaler was administered sequentially. Following Visit 1, participants were treated with salmeterol 50 µg twice daily (BID) via DISKUS inhaler for 4 weeks.

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

### Overall Study

| | Salmeterol 50 µg BID |
|---|---|
| Started | 32 |

| | Salmeterol 50 µg BID |
|---|---|
| Completed | 30 |
| Not Completed | 2 |
| Adverse Event | 2 |

## Baseline Characteristics

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

### Baseline Measures

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants | 32 |
| Age, Continuous<br>[units: Years]<br>Mean (Standard Deviation) | 61.19 (8.41) |
| Gender, Male/Female<br>[units: Participants] | |
| Female | 11 |
| Male | 21 |

## Outcome Measures

1. Primary Outcome Measure:

| | |
|---|---|
| Measure Title | Change in Muscle Sympathetic Nerve Activity (MSNA) at 2 Hours (Week 0) |
| Measure Description | Human MSNA is composed of vasoconstrictor impulses grouped in pulse synchronous bursts that usually occur in sequences, preferentially during transient reductions of blood pressure. Sympathetic activity was measured using microneurographic recordings of efferent in the peroneal nerve. MSNA reflects sympathetic discharge to the vascular bed of the skeletal muscle. The change in MSNA (bursts per 100 heart beats [bursts/100 heart beats]) was calculated as the difference in MSNA change from Baseline to after the inhalation of salmeterol (2 hours, Week 0, Visit 1) minus the MSNA change from Baseline to after the inhalation of placebo (1 hour, Week 0, Visit 1). |
| Time Frame | Baseline and 2 hours (Week 0) |
| Safety Issue? | No |

## Analysis Population Description

ITT-MSNA Population: all participants who received at least one dose of study medication and who had a valid data registration period of the primary endpoint.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 18 |
| Change in Muscle Sympathetic Nerve Activity (MSNA) at 2 Hours (Week 0)<br>[units: Bursts/100 heart beats]<br>Mean (Standard Deviation) | -1.3 (8.13) |

Statistical Analysis 1 for Change in Muscle Sympathetic Nerve Activity (MSNA) at 2 Hours (Week 0)

| | |
|---|---|
| Groups | Salmeterol 50 µg BID |
| Method | Other [paired t-Test, 2-sided] |
| P-Value | 0.5062 |
| | |

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

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

2. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in MSNA (Evaluated by Microneurography as Bursts/100 Heart Beats) at Week 4 |
| Measure Description | Human MSNA is composed of vasoconstrictor impulses grouped in pulse synchronous bursts that usually occur in sequences, preferentially during transient reductions of blood pressure. Sympathetic activity was measured using microneurographic recordings of efferent in the peroneal nerve. MSNA reflects |

| | |
|---|---|
| | sympathetic discharge to the vascular bed of the skeletal muscle. Change in MSNA is expressed in terms of bursts per 100 heart beats (bursts/100 heart beats). Change from Baseline was calculated as the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline and Week 4 |
| Safety Issue? | No |

### Analysis Population Description

ITT-MSNA Population. Only those participants available at the indicated time points were assessed.

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

### Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 12 |
| Change From Baseline in MSNA (Evaluated by Microneurography as Bursts/100 Heart Beats) at Week 4<br>[units: Bursts/100 heart beats]<br>Mean (Standard Deviation) | -3.1 (11.58) |

## 3. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in MSNA (Evaluated by Microneurography as Bursts/Minute) at 2 Hours (Week 0) |

| | |
|---|---|
| Measure Description | Human MSNA is composed of vasoconstrictor impulses grouped in pulse synchronous bursts that usually occur in sequences, preferentially during transient reductions of blood pressure. Sympathetic activity was measured using microneurographic recordings of efferent in the peroneal nerve. MSNA reflects sympathetic discharge to the vascular bed of the skeletal muscle. The change in MSNA (bursts per minute [bursts/minute]) was calculated as the difference in MSNA change from Baseline to after the inhalation of salmeterol (2 hours, Week 0, Visit 1) minus the MSNA change from Baseline to after the inhalation of placebo (1 hour, Week 0, Visit 1). |
| Time Frame | Baseline and 2 hours (Week 0) |
| Safety Issue? | No |

