24h duration of the novel long-acting inhaled beta2 agonist vilanterol trifenatate in asthma patients treated with inhaled corticosteroids

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Online Data Supplement

Appendix 1: **Inclusion/Exclusion Criteria**

Inclusion Criteria

Patients eligible for enrolment in the study had to meet all of the following criteria:

1. Patients were ≥12 years of age at Visit 1. In Germany, the Russian Federation and South Africa, where local regulations or the regulatory status of study medication permitted enrolment of adults only, patients recruited were ≥18 years of age. In Chile, patients recruited by one centre were >15 years of age; patients recruited by another centre were >18 years of age.
2. Patients were male or eligible female. A urine pregnancy test was performed for all female patients prior to study participation. To be eligible for entry into the study, females of childbearing potential had to commit to the consistent and correct use of an acceptable method of birth control: commit to complete abstinence from intercourse from screening until 2 weeks after the follow-up contact, sterile sole partner prior to the patient's entry into the study, implants of levonorgestral, injectable progestogen, oral contraceptives (combined or progestogen only), double barrier method, intrauterine or vaginal devices or systems, or percutaneous contraceptive patches. Female patients were not enrolled if they were pregnant, lactating, or planned to become pregnant during the time of study participation. Females of non-child bearing potential, including females who were post-menopausal, were eligible.
3. Patients had a documented history of persistent asthma that was defined by the National Institute of Health. Their condition had to be first diagnosed at least 6 months prior to Visit 1.

4. Patients had reversible airways disease as demonstrated at screening Visit 1 by an increase in forced expiratory volume in 1 second (FEV_1) of ≥12% and ≥200 mL over the pre-salbutamol FEV_1 at approximately 30 minutes after the inhalation of 400 µg of salbutamol via metered dose inhaler (MDI) or one nebulised salbutamol solution. If a patient did not meet the inclusion criteria based upon FEV_1 percent predicted and/or reversibility, he/she was allowed to return once within 4 days to repeat the lung function tests.
5. Patients had to use inhaled corticosteroids (ICS) and had to have been maintained on a stable dose for 4 weeks prior to Visit 1.
6. Patients had a pre-bronchodilator FEV_1 between ≥40 and ≤90% predicted at Visit 1, as calculated using NHANES III.
7. Patients provided an appropriately signed and dated informed consent.
8. Patients were capable of withholding salbutamol use for ≥6 hours prior to clinic visits.
9. In France, patients were eligible for inclusion in the study only if they were either affiliated to or a beneficiary of a social security category.

Exclusion Criteria

Patients meeting any of the following criteria were not enrolled in the study:

1. Patients with an exacerbation of asthma within 4 weeks of Visit 1, or a culture documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear within 4 weeks of Visit 1 that led to a change in asthma management, or affected the patients asthma status or the patients ability to participate in the study (as judged by the investigator).

2. Patients with a history of life-threatening asthma.
3. Patients with an asthma exacerbation requiring treatment with oral corticosteroids within 3 months prior to Visit 1.
4. Patients who were hospitalised for an asthma exacerbation within 6 months of Visit 1.
5. Patients who had participated in any study using an investigational drug during the previous 30 days or participated simultaneously in another clinical trial.
6. Patients with any clinically significant, uncontrolled condition or disease state that would put the patient's safety at risk through study participation or would confound the interpretation of the efficacy results if the condition/disease exacerbated during the study.
7. Patients with any adverse reaction including immediate or delayed hypersensitivity to any $beta_2$ agonist or sympathomimetic drug, or known (i.e. severe milk protein allergy) or suspected sensitivity to the constituents of GW642444M inhalation powder (e.g. lactose or magnesium stearate).
8. Patients who were likely to be non-compliant with study medication and other study-related requirements (e.g. attendance at clinic visits or completion of the daily eDiary).
9. Patients with a neurological or psychiatric disease or history of drug or alcohol abuse which would interfere with the patients' proper completion of the protocol requirements.
10. Patients who were current smokers or had a smoking history of 10 pack years or more (e.g. 20 cigarettes/day for 10 years). Patients were not allowed to have used tobacco products within the one year prior to the study.

