CLINICAL STUDY REPORT SYNOPSIS

Name of Sponsor Company	*Name of Finished Product*	*Name of Active Ingredient*
Zambon		
Study Code		
Z7200K02		
Eudract Number		
2014-002151-26		

Title of the Study

A DOUBLE-BLIND, DOUBLE-DUMMY, RANDOMIZED, TWO-WAY CROSS-OVER STUDY TO COMPARE THE EFFECTS OF Z7200 AND SYMBICORT® TURBOHALER ON FUNCTIONAL RESPIRATORY IMAGING PARAMETERS IN ASTHMATIC PATIENTS

Principal Investigators and Study Sites

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Study Period	*Phase of Development*
1 September 2014 (first patient enrolled) to 28 November 2014 (last patient completed)	Phase II

Objectives

The primary objective of this study was to evaluate the effect of a single administration of Z7200 (at the strength of 80 µg/2.25 µg, test product) and Symbicort® (at the strength of 160 µg/4.5 µg, reference product) on functional respiratory imaging (FRI) parameters and to evaluate the particle deposition in the lungs using computational fluid dynamics (CFD).

The secondary objectives of this study were to assess the effect of test product and reference product on lung function (spirometry and body plethysmography), exercise capacity (6-Minute Walking Test [6MWT] or equivalent method to measure exercise tolerance), and dyspnea (Borg Category [C] Ratio [R] 10 [Borg CR10] scale and Visual Analogue Scale [VAS] dyspnea). Furthermore, the safety of the test product and reference product was evaluated through monitoring of adverse events (AEs) throughout the study.

Study Design and Methodology

This study was a randomized, double-blind, double-dummy, two-period cross-over study in stable asthma patients. A total of 20 stable asthma patients treated in accordance with the Global Initiative for Asthma (GINA) guidelines were planned to be included.

The study procedures were explained to the patients on the screening visit day (Visit 1). Patients who wanted to participate in the study were asked to sign the Informed Consent Form (ICF). Study procedures commenced only after the patient had signed the ICF.

On the first dosing day (Period 1, Visit 2), asthma stability was assessed based on review of pharmacologic and non-pharmacologic treatment monitoring. Patients were then randomized and allocated to one of 2 treatment sequences (i.e. test [Z7200]/reference [Symbicort® Turbohaler®] or reference/test). Patients were to receive a single dose consisting of 2 inhalations of either the test product or the reference product, according to the assigned treatment sequence, in the presence of the Investigator or authorized site personnel. In addition, patients were to receive 2 inhalations with matching placebo to the alternate treatment as a dummy inhaler to achieve double-blinding.

On the second dosing day (Period 2, Visit 3), patients were to receive a single dose consisting of 2 inhalations of the other treatment (reference in case test product was administered at Visit 2 and vice versa) plus 2 inhalations with matching placebo to the alternate treatment.

At predefined time points in the study, demographic data, medical/surgical history, and medication data were captured, physical examination, vital sign assessment, electrocardiogram (ECG), spirometry, body plethysmography, exercise test and high-resolution computed tomography (HRCT) were performed. The dyspnea scales Borg CR10 and VAS were completed before and after the exercise test. Adverse events were monitored and recorded throughout the study.

Patient Population

Number of patients planned: 20
Number of patients randomized: 20 (12 males/8 females)
Number of patients analyzed for safety (safety population): 20 (20 received Z7200 and 20 received Symbicort)
Number of patients analyzed for pharmacodynamics (per-protocol [PP] population): 20
Number of completers 20

All patients (100.0%) were white and 60.0% were male. The patients' mean (standard deviation []SD]) age was 58.5 (11.6) years and mean (SD) body mass index (BMI) was 26.67 (4.30) kg/m^2. Mean (SD) FEV_1 at screening was 96.79 (22.82) % predicted (%p) and mean (SD) FEV_1/FVC ratio was 67.35 (11.14) %.

Major protocol deviations were reported in 4 (20.0%) patients and were all related to the patient's respiratory belt data for inhalation maneuver being unusable. Minor protocol deviations were reported in 13 (65.0%) patients and were most often related to the predose vital sign assessment being performed outside of the protocol-specified window, i.e. postdose on the same day instead of predose.

Name of Sponsor Company **Zambon**	*Name of Finished Product*	*Name of Active Ingredient*
Study Code **Z7200K02**		
Eudract Number **2014-002151-26**		

Patient Population, Cont'd

None of the protocol deviations reported in this study were thought to have influenced the assessment of the product effect. Therefore, none of the patients were excluded from the PP population (defined as all patients who had correct study drug administration and who did not have any protocol deviations that could possibly have influenced the assessment of the product effect). The PP population thus consisted of 20 patients.