## Analysis Population Description

ITT-MSNA Population

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 18 |
| Change From Baseline in MSNA (Evaluated by Microneurography as Bursts/Minute) at 2 Hours (Week 0)<br>[units: Bursts/minute]<br>Mean (Standard Deviation) | 0.3 (5.60) |

4. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in MSNA (Evaluated by Microneurography as Bursts/Minute) at Week 4 |
| Measure Description | Human MSNA is composed of vasoconstrictor impulses grouped in pulse synchronous bursts that usually occur in sequences, preferentially during transient reductions of blood pressure. Sympathetic activity was measured using microneurographic recordings of efferent in the peroneal nerve. MSNA reflects sympathetic discharge to the vascular bed of the skeletal muscle. Change in MSNA is expressed in terms of bursts per minute (bursts/minute). Change from Baseline was calculated as the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT-MSNA Population. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 12 |

| | Salmeterol 50 µg BID |
|---|---|
| Change From Baseline in MSNA (Evaluated by Microneurography as Bursts/Minute) at Week 4<br>[units: Bursts/minute]<br>Mean (Standard Deviation) | 0.5 (7.58) |

5. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Standard Deviation of NN Intervals (SDNN) at 2 Hours (Week 0) and at Week 4 (ITT Population) |
| Measure Description | Heart rate variability (HRV) refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. SDNN reflects all the cyclic components responsible for variability in the period of recording; therefore, it represents total variability. Change in HRV (SDNN) after salmeterol inhalation is expressed in terms of milliseconds (ms). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Heart Rate Variability (HRV): Standard Deviation of NN Intervals (SDNN) at 2 Hours (Week 0) and at Week 4 (ITT Population)<br>[units: ms]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=32 | -1.7 (26.4) |
| Change from Baseline to Week 4, n=31 | 0.1 (53.9) |

6. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Standard Deviation of NN Intervals (SDNN) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) |
| Measure Description | HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. SDNN reflects all the cyclic components responsible for variability in the period of recording; therefore, it represents total variability. Change in HRV (SDNN) after salmeterol inhalation is expressed in terms of milliseconds (ms). |

| | |
|---|---|
| | Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT-MSNA Population

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 18 |
| Change From Baseline in Heart Rate Variability (HRV): Standard Deviation of NN Intervals (SDNN) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population)<br>[units: ms]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0 | 1.2 (22.5) |
| Change from Baseline to Week 4 | -12.1 (29.5) |

7. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Square Root of the Mean Squared Difference of Successive NNs (RMSSD) at 2 Hours (Week 0) and at Week 4 (ITT Population) |
| Measure Description | HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. Compared with SDNN, RMSSD is a short-term variation of heart rate. Change in HRV (RMSSD) after salmeterol inhalation is expressed in terms of milliseconds (ms). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Heart Rate Variability (HRV): Square Root of the Mean Squared Difference of Successive NNs (RMSSD) at 2 Hours (Week 0) and at Week 4 (ITT Population)<br>[units: ms]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=32 | -11.5 (36.3) |
| Change from Baseline to Week 4, n=31 | -5.2 (96.1) |

8. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Square Root of the Mean Squared Difference of Successive NNs (RMSSD) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) |
| Measure Description | HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. Compared with SDNN, RMSSD is a short-term variation of heart rate. Change in HRV (RMSSD) after salmeterol inhalation is expressed in terms of milliseconds (ms). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |

| | |
|---|---|
| Safety Issue? | No |

Analysis Population Description

ITT-MSNA Population

Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 18 |
| Change From Baseline in Heart Rate Variability (HRV): Square Root of the Mean Squared Difference of Successive NNs (RMSSD) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population)<br>[units: ms]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0 | -10.6 (26.4) |
| Change from Baseline to Week 4 | -32.5 (47.4) |

9. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Absolute Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population) |

| | |
|---|---|
| Measure Description | HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the LF component of the HRV spectrum reflects sympathetic activity. Change in HRV (absolute LF) after salmeterol inhalation is expressed in terms of milliseconds squared (ms^2). Change from Baseline were calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Heart Rate Variability (HRV): Absolute Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population)<br>[units: ms^2]<br>Mean (Standard Deviation) | |

| | Salmeterol 50 µg BID |
|---|---|
| Change from Baseline to 2 hours, Week 0, n=32 | -123.8 (1588.4) |
| Change from Baseline to Week 4, n=31 | -390.1 (1463.3) |

10. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Absolute Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) |
| Measure Description | HRV refers to the complex beat-to-beat (N-N) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: The LF component of the HRV spectrum reflects sympathetic activity. Change in HRV (absolute LF) after salmeterol inhalation is expressed in terms of milliseconds squared (ms2). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation), respectively. |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT-MSNA Population

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 18 |
| Change From Baseline in Heart Rate Variability (HRV): Absolute Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) [units: ms^2] Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0 | 220.7 (1038.2) |
| Change from Baseline to Week 4 | -248.1 (755.2) |

11. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Absolute High Frequency (HF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population) |
| Measure Description | HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the HF component of the HRV spectrum reflects parasympathetic activity. Change in HRV (absolute HF) after salmeterol inhalation is expressed in terms of |

| | |
|---|---|
| | milliseconds squared (ms^2). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Heart Rate Variability (HRV): Absolute High Frequency (HF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population)<br>[units: ms^2]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=32 | -457.9 (1591.6) |
| Change from Baseline to Week 4, n=31 | 817.5 (8754.6) |

12. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Absolute High Frequency (HF) Power at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) |
| Measure Description | HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the HF component of the HRV spectrum reflects parasympathetic activity. Change in HRV (absolute HF) after salmeterol inhalation is expressed in terms of milliseconds squared (ms^2). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT-MSNA Population

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 18 |
| Change From Baseline in Heart Rate Variability (HRV): Absolute High Frequency (HF) Power at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population)<br>[units: ms^2]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0 | -372.1 (1194.4) |
| Change from Baseline to Week 4 | -840.2 (1491.5) |

13. Secondary Outcome Measure:

| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Normalized Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population) |
|---|---|
| Measure Description | HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the LF component of the HRV spectrum reflects sympathetic activity. Change in HRV (normalized LF) after salmeterol inhalation is expressed in terms of normalized units that represent the relative value of LF power component in proportion to the total power minus the very LF (VLF) component (LF/(Total Power–VLF)*100). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any |

| | |
|---|---|
| | inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

### Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

### Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Heart Rate Variability (HRV): Normalized Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population)<br>[units: percent change]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=32 | 8.4 (14.5) |
| Change from Baseline to Week 4, n=31 | 2.5 (23.3) |

## 14. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Heart Rate Variability (HRV): |

| | Normalized Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) |
|---|---|
| Measure Description | HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: The LF component of the HRV spectrum reflects sympathetic activity. Change in HRV (normalized LF) after salmeterol inhalation is expressed in terms of normalized units that represent the relative value of LF power component in proportion to the total power minus the very LF (VLF) component (LF/(Total Power–VLF)*100). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT-MSNA Population

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 18 |

| | Salmeterol 50 µg BID |
|---|---|
| Change From Baseline in Heart Rate Variability (HRV): Normalized Low Frequency (LF) Power at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population)<br>[units: percent change]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0 | 10.8 (14.6) |
| Change from Baseline to Week 4 | 11.6 (19.0) |

15. Secondary Outcome Measure:

| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Normalized High Frequency (HF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population) |
|---|---|
| Measure Description | HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the HF component of the HRV spectrum reflects parasympathetic activity. Change in HRV (normalized HF) after salmeterol inhalation is expressed in terms of normalized units that represent the relative value of HF power component in proportion to the total power minus the very LF (VLF) component (HF/(Total Power–VLF)*100). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |

| | |
|---|---|
| Safety Issue? | No |

### Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

### Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Heart Rate Variability (HRV): Normalized High Frequency (HF) Power at 2 Hours (Week 0) and at Week 4 (ITT Population)<br>[units: percent change]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=32 | -8.4 (14.5) |
| Change from Baseline to Week 4, n=31 | -2.5 (23.3) |

