ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
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Study Identification

Unique Protocol ID:	B2C111045
Brief Title:	A Study To Assess Efficacy And Safety Of Different Doses Of GW642444 In Subjects With Chronic Obstructive Pulmonary Disease (COPD)
Official Title:	Study B2C111045, A Dose-Finding Study of GW642444 Versus Placebo in Patients With COPD
Secondary IDs:	

Study Status

Record Verification:	June 2013
Overall Status:	Completed
Study Start:	February 2008
Primary Completion:	October 2008 [Actual]
Study Completion:	October 2008 [Actual]

Sponsor/Collaborators

Sponsor:	GlaxoSmithKline
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? Yes

	Delayed Posting? No
IND/IDE Protocol?:	Yes
IND/IDE Information:	Grantor: CDER IND/IDE Number: 74696 Serial Number: TBD Has Expanded Access? No
Review Board:	Approval Status: Approved Approval Number: IRB00001313 Board Name: Copernicus Group Independent Review Board Board Affiliation: Copernicus Group Independent Review Board Phone: 888 303-2224 Email:
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	Germany: Federal Institute for Drugs and Medical Devices United States: Food and Drug Administration

Study Description

Brief Summary:	This study will assess the safety and efficacy of 5 doses GW642444 in subjects with Chonic Obstructive Pulmonary Disease (COPD)
Detailed Description:	

Conditions

Conditions:	Pulmonary Disease, Chronic Obstructive
Keywords:	Chronic Obstructive Pulmonary Disease (COPD) COPD GW642444

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment

Number of Arms:	2
Masking:	Double Blind (Subject, Caregiver, Investigator)
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	602 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: GW642444 GW642444	Drug: GW642444 6.25 GW642444 6.25 Drug: GW642444 3mcg once daily Other Names: • GW642444 • GW642444 Drug: GW642444 12.5mcg GW642444 12.5mcg Drug: GW642444 25mcg GW642444 25mcg Drug: GW642444 50mcg GW642444 50mcg
Placebo Comparator: placebo	placebo placebo

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	40 Years
Maximum Age:	80 Years
Gender:	Both
Accepts Healthy Volunteers?:	No
Criteria:	Inclusion Criteria:

Subjects eligible for enrollment in the study must meet all of the following criteria:

- Informed Consent: Subjects who give their signed written informed consent to participate.
- Gender: Male or females who are 40 - 80 years of age at Visit 1. A female is eligible to enter and participate in the study if she is of:
    - Non-child bearing potential (i.e. physiologically incapable of becoming pregnant, including any female who is post-menopausal); or
    - Child bearing potential, has a negative pregnancy test at screening, and agrees to one of the following acceptable contraceptive methods used consistently and correctly (i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study - screening to follow-up contact):
        - Complete abstinence from intercourse from screening until 2 weeks after the follow-up contact; or
        - Male partner is sterile (vasectomy with documentation of azoospermia) prior to female subject entry into the study, and this male partner is the sole partner for that subject; or
        - Implants of levonorgestrel inserted for at least 1 month prior to the study medication administration but not beyond the third successive year following insertion; or
        - Injectable progestogen administered for at least 1 month prior to study medication administration and administered for 1 month following study completion; or
        - Oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study medication administration; or
        - Double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository); or
        - An intrauterine device (IUD), inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year; or
        - Estrogenic vaginal ring; or
        - Percutaneous contraceptive patches
- COPD Diagnosis: Subjects with an established clinical history of COPD in accordance with the following definition by the American Thoracic Society/European Respiratory Society [Celli, 2004]: COPD is a preventable and treatable disease characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.
- Tobacco Use: Must have current or prior history of at least 10 pack-years of cigarette smoking. [number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years]. Previous smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1.
- Severity of Disease:
- Subjects with a measured post-salbutamol FEV1/FVC ratio of ≤0.70 at Visit 1 (Screening).
- Subjects with a measured post-salbutamol FEV1 ≥35 and ≤70% of predicted normal values calculated using NHANES III reference equations at Visit 1 (Screening).