11. Patients administered systemic, oral or depot corticosteroids or administration of anti-IgE (e.g. omalizumab [Xolair]) within 12 weeks of Visit 1.
12. Patients administered any of the asthma medications theophyllines, oral $beta_2$ agonists (e.g. bambuterol), slow-release bronchodilators, short- or long-acting anticholinergics, oral leukotriene receptor antagonists (e.g. montelukast), inhaled sodium cromoglicate, or inhaled nedocromil sodium within 14 days of Visit 1.
13. Patients administered inhaled long-acting $beta_2$ agonists (LABAs [e.g. salmeterol]) within 7 days of Visit 1.
14. Patients administered any other prescription or over the counter medication which could affect the course of asthma or interact with sympathomimetic amines, such as: anticonvulsants (barbiturates, hydantoins, and carbamazepine); polycyclic antidepressants; beta-adrenergic blocking agents; phenothiazines and monoamine oxidase (MAO) inhibitors.
15. Patients administered a potent P-glycoprotein inhibitor or potent Cytochrome P450 3A4 inhibitor within 4 weeks prior to Visit 1 (e.g. ritonavir and ketoconazole).
16. Patients who were immediate family members of the participating investigator, sub-investigator, study co-ordinator, or employees of the participating investigator.

Appendix 2: **Full Methodological Details**

Methods

Setting

A randomised, double-blind, placebo-controlled, parallel group, dose-ranging study conducted at 88 centres in 16 countries (GSK study number B2C109575; www.clinicaltrials.gov registration number NCT00600171). The study started in December 2007 and ended September 2008.

Patients

Eligible patients were aged ≥12 years with a documented history of asthma [1] first diagnosed at least 6 months prior to screening, with reversibility to salbutamol (400 µg; increase in baseline FEV_1 of ≥12% and ≥200 mL), pre-bronchodilator FEV_1 of between ≥40% and ≤90% of the predicted value [2], and maintained on a stable dose of an ICS for ≥4 weeks prior to screening. Full inclusion and exclusion criteria are described in Appendix 1 (online data supplement).

The study was approved by local ethics review committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave written informed consent.

Interventions

After a 14-day run-in period, patients were randomly assigned to receive one of six treatments (VI 3 µg, 6.25 µg, 12.5 µg, 25 µg or 50 µg, or placebo), administered once daily

for 28 days via a novel, single-step activation dry powder inhaler developed by GlaxoSmithKline; dosing occurred in the evening. The follow-up period was 7 days. Trained clinic personnel observed administration of study treatment on Days 1, 7, 14 and 28, and on these days, treatment adherence for the period was assessed by recording the number of doses remaining in each inhaler. Patients continued on their maintenance ICS throughout the study. Short-acting $beta_2$ agonists (replaced by rescue salbutamol metered-dose inhalers at screening) were permitted throughout the study, but were required to be withheld for 6 hours prior to and during clinic visits, if possible. Prohibited medications were: *Within 7 days of Visit 1*: LABAs, ICSs and LABA combination products; *Within 14 days of Visit 1*: theophyllines, oral $beta_2$ agonists, slow-release bronchodilators, anticholinergics, short- or long-acting, oral leukotriene receptor antagonists, inhaled sodium cromoglicate, inhaled nedocromil sodium; *Within 4 weeks of Visit 1*: potent P-glycoprotein inhibitors, potent Cytochrome P 3A4 inhibitors; *Within 12 weeks of Visit 1*: systemic, oral, parenteral or depot corticosteroids, anti-IgE therapy; *In addition*: a patient was not concurrently allowed to use any other prescription or over-the-counter medication which could affect the course of asthma, or interact with sympathomimetic amines throughout the study (Visit 1 to Visit 6 inclusive), such as anticonvulsants, polycyclic antidepressants, beta-adrenergic blocking agents, phenothiazines, and MAO inhibitors.

After randomisation, patients visited the clinic on Days 1, 7, 14, and 28 for FEV_1 measurements. Clinic visits on Days 1 and 28 occurred over two days; in selected (66%) centres, patients remained overnight, while in others patients returned to the clinic mid-morning on Days 2 and 29. On Days 1 and 28, serial measurements FEV_1 were made pre-dose, at 15 and 30 minutes, and at 1, 2, 3, 4, 6, 12, 16, 20, 22, 23, and 24 hours post-dose (6 and 12 hour post-dose data were only available for patients who remained in the clinic

overnight). Morning and evening peak expiratory flow (PEF), day-time and night-time asthma symptom scores, and number of inhalations of rescue medication during the day and night were recorded in the electronic daily eDiary from screening to end of follow-up.

Following completion of the serial 24-hour FEV_1 measurements at Visit 2 and Visit 5, post salbutamol FEV_1 was measured. The patient was administered a single 400 µg dose of inhaled salbutamol via MDI or 1 dose of nebulised salbutamol solution and FEV_1 was measured 30 minutes after this administration. The highest of three technically acceptable measurements was recorded. These assessments were performed as follows: between 5PM and 10PM; ≥6 hours after the last use of salbutamol (compliance with this was recorded in the spirometry equipment); ≥6 hours after the last caffeine consumption; ≥2 hours after exercise (or strenuous activity); ≥24 hours after the first dose (Visit 2) or last dose (Visit 5) of study medication; and for Visit 2/2A only, before the dose of study medication was taken on treatment Day 2.

Randomisation and Masking

The central randomisation schedule was generated by GlaxoSmithKline using RandAll, a web server-based, clinical trials randomisation system. Patients were randomised centrally using Registration and Medication Ordering System (RAMOS), an automated, interactive telephone based system which was used by the investigator or designee to register the patient, randomise the patient and receive medication assignment information. Prior to randomisation, patients were stratified by baseline % predicted FEV_1 (≥40% to ≤65% and >65% to ≤90%) in an approximately 1:1 ratio prior to randomisation. Within each stratum, allocation was centralised, with a block size of 6.

This was a double-blind study. Neither the patient nor the investigator knew which study medication the subject was receiving. The placebo dry powder formulation was indistinguishable from the GW642444M formulation. The investigator or treating physician was able to unblind a patient's treatment assignment only in the case of an emergency, when knowledge of the study treatment was essential for the appropriate clinical management or welfare of the patient. Furthermore, GSK's Global Clinical Safety and Pharmacovigilance staff could unblind the treatment assignment for any patient with a serious adverse event (SAE).

Outcome Measurements

The primary efficacy endpoint was change from baseline in trough FEV_1 at the end of the 28-day treatment period. Trough FEV_1 was defined as the mean of the evening pre-bronchodilator FEV_1 values obtained 23 and 24 hours after dosing on Day 28.

Secondary endpoints were: change from baseline in weighted mean 24-hour serial FEV_1 on Days 1 and 28; change from baseline in daily morning and evening PEF averaged over Days 1–28; change from baseline in percentage of symptom-free and rescue-free 24-hour periods during the 28-day treatment period; and difference in post-salbutamolFEV_1 between 24 hours after dosing on Days 1 and 28, between screening and 24 hours after dosing on Day 1; and between screening and 24 hours after dosing on Day 28.

The proportion of patients obtaining both ≥200 mL and ≥12% increase from baseline in FEV_1 was calculated over 0–24 hours on Days 1 and 28. The change over 0–4 hours was an 'other' endpoint, while the change after 4 hours to 24 hours was a post-hoc analysis.

Safety Evaluation

Safety was assessed by monitoring AEs, SAEs, clinical laboratory tests (haematology, chemistry, and urinalysis), vital signs (pulse rate, and systolic and diastolic blood pressure), 12-lead electrocardiogram, and potassium and glucose levels. Worsening of asthma and exacerbations were monitored. AEs were coded using the Medical Dictionary for Regulatory Activities.

Statistical Analysis

All reported efficacy analyses were prespecified in the intent-to-treat (ITT) population. Power calculations suggested 594 patients (99 per treatment group) would be needed to detect a dose-response effect of 200 mL improvement in FEV_1 per 50 µg of VI, assuming a standard deviation of 430 mL (GlaxoSmithKline, data on file). Based on these assumptions it was estimated that the study had 97% power at a two-sided α level of 0.05.

The primary analyses were performed using SAS software version 8.2 or higher (SAS Institute Inc., Cary, NC, USA) in a step-wise approach to control the overall Type I error. Firstly, a dose-response test at Day 28 was performed. If the dose-response test was statistically significant, pair-wise testing of each dose of VI *versus* placebo was performed. The primary analyses were performed using an ANCOVA model adjusted for baseline FEV_1, country amalgamation, age, sex, baseline % predicted FEV_1 stratum and dose/treatment group, imputing missing data using a last observation carried forward approach (for patients

with missing Day 28 data the preceding non-missing trough FEV_1 value was used, but not those prior to Day 7 pre-dose). The primary analyses were also performed on the per-protocol (PP) population.

Strata analyses of trough FEV_1: the primary endpoint of change from baseline in trough FEV_1 at the end of treatment was analyzed for each percent predicted FEV_1 strata separately, in order to investigate the consistency of the dose-response relationship for the different disease severities. An ANCOVA model with effects due to baseline trough FEV_1, country amalgamation, age, sex and dose was used to estimate the dose response slope for each baseline percent predicted FEV_1 stratum. An ANCOVA model with effects due to baseline trough FEV_1, country amalgamation, age, sex, stratum, treatment group and treatment group-by-stratum interaction was used to estimate the treatment differences for all pair wise comparisons for each stratum. Statistical significance testing was not performed for the strata analyses.

0-24 hours weighted mean serial FEV_1: the 24-hour serial FEV_1 was measured on Days 1 and 28 (pre-dose, and 15, 30, and 60 minutes and 2, 3, 4, 6, 12, 16, 20, 22, 23, and 24 hour post-dose), with the 6 and 12 hour time points only measured in a subgroup of patients. The change from baseline in weighted mean for 24-hour serial FEV_1 on Days 1 and 28 was compared using an ANCOVA model for each GW642444M group *versus* placebo.

PEF: For PEF-related endpoints, the baseline value was derived from the last 7 days of the daily eDiary prior to the randomisation of the patient.

Evening trough PEF: the change from baseline in daily trough (pre-dose and pre-rescue bronchodilator) evening PEF averaged over the 28-day treatment period was compared using an ANCOVA model for each GW642444M dose *versus* placebo, adjusted for baseline evening PEF, country amalgamation, age, sex, baseline % predicted FEV_1 stratum, and treatment group.

Morning PEF: the change from baseline in daily morning PEF averaged over the 28-day treatment period was compared using an ANCOVA model for each GW642444M dose *versus* placebo, adjusted for baseline AM PEF, country amalgamation, age, sex, baseline % predicted FEV_1 stratum, and treatment group.

Percentage of symptom- and rescue-free 24-hour periods: the change from baseline in the percentage of symptom-free 24-hour periods and rescue- free 24-hour periods over the 28-day treatment period was calculated for each patient. Baseline was derived from the last 7 days of the daily eDiary prior to randomisation of the patient. Comparisons were then made using an ANCOVA model of each GW642444M dose *versus* placebo, adjusted for baseline symptom-/rescue-free 24-hour periods, country amalgamation, age, sex, baseline % predicted FEV_1 stratum, and treatment group.

Baseline for response to salbutamol was the screening pre-salbutamol assessment. Response to salbutamol was assessed using an ANCOVA model adjusted for baseline, country amalgamation, age, sex, baseline % predicted FEV_1 stratum, and treatment group.

QTc interval was calculated by Fridericia formula (QTcF). Weighted mean (0–4 hours) QTcF and maximum change from baseline (0-4 hours) in QTcF were analyzed using an ANCOVA

model adjusted for baseline (pre-dose, Day 1) QTcF, country amalgamation, age, sex, baseline % predicted FEV_1 stratum, and treatment group.

Weighted mean (0–4 hours) glucose and potassium, maximum decrease from baseline (0–4 hours) in potassium, and maximum increase from baseline (0–4 hours) in glucose were analyzed using an ANCOVA model adjusted for baseline (pre-dose, Day 1) glucose/potassium, country amalgamation, age, sex, baseline % predicted FEV_1 stratum, and treatment group.

Countries enrolling less than 12 patients in total were pooled with other countries within a similar geographical region and these amalgamations were used whenever country was included in the analysis.

The ITT population comprised all patients who were randomised to treatment and who received at least one dose of study medication. Randomised patients were assumed to have received trial medication unless definitive evidence to the contrary existed. This constituted the primary population for all analyses of efficacy measures and safety measures. The PP population consisted of all patients in the ITT population who did not have any full protocol deviations. Protocol deviations could be either full or partial. Patients with only partial deviations were considered part of the PP population but from the date of their deviation onwards, their data were excluded. The decision to exclude a patient from the PP population was made prior to breaking the blind. The PP population was used for confirmatory analyses of the primary efficacy endpoint only.

Appendix 3: Additional Safety Data

Small differences in the incidence of values outside normal range for creatine phosphokinase were observed for VI compared with placebo. For glucose and potassium, differences *versus* placebo in the least squares mean of maximum change from baseline and weighted mean change from baseline (0–4 hours), did not exceed the predefined levels of clinically relevant concern (–0.3 mmol/l for potassium; 1.5 mmol/l for glucose). There were no statistically or clinically significant treatment differences in weighted mean or maximum change from baseline (0–4 hours) in QTcF for any treatment group, at any time point.

References

1. National Institutes of Health. Guidelines for the diagnosis and management of asthma (EPR-3) 2007. NHLBI, August; 2007. NIH publication no. 08-4051.

2. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; 159: 179–187.

APPENDIX TABLE 1. Response to salbutamol 24 hours after the day 1 and day 28 dose of VI. Plus-minus values are mean ± standard error

	Placebo n=102[#]	3 µg VI n=101[#]	6.25 µg VI n=101[#]	12.5 µg VI n=100[#]	25 µg VI n=101[#]	50 µg VI n=102[#]
Mean response, l (SD)						
Screening	2.77 (0.80)	2.78 (0.95)	2.81 (0.78)	2.79 (0.74)	2.67 (0.70)	2.70 (0.71)
Day 1	2.71 (0.86)	2.75 (0.95)	2.73 (0.80)	2.74 (0.80)	2.64 (0.75)	2.66 (0.70)
Day 28	2.64 (0.83)	2.81 (0.91)	2.80 (0.80)	2.69 (0.80)	2.58 (0.73)	2.63 (0.69)
Day 28 minus Day 1[¶]						
n	83	80	87	86	86	92
LS mean, mL	–39 ± 23	–35 ± 24	–12 ± 23	–17 ± 23	–62 ± 23	–49 ± 22
Active treatment minus placebo, mL		4	27	22	–23	–10
95% CI		–62, 69	–37, 91	–42, 87	–87, 41	–74, 54
p-Value		0.92	0.41	0.50	0.48	0.76
Day 1 minus screening[¶]						
n	97	97	98	99	96	98
LS mean, mL	–40 ± 28	8 ± 28	–61 ± 28	–29 ± 28	–20 ± 28	–60 ± 28
Active treatment minus placebo, mL		47	–21	11	20	–20
95% CI		–32, 126	–99, 57	–67, 89	–58, 98	–99, 58
p-Value		0.24	0.60	0.79	0.62	0.61
Day 28 minus screening[¶]						
n	84	80	89	86	88	93
LS mean, mL (SE)	–76 ± 31	–22 ± 31	–55 ± 30	–48 ± 30	–86 ± 30	–104 ± 29
Active treatment minus placebo, mL		55	21	29	–9	–27
95% CI		–32, 141	–62, 105	–56, 114	–93, 75	–111, 56
p-Value		0.22	0.62	0.51	0.83	0.52

CI: confidence interval; LS: least square; SE: standard error; SD: standard deviation; VI: vilanterol trifenatate. [#]: Patient numbers at screening; [¶]: analysis performed using ANCOVA with covariates of baseline (pre-salbutamol measurement at screening), country, sex, age, stratum, and treatment.

APPENDIX FIGURE 1. Proportion of patients experiencing ≥200 mL and ≥12% increase from baseline FEV_1, by treatment group, on Day 1 (A) and Day 28 (B).