## 16. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Normalized High Frequency Power (HF) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) |

| | |
|---|---|
| Measure Description | HRV refers to the complex beat-to-beat (NN) variation in heart rate produced by the interplay of sympathetic and parasympathetic neural activity at the sinus node of the heart. HRV frequencies can be analyzed with frequency domain methods: the HF component of the HRV spectrum reflects parasympathetic activity. Change in HRV (normalized HF) after salmeterol inhalation is expressed in terms of normalized units that represent the relative value of HF power component in proportion to the total power minus the very LF (VLF) component (HF/(Total Power–VLF)*100). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT-MSNA Population

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 18 |
| Change From Baseline in Heart Rate Variability (HRV): Normalized High | |

| | Salmeterol 50 µg BID |
|---|---|
| Frequency Power (HF) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population)<br>[units: percent change]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0 | -10.8 (14.6) |
| Change from Baseline to Week 4 | -11.6 (19.0) |

17. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Heart Rate at 2 Hours (Week 0) and at Week 4 (ITT Population) |
| Measure Description | Heart rate refers to the speed of the heartbeat, specifically the number of heartbeats per unit of time. Change in HRV (heart rate) after salmeterol inhalation is expressed in terms of the heart rate (beats) per minute (heart rate/min). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0 before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Heart Rate Variability (HRV): Heart Rate at 2 Hours (Week 0) and at Week 4 (ITT Population)<br>[units: beats per minute (bpm)]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=32 | 3.7 (4.2) |
| Change from Baseline to Week 4, n=31 | 3.9 (4.3) |

18. Secondary Outcome Measure:

| Measure Title | Change From Baseline in Heart Rate Variability (HRV): Heart Rate at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) |
|---|---|
| Measure Description | Heart rate refers to the speed of the heartbeat, specifically the number of heartbeats per unit of time. Change in HRV (heart rate) after salmeterol inhalation is expressed in terms of the heart rate (beats) per minute (heart rate/min). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0 before any inhalation). |

| | |
|---|---|
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

### Analysis Population Description

ITT-MSNA Population

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

### Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 18 |
| Change From Baseline in Heart Rate Variability (HRV): Heart Rate at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population)<br>[units: beats per minute (bpm)]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0 | 4.4 (4.7) |
| Change from Baseline to Week 4 | 4.9 (4.8) |

## 19. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Spontaneous Baroreflex Sensitivity (BRS) at 2 Hours (Week 0) and at Week 4 (ITT |

| | |
|---|---|
| | Population) |
| Measure Description | BRS is an important characteristic of baroreflex control and is often noninvasively assessed by relating heart rate (HR) fluctuations to blood pressure (BP) fluctuations. Change in BRS after salmeterol inhalation is expressed in terms of milliseconds per millimeters of mercury (ms/mmHg). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0 before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT Population. Only those participants available at the specified time points were assessed (represented by n=X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT Population.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Spontaneous Baroreflex Sensitivity (BRS) at 2 Hours (Week 0) and at Week 4 (ITT Population)<br>[units: ms/mmHg]<br>Mean (Standard Deviation) | |

| | Salmeterol 50 µg BID |
|---|---|
| Change from Baseline to 2 hours, Week 0, n=31 | 0.1 (1.9) |
| Change from Baseline to Week 4, n=29 | 0.2 (2.6) |

20. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Spontaneous Baroreflex Sensitivity (BRS) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) |
| Measure Description | BRS is an important characteristic of baroreflex control and is often noninvasively assessed by relating heart rate (HR) fluctuations to blood pressure (BP) fluctuations. Change in BRS after salmeterol inhalation is expressed in terms of milliseconds per millimeters of mercury (ms/mmHg). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0 before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

Analysis Population Description

ITT-MSNA Population. Only those participants available at the indicated time points were assessed.

Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 17 |
| Change From Baseline in Spontaneous Baroreflex Sensitivity (BRS) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population)<br>[units: ms/mmHg]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0 | 0.28 (2.2) |
| Change from Baseline to Week 4 | 0.44 (3.2) |

21. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Forced Expiratory Volume in One Second (FEV1) at 2 Hours (Week 0) and at Week 4 (ITT Population) |
| Measure Description | Pulmonary function was measured by FEV1, defined as the volume of air that which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Change in FEV1 after salmeterol inhalation is expressed in terms of liters (L). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

### Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

### Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Forced Expiratory Volume in One Second (FEV1) at 2 Hours (Week 0) and at Week 4 (ITT Population)<br>[units: L]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=32 | -0.04 (0.23) |
| Change from Baseline to Week 4, n=31 | -0.04 (0.21) |

## 22. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Forced Expiratory Volume in One Second (FEV1) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population) |
| Measure Description | Pulmonary function was measured by FEV1, defined as the volume of air that which can be forcibly exhaled from the lungs in the first second |

| | |
|---|---|
| | of a forced exhalation. Change in FEV1 after salmeterol inhalation is expressed in terms of liters (L). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT-MSNA Population. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 18 |
| Change From Baseline in Forced Expiratory Volume in One Second (FEV1) at 2 Hours (Week 0) and at Week 4 (ITT-MSNA Population)<br>[units: L]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0 | -0.05 (0.26) |
| Change from Baseline to Week 4 | -0.08 (0.21) |

23. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Systolic and Diastolic Blood Pressure (BP) at 2 Hours (Week 0) and at Week 4 |
| Measure Description | Systolic and diastolic BP was manually measured. Change in BP after salmeterol inhalation is expressed in terms of millimeters of mercury (mmHg). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 31 |
| Change From Baseline in Systolic and Diastolic Blood Pressure (BP) at 2 Hours (Week 0) and at Week 4<br>[units: mmHg] | |

| | Salmeterol 50 µg BID |
|---|---|
| Mean (Standard Deviation) | |
| Systolic: Change from Baseline to 2 hours, Week 0 | 3.6 (12.3) |
| Systolic: Change from Baseline to Week 4 | 3.7 (15.7) |
| Diastolic: Change from Baseline to 2 hours, Week 0 | 1.9 (6.7) |
| Diastolic: Change from Baseline to Week 4 | 0.7 (6.8) |

## 24. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Respiratory Rate at 2 Hours (Week 0) and at Week 4 |
| Measure Description | Respiratory rate is defined as the number of breaths taken within a set amount of time (typically within 60 seconds). Change in respiratory rate after salmeterol inhalation is expressed in terms of respiratory rate (breaths) per minute (min). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

### Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Respiratory Rate at 2 Hours (Week 0) and at Week 4<br>[units: breaths per minute]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=32 | -0.5 (1.6) |
| Change from Baseline to Week 4, n=31 | -0.1 (2.6) |

25. Secondary Outcome Measure:

| Measure Title | Change From Baseline in Tidal Volume at 2 Hours (Week 0) and at Week 4 |
|---|---|
| Measure Description | Tidal volume is defined as the lung volume representing the normal volume of air displaced between normal inspiration and expiration when extra effort is not applied (normal value is approximately 500 milliliters or 7 milliliters per kilogram of body weight). Change in tidal volume after salmeterol inhalation is expressed in terms of milliliters (mL). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week |

| | |
|---|---|
| | 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

### Analysis Population Description

ITT Population. Only those participants available at the specified time points were assessed (represented by n=X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT Population.

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

### Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Tidal Volume at 2 Hours (Week 0) and at Week 4<br>[units: mL]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=30 | 60.4 (118.0) |
| Change from Baseline to Week 4, n=24 | 55.6 (183.7) |