Exclusion Criteria:

Subjects meeting any of the following criteria must not be enrolled in the study:

- Pregnancy: Women who are pregnant or lactating.
- Asthma: Subjects with a primary diagnosis of asthma. (Subjects with a prior history of asthma are eligible if COPD is currently their primary diagnosis)

- a1-antitrypsin deficiency: Subjects with a1-antitrypsin deficiency as the underlying cause of COPD.
- Other Respiratory disorders: Subjects with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung disease or other active pulmonary disease.
- Lung Resection: Subjects with lung volume reduction surgery within the previous 12 months.
- Chest X-ray: Chest X-ray (or CT scan) reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest x-ray must be taken if a chest x-ray or CT scan is not available within the 6 months preceding the Screening Visit. For sites in Germany, if a chest x-ray (or CT scan) is not available in the 6 months preceding the Screening (Visit 1), the subject will not be eligible for the study.
- Hospitalization: Subjects who are hospitalized due to poorly controlled COPD within 12 weeks of the screening visit.
- Poorly controlled COPD: Subjects with poorly controlled COPD, defined as the occurrence of any of the following in the 6 weeks prior to Visit 1:
- acute worsening of COPD that is managed by subject with corticosteroids or antibiotics, or
- acute worsening of COPD that requires treatment prescribed by a physician
- Other Diseases/Abnormalities: Subjects with clinically significant cardiovascular neurological, psychiatric, renal, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled.
- Lower Respiratory Tract Infection: Subjects with lower respiratory tract infections which required the use of antibiotics within 6 weeks prior to visit 1.
- 12-Lead ECG: An abnormal and clinically significant 12-lead electrocardiogram (ECG) that results in an active medical problem. For the purposes of this study, an abnormal ECG is defined as a 12-lead tracing which is interpreted with (but not limited to) any of the following:
- Clinically significant conduction abnormalities (e.g., left bundle branch block, Wolff-Parkinson-White syndrome)
- Clinically significant arrhythmias (e.g., atrial fibrillation, ventricular tachycardia)

The investigator will determine the clinical significance of any ECG abnormality and determine if a subject is precluded from entering the study. However, the following predetermined ECG abnormalities are considered clinically significant and will result in exclusion of a subject:

- A mean QTc(B) value at screening >450msec, or uncorrected QT>600msec or an ECG that is not suitable for QT measurements (e.g. poorly defined termination of the T wave)
- Ventricular rate < 45 beats per minute.
- PR interval > 240msec.
- Evidence of second or third degree atrioventricular (AV) block
- Pathological Q waves
- Non-specific intraventricular conduction delay
- ST-T wave abnormalities (excluding non-specific ST-T wave abnormalities)
- Right or left complete bundle branch block
- Hypertension: Subjects with clinically significant hypertension that is uncontrolled.
- Hepatitis: Subjects with a positive Hepatitis B surface antigen or positive hepatitis C antibody pre-study or at Screening.
- Cancer: Subjects with carcinoma that has not been in complete remission for at least 5 years. Carcinoma in situ of the cervix, squamous cell carcinoma and basal cell carcinoma would not be excluded if the subject was considered cured in less than 5 years since diagnosis.
- Drug allergy: Subjects with a history of hypersensitivity to any beta-agonist or any component of the MDI and/or nebule or sensitivity to any of the constituents of the dry powder product (magnesium stearate or lactose). In addition patients with a history of severe milk protein allergy would also be excluded.
- Drug abuse: Subjects with a known or suspected history of alcohol or drug abuse within the last 2 years.

