

[Home](#) [Inspections, Compliance, Enforcement, and Criminal Investigations](#) [Enforcement Actions](#) [Warning Letters](#)

Inspections, Compliance, Enforcement, and Criminal Investigations

11/19/13



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

NOV 19, 2013

WARNING LETTER

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Ref: 13-HFD-45-11-01

Dear Dr. Samudrala:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between March 12 and March 28, 2013. Ms. Laura Staples and Ms. Bonnie Pierson, representing the FDA, reviewed your conduct of the following clinical investigations:

- Protocol HZC113782, "A Clinical Outcomes Study to Compare the Effect of Fluticasone Furoate/Vilanterol Inhalation Powder 100/25 mcg with Placebo on Survival in Subjects with Moderate Chronic Obstructive Pulmonary Disease (COPD) and a History of or at Increased Risk for Cardiovascular Disease", of the investigational drug fluticasone furoate, performed for GlaxoSmithKline
- Protocol **(b)(4)**, "**(b)(4)**", of the investigational drug **(b)(4)**, performed for **(b)(4)**.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Investigators Staples and Pierson presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your April 15, 2013, written response to the Form FDA 483.

From our review of the FDA establishment inspection report, the documents submitted with that report, and your April 15, 2013 written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

You failed to ensure that the investigation was conducted according to the investigational plan [21

CFR 312.60].

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol HZC113782 requires that you enroll subjects who meet specific inclusion criteria. You failed to adhere to these requirements. Specifically:

a. Protocol HZC113783 requires enrolled subjects to have a measured post-albuterol/salbutamol Forced Expiratory Volume in One Second (FEV₁)/Forced Vital Capacity (FVC) ratio of ≤ 0.70 at screening (Visit 1). However, 11 of 31 subjects enrolled at your site did not meet this enrollment criterion, as shown in Table 1 below.

Table 1. Enrolled subjects with post-albuterol/salbutamol FEV₁/FVC ratios > 0.70 at screening

Subject #	Screening Visit Date	FEV ₁ /FVC Ratios
300172	May 25, 2011	0.79 (best value)
300173	May 25, 2011	0.77 (best value)
300212	June 6, 2011	0.87 (best value)
300214	June 6, 2011	0.80 (best value)
300256	June 14, 2011	0.80 (best value)
300283	June 20, 2011	0.77 (best value)
300342	June 28, 2011	0.80 (best value)
300422	July 14, 2011	0.74 (best value)
300448	July 12, 2011	0.80 (best value)
300566	July 26, 2011	0.75 (best value)
300643	August 3, 2011	0.75 (best value)

b. Protocol HZC113783 requires enrolled subjects to have a measured post-albuterol/salbutamol FEV₁ $\geq 50\%$ and $\leq 0.70\%$ of predicted normal values calculated using the National Health and Nutrition Examination Survey (NHANES) III reference equations at screening (Visit 1). However, 4 of 31 subjects enrolled at your site did not meet this enrollment criterion, as shown in Table 2 below.

Table 2. Enrolled subjects without a post-albuterol/salbutamol FEV₁ $\geq 50\%$ and $\leq 70\%$ of predicted normal value at screening

Subject	Screening Visit Date	FEV ₁ Percentage(s) of Predicted Normal Value
300167	May 24, 2011	46%
300212	June 6, 2011	74%
300214	June 6, 2011	73%
300335	June 26, 2011	78%

c. Protocol #HZC113783 requires enrolled subjects 60 years of age or older to be under treatment for any 2 of the following conditions: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral vascular disease. Subject 300296 was 73 years of age at enrollment and was not being treated for any of the conditions listed above. In addition, Subject 300555 was 63 years of age at enrollment and was being treated for peripheral vascular disease only.

In your written response, you indicate that you have the following corrective action plan: "Investigators are required to sign a document prior to randomization that states that whether [sic] Inclusion/Exclusion Criteria have been met. All Investigators and study staff personnel were re-educated. A new spirometer was purchased to replace the spirometer that was inadequate for this study."

Your response is inadequate because it is insufficiently detailed with respect to your corrective action plan. You have not provided details regarding the document that investigators are required to sign, and you have not submitted a copy of that document. You also have not provided details or documentation regarding the re-education that took place. Without this information, we cannot assess whether these