## 26. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Respiratory Minute Volume at 2 |

| | Hours (Week 0) and at Week 4 |
|---|---|
| Measure Description | Respiratory minute volume is defined as the volume of gas inhaled (inhaled minute volume) or exhaled (exhaled minute volume) from a person's lungs per minute. Change in respiratory minute volume after salmeterol inhalation is expressed in terms of milliliters per minute (mL/min). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT Population. Only those participants available at the specified time points were assessed (represented by n=X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT Population.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Respiratory Minute Volume at 2 Hours (Week 0) and at Week 4<br>[units: mL/min]<br>Mean (Standard Deviation) | |

| | Salmeterol 50 µg BID |
|---|---|
| Change from Baseline to 2 hours, Week 0, n=30 | 572.0 (1529.7) |
| Change from Baseline to Week 4, n=24 | 671.4 (2963.3) |

27. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Catecholamines (Plasma Norepinephrine) at 2 Hours (Week 0) and at Week 4 |
| Measure Description | Catecholamines are important neurotransmitters in the central nervous system and play a crucial role in the autonomic regulation of many homeostatic functions. Change in catecholamines (plasma norepinephrine) after salmeterol inhalation is expressed in terms of nanogramms per liter (ng/L). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

### Analysis Population Description

ITT Population. Only those participants available at the specified time points were assessed (represented by n=X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT Population.

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS |

| | Description |
|---|---|
| | inhaler twice daily (BID) over the course of 4 weeks. |

Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Catecholamines (Plasma Norepinephrine) at 2 Hours (Week 0) and at Week 4<br>[units: ng/L]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=26 | -42.4 (103) |
| Change from Baseline to Week 4, n=29 | -5.7 (133) |

28. Secondary Outcome Measure:

| Measure Title | Change From Baseline in Catecholamines (Plasma Epinephrine) at 2 Hours (Week 0) and at Week 4 |
|---|---|
| Measure Description | Catecholamines are important neurotransmitters in the central nervous system and play a crucial role in the autonomic regulation of many homeostatic functions. Change in catecholamines (plasma epinephrine) after salmeterol inhalation is expressed in terms of nanograms per milliliter (ng/mL). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |

| | |
|---|---|
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

### Analysis Population Description

ITT Population. Only those participants available at the specified time points were assessed (represented by n=X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT Population.

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

### Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Catecholamines (Plasma Epinephrine) at 2 Hours (Week 0) and at Week 4<br>[units: ng/mL]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=26 | 6.7 (12.7) |
| Change from Baseline to Week 4, n=29 | -0.3 (10.4) |

## 29. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Catecholamines (Brain Natriuretic Peptide [BNP]) at 2 Hours (Week 0) and at |

| | Week 4 |
|---|---|
| Measure Description | Catecholamines are important neurotransmitters in the central nervous system and play a crucial role in the autonomic regulation of many homeostatic functions. Change in catecholamines (BNP) after salmeterol inhalation is expressed in terms of picograms per milliliter (pg/mL). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 27 |
| Change From Baseline in Catecholamines (Brain Natriuretic Peptide [BNP]) at 2 Hours (Week 0) and at Week 4<br>[units: pg/mL]<br>Mean (Standard Deviation) | |

| | Salmeterol 50 µg BID |
|---|---|
| Change from Baseline to 2 hours, Week 0 | 2.4 (7.0) |
| Change from Baseline to Week 4 | -6.1 (28.5) |

30. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in Oxygen Saturation Measured Via Pulse Oxymetry (SpO2) at 2 Hours (Week 0) and at Week 4 |
| Measure Description | Oxygen saturation measures the capacity of blood to transport oxygen to other parts of the body. Oxygen binds to hemoglobin in red blood cells when moving through the lungs. A pulse oximeter uses two frequencies of light (red and infrared) to determine the percentage of hemoglobin in the blood that is saturated with oxygen. The percentage is called blood oxygen saturation, or SpO2. Change in SpO2 after salmeterol inhalation is expressed in terms of percent. Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

Safety Population: all participants included in the study who received at least one dose of study medication. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Oxygen Saturation Measured Via Pulse Oxymetry (SpO2) at 2 Hours (Week 0) and at Week 4<br>[units: percent]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=32 | -0.2 (1.1) |
| Change from Baseline to Week 4, n=31 | -0.5 (2.0) |