Eligibility Criteria

Inclusion criteria:

1. Male or female patient ≥18 years old;
2. Written informed consent obtained;
3. Patient had documented diagnosis of asthma;
4. Patient had a cooperative attitude and was able to correctly use the dry powder inhaler (DPI);
5. Female patient of childbearing potential was to confirm that she had been using a reliable method of contraception from at least 14 days before Visit 1 onwards and that she was willing to continue to use a reliable method of contraception during the study, or female patient was post-menopausal (at least 12 months of amenorrhea);
6. Patient's condition was stable and treated in accordance with the GINA guidelines;
7. Patient was a non-smoker or ex-smoker who had stopped smoking at least 1 month prior to Visit 1 and had a smoking history of less than 10 pack-years;
8. Patient was able to understand and complete the protocol requirements, instructions, questionnaires and protocol-stated restrictions.

Exclusion criteria:

1. Patient was pregnant or lactating;
2. Patient's condition was unstable; the patient developed an exacerbation of his/her condition in the 4 weeks before screening;
3. Patient had upper or lower airways infection in the 4 weeks before screening;
4. Patient was unable to withdraw fixed combination or long-acting bronchodilator inhalation products;
5. Patient was unable to perform pulmonary function testing;
6. Patient had an uncontrolled disease or any condition that could, in the judgment of the Investigator, place the patient at undue risk or potentially compromise the results or interpretation of the study;
7. Patient had active lung cancer or any other chronic disease with poor prognosis and/or affecting patient status;
8. Patient had allergy, sensitivity or intolerance to the study drugs and/or study drug formulation ingredients;
9. Patient was unlikely to comply with the protocol or unable to understand the nature, scope and possible consequences of the study;
10. Patient received systemic corticosteroids within 4 weeks prior to Visit 1;
11. Patient received an investigational new drug within 4 weeks prior to Visit 1 or participated in another clinical study;
12. Patient had a history of alcohol or substance abuse that, in the opinion of the Investigator, could be of clinical significance;
13. Patient had diagnosis of Chronic Obstructive Lung Disease (COPD);
14. Patient was lactose intolerant or had a history of allergy to milk proteins;
15. Patient was treated with medications or herbal medicines that are strong cytochrome P450 (CYP) 3A4 inhibitors or inducers within 2 weeks prior to Visit 1 and during the study.

Study Products

	Z7200	Symbicort
Dose (mg/inhalation)		
Budesonide	0.080	0.160
Formoterol fumarate dehydrate	0.00225	0.0045
Inhaler	RS-01 DPI	Turbohaler DPI
Batch number (Expiry date)	MS14FIB028BR10 (11/2014) (active) MS14FIB026BR4 (11/2014) (placebo)	SBWU (07/2015) (active) SBVY (07/2015*) (placebo)*

Name of Sponsor Company **Zambon**	*Name of Finished Product*	*Name of Active Ingredient*
Study Code **Z7200K02**		
Eudract Number **2014-002151-26**		

Study Products, Cont'd

The run-in period was 7 (minimum) to 31 (maximum) days. Patients were asked to return to the clinic on the agreed dosing day (Visit 2). There was a washout period of at least 3 days but not more than 31 days between Visit 2 and the second dosing day (Visit 3). Two to 21 days after Visit 3, patients were contacted by telephone for AE assessment and review of concomitant therapy (Visit 4). If there were no follow-up actions for a patient at this visit, study participation was considered completed for that particular patient.

Study Endpoints

The primary endpoints in the study were:

- total image-based airway volume (iVaw) and total image-based airway resistance (iRaw)
- the number of deposited particles per pre-defined airway section

Secondary endpoints were:

1. Spirometry parameters - Lung function:
   - Forced expiratory volume in one second (FEV_1)
   - Forced vital capacity (FVC)
   - Peak expiratory flow (PEF)
   - Maximum expiratory flow at 25% of FVC (MEF25)
   - Maximum expiratory flow at 50% of FVC (MEF50)
   - Tiffeneau index (FEV_1/FVC ratio)
2. Body plethysmography:
   - Functional residual capacity (FRC)
   - Total lung capacity (TLC)
   - Airway resistance: airway resistance (Raw), specific airway resistance (sRaw)
3. Inhalation profile with respiration belt: inspiration volume (IV)
4. Exercise capacity: 6MWT distance walked in 6 minutes (m) or an equivalent method to measure exercise tolerance
5. Borg CR10 Scale: measure of the present dyspnea
6. VAS: measure of the difference in dyspnea before and after treatment

(Note that endpoints 4, 5, and 6 were defined as 'Patient Feeling' parameters)

Safety endpoint was:

- incidences of AEs

Statistical Methods

Descriptive statistics were used to characterize the predose values at both dosing visits. For continuous parameters, descriptive statistics are presented when the number of non-missing data points is n≥2. Descriptive statistics include the number of non-missing data points, the arithmetic mean, SD and standard error (SE), the median, minimum and maximum.

Regarding the primary objective of this study, treatment effects on the different outcome parameters (except for dosimetry, VAS and inhalation profile) were assessed by comparing the data at predose and postdose using 2-sided paired t-test and Wilcoxon matched-pairs tests. The p-values of the 2-sided paired t-test and Wilcoxon matched-paired tests are reported without correction, after Benjamini-Hochberg correction (BH) to control the false discovery rate and after Holm-Bonferroni correction (Holm) to control the family-wise error rate. For every parameter and every hypothesis, N, mean, SD, median, min, max, uncorrected 90% confidence intervals (CI) in mean, p-values for a 2-sided paired t-test and p-values for a Wilcoxon matched-pairs test are given. Differences in effect size between the test and reference product were also assessed by comparing the difference between the postdose and predose values of test with the difference between the postdose and predose values of reference using the above mentioned tests. Any differences in postdose values between the test and reference product were also investigated.

In order to get more insights in the efficacy data, particle simulations were performed for both test product and reference product independently, using the product specific particle characteristics and patient and inhaler specific inhalation profiles.

No imputation for missing values was done.

Adverse event data were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 17.0). Adverse events were listed individually and summarized by MedDRA system organ class (SOC) and preferred term (PT). Safety data are summarized per treatment.

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SUMMARY

Pharmacodynamic Results

A statistically significant increase in total iVaw and a statistically significant decrease in total iRaw at postdose was observed for both the test and reference product, indicating the bronchodilating effect of both treatments. There were no statistically significant differences in treatment effect between the test and reference product for both total iVaw and total iRaw.

The results of the particle simulations show a higher number of particles deposited in the lung for both budesonide and formoterol with the test product in comparison to the reference product.

The results from the spirometry tests showed a statistically significant increase in FEV_1, Tiffeneau index, PEF, MEF25 and MEF50 after administration of both the test and reference product in comparison to predose, with no difference in change from predose between the two products.

Body plethysmography analysis revealed a statistically significant reduction in FRC postdose, but not a reduction in TLC for both products. Airway resistance also decreased after both treatments while the specific airway resistance only decreased after administration of the test product. No difference in treatment effects between the test and reference product was found for any of the body plethysmography parameters.

Regarding the inhalation profiles, slightly higher inhalation times were observed for the test product compared to the reference product, while analysis of the inhalation volumes revealed only a small difference between the test and reference product.

Concerning the parameters related to patient feeling, a statistically significant difference in value in favor of the test product was only observed for the VAS pre-6MWT value. For the other parameters related to patient feeling, no statistically significant difference was revealed in the postdose values or in changes from predose between the test and reference products, nor were any statistically significant differences detected between the values predose versus postdose.

An additional comparison of the imaging parameters change at a local level (central and distal) confirmed the findings obtained in the total region analysis, indicating an improvement in the lung function after the administration of the products, without any difference in treatment effect.

Safety Results

Analysis of AEs and other safety parameters indicated a similar and good safety profile for both test and reference product.

No deaths or other SAEs were reported during the study. Two (10.0%) patients were reported to each have one treatment-emergent AE (TEAE) during the study, i.e. headache and influenza-like illness, after Z7200 inhalation but the AEs were considered not to be related to the study drug by the Investigator. Neither of the TEAEs was severe in intensity or led to discontinuation of the study drug.

Changes in vital sign parameters over time were small and not clinically relevant.

Few abnormalities were seen during physical examination and none were indicated to be clinically relevant by the Investigator.

Conclusions

In this randomized, double-blind, two-period cross-over study in patients with asthma, a single dose of Z7200 (80 µg/2.25 µg, test product) was compared with a single dose of Symbicort Turbohaler (160 µg/4.5 µg, reference product).

Notably considering that the delivered dose of the test product was half of the delivered dose of the reference product, the results of the study show a similar bronchodilating effect of the test and reference product, with an observed comparable improvement in the lung function as demonstrated by the changes in the imaging parameters and spirometry test. The patient feeling did not change throughout the study, with the exception of the VAS pre-6MWT in favor of the test product. There was no difference in efficacy parameters between the two products; this confirms the expectations for Z7200: equal efficacy with a delivered dose that is half of the delivered dose of Symbicort. Simulation suggested a possible larger lung deposition of both budesonide and formoterol with Z7200; no consequences of this finding could be detected in this single dose study.

Finally, there were no safety concerns; the test product showed a similar and good safety profile compared to the reference product.

Version and Date of the Report

Final – 2 October 2015