- Medication prior to spirometry: Subjects who are medically unable to withhold their salbutamol for the 6 hour period required prior to spirometry testing at each study visit would be ineligible for the study.
- Additional Medications: The following medications are not permitted during this study and must not have been taken for the indicated times prior to Visit 1 (See Prohibited Medications): Medication (Required period of time prior to screening visit):
    - Ipratropium or ipratropium/salbutamol combination product (6 hours)
    - Inhaled short acting beta-agonists (study salbutamol will be provided)(6 hours)
    - Oral beta2-agonists (48 hours)
    - LABAs (salmeterol and formoterol)(48 hours)
    - Corticosteroids/Long acting beta-agonist combination products (48 hours for the LABA component)
    - Theophylline preparations (48 hours)
    - Cromolyn and nedocromil inhalers(24 hours)
    - Zafirlukast, montelukast, zileuton(48 hours)
    - Tiotropium (1 Week)
    - Depot corticosteroids (12 Weeks)
    - Intra-articular corticosteroids (24 hours)
    - Inhaled corticosteroids>1000mcg/day of fluticasone propionate or equivalent (4 Weeks)
    - Any other investigational medication (30 days or within 5 drug half-lives of the investigational drug (whichever is longer))
    - P-glycoprotein inhibitors (e.g., ritonavir, ketoconazole) or Cytochrome P 3A4 inhibitors (e.g., cimetidine) (4 weeks (grapefruit is allowed up to the screening visit))
- Other Medications: Subjects receiving treatment with tricyclic antidepressants, MAOs, beta-adrenergic antagonists, anticonvulsants (barbiturates, hydantoins, and carbamazepine) or phenothiazines would be ineligible for the study.
- Oxygen: Subjects receiving long-term-oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours a day. Oxygen prn use is not exclusionary.
- Sleep apnea: Subjects with clinically significant sleep apnea that is uncontrolled.
- Pulmonary Rehabilitation: Subjects who have participated in the acute phase of a Pulmonary Rehabilitation Program within 4 weeks prior to Visit 1 (Screening) or who will enter the acute phase of a Pulmonary Rehabilitation Program during the study. Subjects who are in the maintenance phase of a Pulmonary Rehabilitation program are not excluded.
- Non-compliance: Subjects unable to comply with study procedures.
- Affiliation with investigator site: Study investigators, sub-investigators, study coordinators, employees of a participating investigator or immediate family members of the aforementioned are excluded from participation in this study.
- Questionable validity of Consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse, (including drug and alcohol), or other conditions, which will limit the validity of informed consent to participate in the study.
- Prior use of Study Medication: Subjects who have received the investigational drug GW642444 in previous studies.

Contacts/Locations

Study Officials: GSK Clinical Trials
Study Director
GlaxoSmithKline

Locations: Argentina

GSK Investigational Site
Mendoza, Mendoza, Argentina, M5500CCG

GSK Investigational Site
Mendoza, Mendoza, Argentina, M5500CCG

References

Citations: Hanania NA, Feldman G, Zachgo W, Shim J, Crim C, Sanford L, Lettis S, Barnhart F, Haumann B. The efficacy and safety of the novel long-acting beta2 agonist vilanterol trifenatate in COPD patients: a randomised placebo-controlled trial. [Chest]. 2012;142(1):119-127.

Links:

Study Data/Documents:

Study Results

Participant Flow

Pre-Assignment Details	At Visit (V) 1, eligible participants (par.) entered a 2-week, single-blind placebo Run-in Period (RIP) to establish a stable Baseline. At V 2, eligible par. were randomized to a 28 day, double-blind Treatment Period. 1206 par. were screened, 851 par. entered the RIP and 605 par. were randomized, out of which 602 par. received >=1 treatment dose.

Reporting Groups

	Description
Placebo Run-in	Participants received placebo once daily (OD) in the morning from the novel dual strip dry powder inhaler. In addition, all participants were provided supplemental albuterol (salbutamol) (metered dose inhaler [MDI] and/or nebules) to be used asneeded throughout the study.
Placebo	Participants received placebo (1 actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 3 µg	Participants received GW642444M 3 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.

	Description
GW642444M 6.25 µg	Participants received GW642444M 6.25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 12.5 µg	Participants received GW642444M 12.5 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 25 µg	Participants received GW642444M 25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 50 µg	Participants received GW642444M 50 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.

2-week Single-Blind Run-in Period

	Placebo Run-in	Placebo	GW642444M 3 µg	GW642444M 6.25 µg	GW642444M 12.5 µg	GW642444M 25 µg
Started	851	0	0	0	0	0
Completed	605	0	0	0	0	0
Not Completed	246	0	0	0	0	0
Did Not Meet Continuation Criteria	173	0	0	0	0	0
Study Closed/Terminated	32	0	0	0	0	0
Physician Decision	18	0	0	0	0	0
Withdrawal by Subject	15	0	0	0	0	0
Lost to Follow-up	5	0	0	0	0	0
Adverse Event	2	0	0	0	0	0
Received Study Medication in Error	1	0	0	0	0	0

	GW642444M 50 µg
Started	0
Completed	0

	GW642444M 50 µg
Not Completed	0
Did Not Meet Continuation Criteria	0
Study Closed/Terminated	0
Physician Decision	0
Withdrawal by Subject	0
Lost to Follow-up	0
Adverse Event	0
Received Study Medication in Error	0

Double-Blind Treatment Period

	Placebo Run-in	Placebo	GW642444M 3 µg	GW642444M 6.25 µg	GW642444M 12.5 µg	GW642444M 25 µg
Started	0	101	99	101	101	101
Completed	0	85	88	91	92	92
Not Completed	0	16	11	10	9	9
Adverse Event	0	3	2	4	2	0
Lack of Efficacy	0	1	0	0	1	0
Protocol Violation	0	5	5	3	0	3
Met Protocol Defined Stopping Criteria	0	1	2	1	2	3
Physician Decision	0	5	1	0	3	1
Withdrawal by Subject	0	1	1	2	1	2

	GW642444M 50 µg
Started	99
Completed	91
Not Completed	8
Adverse Event	1

	GW642444M 50 µg
Lack of Efficacy	0
Protocol Violation	4
Met Protocol Defined Stopping Criteria	1
Physician Decision	2
Withdrawal by Subject	0

Baseline Characteristics

Reporting Groups

	Description
Placebo	Participants received placebo (1 actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 3 µg OD	Participants received GW642444M 3 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 6.25 µg OD	Participants received GW642444M 6.25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 12.5 µg OD	Participants received GW642444M 12.5 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 25 µg OD	Participants received GW642444M 25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 50 µg OD	Participants received GW642444M 50 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.

Baseline Measures

	Placebo	GW642444M 3 µg OD	GW642444M 6.25 µg OD	GW642444M 12.5 µg OD	GW642444M 25 µg OD	GW642444M 50 µg OD	Total
Number of Participants	101	99	101	101	101	99	602

	Placebo	GW642444M 3 µg OD	GW642444M 6.25 µg OD	GW642444M 12.5 µg OD	GW642444M 25 µg OD	GW642444M 50 µg OD	Total
Age, Continuous [units: Years] Mean (Standard Deviation)	61.6 (8.53)	61.1 (8.57)	62.0 (7.94)	62.6 (8.03)	62.6 (8.88)	61.4 (8.12)	61.9 (8.34)
Gender, Male/Female [units: Participants]							
Female	44	31	37	44	42	34	232
Male	57	68	64	57	59	65	370
Race/Ethnicity, Customized [units: Participants]							
African American/African Heritage (HER)	3	1	3	2	4	3	16
American Indian or Alaska Native	0	2	0	4	2	3	11
Central/South Asian HER	0	0	0	1	0	0	1
Japanese/East Asian HER/ South East Asian HER	7	11	13	8	10	6	55
White	90	84	84	86	84	87	515
American Indian or Alaska Native & White	1	1	1	0	1	0	4

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Mean Change From Baseline in Trough (Pre Bronchodilator and Pre Dose) FEV1 on Day 29
Measure Description	Pulmonary function was measured by forced expiratory volume in one second (FEV1), defined as the maximal amount of air that can be forcibly exhaled from the lungs in one second. Baseline FEV1 is defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1. If one of these two assessments was missing then Baseline is defined as the single pre-dose FEV1 value at Day 1. The trough FEV1 is defined as the mean of the FEV1 values obtained at 23 and 24-hours after dosing on Day 28 and the Baseline FEV1 is defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1. Change from Baseline in trough FEV1 was calculated as the value on Day 29 minus the value at Baseline. Analysis was performed using Analysis of Covariance (ANCOVA) using Last Observation Carried Forward (LOCF) with covariates of baseline, sex, age, smoking status (at screening), reversibility stratum, and treatment (trt).
Time Frame	Baseline (BL) and Day 29

Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who were randomized to trt and received >= 1 dose of study medication. When the endpoint was missing, the last valid non-missing on-trt, post-BL trough assessment was used instead. Only those participants available at the specified time points without missing covariate information were analyzed.

Reporting Groups

	Description
Placebo	Participants received placebo (1 actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 3 µg OD	Participants received GW642444M 3 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 6.25 µg OD	Participants received GW642444M 6.25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 12.5 µg OD	Participants received GW642444M 12.5 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 25 µg OD	Participants received GW642444M 25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 50 µg OD	Participants received GW642444M 50 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.

Measured Values

	Placebo	GW642444M 3 µg OD	GW642444M 6.25 µg OD	GW642444M 12.5 µg OD	GW642444M 25 µg OD	GW642444M 50 µg OD
Number of Participants Analyzed	101	99	100	99	99	99
Mean Change From Baseline in Trough (Pre Bronchodilator and Pre Dose) FEV1 on Day 29 [units: Liters] Least Squares Mean (Standard Error)	0.029 (0.0188)	0.120 (0.0190)	0.127 (0.0188)	0.138 (0.0190)	0.166 (0.0190)	0.194 (0.0190)

Statistical Analysis 1 for Mean Change From Baseline in Trough (Pre Bronchodilator and Pre Dose) FEV1 on Day 29

Statistical Analysis Overview	Comparison Groups	Placebo, GW642444M 3 µg OD
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other [Least squares mean difference]
	Estimated Value	0.092
	Confidence Interval	(2-Sided) 95% 0.039 to 0.144
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Mean Change From Baseline in Trough (Pre Bronchodilator and Pre Dose) FEV1 on Day 29

Statistical Analysis Overview	Comparison Groups	Placebo, GW642444M 6.25 µg OD
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other [Least squares mean difference]
	Estimated Value	0.098
	Confidence Interval	(2-Sided) 95% 0.046 to 0.150

	Estimation Comments	[Not specified]

Statistical Analysis 3 for Mean Change From Baseline in Trough (Pre Bronchodilator and Pre Dose) FEV1 on Day 29

Statistical Analysis Overview	Comparison Groups	Placebo, GW642444M 12.5 µg OD
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other [Least squares mean difference]
	Estimated Value	0.110
	Confidence Interval	(2-Sided) 95% 0.057 to 0.162
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Mean Change From Baseline in Trough (Pre Bronchodilator and Pre Dose) FEV1 on Day 29

Statistical Analysis Overview	Comparison Groups	Placebo, GW642444M 25 µg OD
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other [Least squares mean difference]
	Estimated Value	0.137

	Confidence Interval	(2-Sided) 95% 0.085 to 0.190
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Mean Change From Baseline in Trough (Pre Bronchodilator and Pre Dose) FEV1 on Day 29

Statistical Analysis Overview	Comparison Groups	Placebo, GW642444M 50 µg OD
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Least squares mean difference]
	Estimated Value	0.165
	Confidence Interval	(2-Sided) 95% 0.112 to 0.217
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Time-adjusted Area Under the Curve (AUC) (i.e. Weighted Mean Change From Baseline) for 24 Hour Serial FEV1 on Days 1 and 28
Measure Description	Weighted mean was derived by calculating the AUC, and then dividing by the relevant time interval. The weighted mean change from Baseline was calculated as the weighted mean of the 24 hour serial FEV1 measures on Day 1 and Day 28 minus the Baseline value. Serial FEV1 measurements were taken on Day 1 and Day 28 (post-dose FEV1 after 5, 15, 30 minutes and 1, 2, 4, 8, 12, 23 and 24 hours). AUC was calculated only when there was at least 3 non-missing values between 0 and 24 hours and must have a value at 23 or 24 hours. Analysis performed used a repeated measures model with covariates of treatment, baseline, sex, age, smoking status (at Screening), reversibility stratum, Day (nominal), day by Baseline, and day by treatment interactions.
Time Frame	Baseline to Day 28
Safety Issue?	No

Analysis Population Description

ITT Population. The number of participants presented represents those with data available at either of time points being presented. The numbers given in the category titles represent the number of participants with data available at the time point given.

Reporting Groups

	Description
Placebo	Participants received placebo (1 actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 3 µg OD	Participants received GW642444M 3 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 6.25 µg OD	Participants received GW642444M 6.25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 12.5 µg OD	Participants received GW642444M 12.5 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 25 µg OD	Participants received GW642444M 25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 50 µg OD	Participants received GW642444M 50 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.

Measured Values

	Placebo	GW642444M 3 µg OD	GW642444M 6.25 µg OD	GW642444M 12.5 µg OD	GW642444M 25 µg OD	GW642444M 50 µg OD
Number of Participants Analyzed	101	99	100	99	99	99
Time-adjusted Area Under the Curve (AUC) (i.e. Weighted Mean Change From Baseline) for 24 Hour Serial FEV1 on Days 1 and 28 [units: Liters] Least Squares Mean (Standard Error)						
Day 1, n=100, 97, 100, 99	0.028 (0.0135)	0.085 (0.0137)	0.132 (0.0135)	0.149 (0.0136)	0.178 (0.0136)	0.202 (0.0137)
Day 28, n=84, 88, 91, 92	0.010 (0.0189)	0.114 (0.0187)	0.135 (0.0185)	0.152 (0.0185)	0.168 (0.0185)	0.186 (0.0186)

3. Secondary Outcome Measure:

Measure Title	Time to >= 12% Increase From Baseline in FEV1 (0-4 Hours Post-dose)
Measure Description	Forced expiratory volume in one second (FEV1) is a measure of lung function defined as the maximal amount of air that can be forcibly exhaled from the lungs in one second. Time until participants achieved a >=12% increase from Baseline FEV1 (0-4 hours post-dose) are presented. Baseline FEV1 is defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1. If one of these two assessments was missing then Baseline is defined as the single pre-dose FEV1 on Day 1.Time to >= 12% increase from Baseline (on Day 1) is defined as the time when the first post-dose FEV1 (on Day 1) is >=12% above Baseline FEV1. Time to >= 12% increase from Baseline was assessed over the 0-4 hour time period and only used lung function data recorded up to 6 hours post the Day 1 dose.
Time Frame	Baseline and Day 1
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received placebo (1 actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 3 µg OD	Participants received GW642444M 3 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 6.25 µg OD	Participants received GW642444M 6.25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 12.5 µg OD	Participants received GW642444M 12.5 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 25 µg OD	Participants received GW642444M 25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 50 µg OD	Participants received GW642444M 50 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.

Measured Values

	Placebo	GW642444M 3 µg OD	GW642444M 6.25 µg OD	GW642444M 12.5 µg OD	GW642444M 25 µg OD	GW642444M 50 µg OD
Number of Participants Analyzed	101	99	101	100	100	99
Time to >= 12% Increase From Baseline in FEV1 (0-4 Hours Post-dose) [units: Minutes] Median (Full Range)	NA (5 to 240) [1]	120 (5 to 240)	30 (5 to 240)	30 (5 to 240)	18 (5 to 240)	16 (5 to 240)

[1] > 50% of subjects were censored; therefore, the median could not be calculated.

4. Secondary Outcome Measure:

Measure Title	Time to >= 100 Milliliter (mL) Increase From Baseline in FEV1 (0-4 Hours Post-dose)
Measure Description	Pulmonary function was measured by forced expiratory volume in one second (FEV1), defined as the maximal amount of air that can be forcibly exhaled from the lungs in one second. Time until participants achieve >=100 mL increase from Baseline FEV1 (0-4 hours post-dose) are presented. Baseline FEV1 is defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1. Time to >= 100mL increase from Baseline (on Day 1) is defined as the time until the first post-dose FEV1 (on Day 1) is >= 100mL above Baseline FEV1. Time to >= 100mL increase from Baseline (on Day 1) was calculated only if there was at least one non-missing FEV1 value recorded within the first hour of dosing. Time to >= 100mL increase from Baseline was assessed over the 0-4 time period and only used lung function data recorded up to 6 hours post the Day 1 dose. Participants who did not achieve >= 100mL increase from Baseline over this time period were censored.
Time Frame	Baseline and Day 1
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Placebo	Participants received placebo (1 actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 3 µg OD	Participants received GW642444M 3 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.

	Description
GW642444M 6.25 µg OD	Participants received GW642444M 6.25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 12.5 µg OD	Participants received GW642444M 12.5 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 25 µg OD	Participants received GW642444M 25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 50 µg OD	Participants received GW642444M 50 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.

Measured Values

	Placebo	GW642444M 3 µg OD	GW642444M 6.25 µg OD	GW642444M 12.5 µg OD	GW642444M 25 µg OD	GW642444M 50 µg OD
Number of Participants Analyzed	101	99	101	100	100	99
Time to >= 100 Milliliter (mL) Increase From Baseline in FEV1 (0-4 Hours Post-dose) [units: Minutes] Median (Full Range)	NA (5 to 240) [1]	32 (5 to 240)	16 (5 to 240)	16 (5 to 240)	6 (5 to 240)	6 (5 to 240)

[1] > 50% of subjects were censored; therefore, the median could not be calculated.

Reported Adverse Events

Time Frame	Serious adverse events (SAEs) and non-serious AEs were collected from the start of study medication to the end of the the treatment period (up to Day 28).
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.

Reporting Groups

	Description
Placebo	Participants received placebo (1 actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 3 µg OD	Participants received GW642444M 3 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 6.25 µg OD	Participants received GW642444M 6.25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 12.5 µg OD	Participants received GW642444M 12.5 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 25 µg OD	Participants received GW642444M 25 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.
GW642444M 50 µg OD	Participants received GW642444M 50 µg (one actuation) OD in the morning from the novel dual strip dry powder inhaler for 28 days. In addition, participants were provided supplemental salbutamol (MDI and/or nebules) inhalation to be used as needed throughout the study.

Serious Adverse Events

	Placebo	GW642444M 3 µg OD	GW642444M 6.25 µg OD	GW642444M 12.5 µg OD	GW642444M 25 µg OD	GW642444M 50 µg OD
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Total	0/101 (0%)	1/99 (1.01%)	1/101 (0.99%)	2/101 (1.98%)	0/101 (0%)	0/99 (0%)
Cardiac disorders						
Atrial fibrillation [A] †	0/101 (0%)	0/99 (0%)	0/101 (0%)	1/101 (0.99%)	0/101 (0%)	0/99 (0%)
Infections and infestations						
Pneumonia [A] †	0/101 (0%)	0/99 (0%)	0/101 (0%)	1/101 (0.99%)	0/101 (0%)	0/99 (0%)
Nervous system disorders						
Syncope vasovagal [A] †	0/101 (0%)	1/99 (1.01%)	0/101 (0%)	0/101 (0%)	0/101 (0%)	0/99 (0%)
Respiratory, thoracic and mediastinal disorders						

	Placebo	GW642444M 3 µg OD	GW642444M 6.25 µg OD	GW642444M 12.5 µg OD	GW642444M 25 µg OD	GW642444M 50 µg OD
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Chronic obstructive pulmonary disease [A] †	0/101 (0%)	0/99 (0%)	0/101 (0%)	1/101 (0.99%)	0/101 (0%)	0/99 (0%)
Vascular disorders						
Aortic aneurysm [A] †	0/101 (0%)	0/99 (0%)	1/101 (0.99%)	0/101 (0%)	0/101 (0%)	0/99 (0%)

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

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 3%

	Placebo	GW642444M 3 µg OD	GW642444M 6.25 µg OD	GW642444M 12.5 µg OD	GW642444M 25 µg OD	GW642444M 50 µg OD
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Total	15/101 (14.85%)	9/99 (9.09%)	14/101 (13.86%)	5/101 (4.95%)	5/101 (4.95%)	10/99 (10.1%)
Cardiac disorders						
Ventricular extrasystoles [A] †	2/101 (1.98%)	0/99 (0%)	1/101 (0.99%)	0/101 (0%)	0/101 (0%)	3/99 (3.03%)
Gastrointestinal disorders						
Nausea [A] †	4/101 (3.96%)	1/99 (1.01%)	3/101 (2.97%)	2/101 (1.98%)	2/101 (1.98%)	1/99 (1.01%)
Infections and infestations						
Nasopharyngitis [A] †	3/101 (2.97%)	2/99 (2.02%)	5/101 (4.95%)	0/101 (0%)	1/101 (0.99%)	0/99 (0%)
Nervous system disorders						
Headache [A] †	10/101 (9.9%)	6/99 (6.06%)	5/101 (4.95%)	3/101 (2.97%)	3/101 (2.97%)	7/99 (7.07%)

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

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

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

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

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.

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