31. Secondary Outcome Measure:

| Measure Title | Change From Baseline in Transcutaneous Carbon Dioxide (tCO2) at 2 Hours (Week 0) and at Week 4 |
|---|---|
| Measure Description | Transcutaneous carbon dioxide monitoring is a noninvasive way of continuously measuring the tension of these gases in the skin. This methodology provides a continuous noninvasive estimation of the arterial CO2 value. Change in tCO2 after salmeterol inhalation is expressed in terms of millimeters of mercury (mmHg). Change from Baseline was calculated as the value at 2 hours (Week 0 [Visit 1, after salmeterol inhalation]) and the value at Week 4 (Visit 2, after salmeterol inhalation) minus the value at Baseline (Week 0, before any |

| | |
|---|---|
| | inhalation). |
| Time Frame | Baseline, 2 hours (Week 0), and Week 4 |
| Safety Issue? | No |

### Analysis Population Description

Safety Population. Only those participants available at the indicated time points were assessed.

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

### Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Change From Baseline in Transcutaneous Carbon Dioxide (tCO2) at 2 Hours (Week 0) and at Week 4<br>[units: mmHg]<br>Mean (Standard Deviation) | |
| Change from Baseline to 2 hours, Week 0, n=32 | -0.94 (2.19) |
| Change from Baseline to Week 4, n=31 | -0.82 (4.17) |

## 32. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Lung Function (Forced Vital Capacity [FVC], Functional |

| | |
|---|---|
| | Residual Capacity [FRC; Body and Helium], Total Lung Capacity [TLC], and Residual Volume [RV]) at Baseline (Week 0) and at Week 4 |
| Measure Description | FVC is defined as the volume of air that can be forcibly blown out from the lungs after a full inspiration. FRC is defined as the volume of air present in the lungs, specifically the parenchyma tissues, at the end of a passive expiration. TLC is defined as the maximum volume to which the lungs can be expanded with the greatest possible inspiratory effort; it is equal to VC plus the RV and is approximately 5800 milliliters. RV is defined as the amount of gas remaining in the lungs at the end of a maximal exhalation. All parameters describing lung function are expressed in terms of liters (L). Lung function (FVC, FRC [body and helium], TLC, and RV) was evaluated at Baseline (Week 0, [Visit 1, before any inhalation]) and at Week 4 (Visit 2, after salmeterol inhalation). |
| Time Frame | Baseline and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |

| | Salmeterol 50 µg BID |
|---|---|
| Lung Function (Forced Vital Capacity [FVC], Functional Residual Capacity [FRC; Body and Helium], Total Lung Capacity [TLC], and Residual Volume [RV]) at Baseline (Week 0) and at Week 4<br>[units: L]<br>Mean (Standard Deviation) | |
| FVC at Baseline, Week 0, n=32 | 2.60 (0.7) |
| FVC at Week 4, n=31 | 2.64 (0.7) |
| FRC (body) at Baseline, Week 0, n=32 | 4.65 (1.3) |
| FRC (body) at Week 4, n=27 | 3.67 (1.8) |
| FRC (helium) at Baseline, Week 0, n=24 | 3.64 (1.0) |
| FRC (helium) at Week 4, n=24 | 3.38 (0.8) |
| TLC at Baseline, Week 0, n=32 | 6.61 (1.4) |
| TLC at Week 4, n=27 | 5.67 (1.8) |
| RV at Baseline, Week 0, n=32 | 3.90 (1.3) |
| RV at Week 4, n=27 | 2.90 (1.8) |

33. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Number of Participants With Diastolic Dysfunction on Echocardiography at Baseline (Week 0) and at Week 4 |
| Measure Description | Diastolic dysfunction refers to the decline in performance of one (usually the left ventricle) or both (left and right) ventricles during |

| | |
|---|---|
| | diastole. The number of participants with diastolic dysfunction on echocardiography was evaluated at Baseline (Week 0, [Visit 1, before any inhalation]) and at Week 4 (Visit 2, after salmeterol inhalation). |
| Time Frame | Baseline and Week 4 |
| Safety Issue? | No |

## Analysis Population Description

ITT Population. Only those participants available at the indicated time points were assessed.

## Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

## Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Number of Participants With Diastolic Dysfunction on Echocardiography at Baseline (Week 0) and at Week 4<br>[units: participants] | |
| Baseline: Diastolic dysfunction: Yes, n=32 | 3 |
| Baseline: Diastolic dysfunction: No, n=32 | 29 |
| Week 4: Diastolic dysfunction: Yes, n=31 | 5 |

| | Salmeterol 50 µg BID |
|---|---|
| Week 4: Diastolic dysfunction: No, n=31 | 26 |

34. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Arterial Stiffness at Baseline (Week 0) and at Week 4 |
| Measure Description | Arterial stiffness occurs as a consequence of age and arteriosclerosis. Carotid-femoral pulse wave velocity (PWV), a measure of arterial stiffness, is determined from the time taken for the arterial pulse to propagate from the carotid to the femoral artery. PWV was evaluated in terms of meters per second (m/s). PWV after salmeterol inhalation at Baseline (Week 0, [Visit 1, before any inhalation]) and at Week 4 (Visit 2, after inhalation of salmeterol) was assessed. |
| Time Frame | Baseline and Week 4 |
| Safety Issue? | No |

Analysis Population Description

ITT Population. Only those participants available at the specified time points were assessed (represented by n=X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

Measured Values

| | Salmeterol 50 µg BID |
|---|---|
| Number of Participants Analyzed | 32 |
| Arterial Stiffness at Baseline (Week 0) and at Week 4<br>[units: m/s]<br>Mean (Standard Deviation) | |
| PWV at Baseline, Week 0, n=30 | 9.2 (2.1) |
| PWV at Week 4, n=29 | 8.8 (2.2) |

## Reported Adverse Events

### Reporting Groups

| | Description |
|---|---|
| Salmeterol 50 µg BID | Participants received salmeterol 50 micrograms (µg) via DISKUS inhaler twice daily (BID) over the course of 4 weeks. |

### Time Frame

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of the study medication to the end of treatment (up to 37 days/average of 28.2 days)

### Additional Description

SAEs and non-serious AEs were reported for members of the Intent-to-Treat (ITT) Population, comprised of all participants randomized to treatment who received at least one dose of trial medication during the treatment period.

### Serious Adverse Events

| | Salmeterol 50 µg BID |
|---|---|
| Total # participants affected/at | 0/32 (0%) |

| | Salmeterol 50 µg BID |
|---|---|
| risk | |

## Other Adverse Events

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

| | Salmeterol 50 µg BID |
|---|---|
| Total # participants affected/at risk | 19/32 (59.38%) |
| Cardiac disorders | |
| Palpitations † [A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Gastrointestinal disorders | |
| Diarrhoea † [A] | |
| # participants affected/at risk | 2/32 (6.25%) |
| # events | |
| Dry mouth † [A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Swollen tongue † [A] | |

| | Salmeterol 50 µg BID |
|---|---|
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Vomiting † [A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Infections and infestations | |
| Bronchitis † [A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Gingivitis † [A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Nasopharyngitis † [A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Injury, poisoning and procedural complications | |

| | Salmeterol 50 µg BID |
|---|---|
| Arthropod bite †[A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Fibula fracture †[A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Musculoskeletal and connective tissue disorders | |
| Muscle spasms †[A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Musculoskeletal pain †[A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Pain in extremity †[A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |

| | Salmeterol 50 µg BID |
|---|---|
| Nervous system disorders | |
| Headache †[A] | |
| # participants affected/at risk | 2/32 (6.25%) |
| # events | |
| Hypoaesthesia †[A] | |
| # participants affected/at risk | 2/32 (6.25%) |
| # events | |
| Paraesthesia †[A] | |
| # participants affected/at risk | 2/32 (6.25%) |
| # events | |
| Respiratory, thoracic and mediastinal disorders | |
| Cough †[A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # events | |
| Dyspnoea †[A] | |
| # participants affected/at risk | 1/32 (3.12%) |

| | Salmeterol 50 µg BID |
|---|---|
| # events | |
| Sputum increased † [A] | |
| # participants affected/at risk | 1/32 (3.12%) |
| # 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: