CLINICAL TRIAL SUMMARY REPORT

EUDRACT NUMBER: 2010-018712-32

21 December 2011

A Pilot Pharmacodynamic/Pharmacokinetic Study of Salmeterol Xinofoate as a Dry Powder in Combination with Fluticasone in Patients with Asthma for Dose-Scale Bronchodilator Model Development

Protocol No:	OTT329/302
Development Phase:	Phase I/IIa
Investigational Product:	Advair® Diskus® 100/50 (fluticasone propionate 100 µg/ salmeterol xinofoate 50 µg)
Indication:	Asthma
Date of Admission of First Subject:	16 March 2010
Date of Follow-up of Last Subject:	30 October 2010
Sponsor Representative:	[redacted], PhD
Sponsor:	Oriel Therapeutics, Inc, a Sandoz Company Post Office Box 14087 Research Triangle Park, NC 27709 United States of America
Principal Investigator:	Darren Wilbraham MBBS, DCPSA
Investigating Site:	Quintiles Drug Research Unit at Guy's Hospital 6 Newcomen Street, London SE1 1YR United Kingdom Tel: 0207 910 7700 Fax: 0207 910 7800

This Clinical Trial was conducted, and essential study documentation archived, in compliance with International Conference on Harmonization Guidelines and Good Clinical Practice (ICH-GCP)

Name of Sponsor/Company: Oriel Therapeutics Inc, a Sandoz Company **Name of Finished Product:** Advair® Diskus® 100/50 **Name of Active Ingredient:** Fluticasone propionate/ salmeterol xinofoate	**Individual Study Table Referring to Part of the Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**

Title of Study:

A Pilot Pharmacodynamic/Pharmacokinetic Study of Salmeterol Xinofoate as a Dry Powder in Combination with Fluticasone in Patients with Asthma for Dose-Scale Bronchodilator Model Development

Investigator:
Darren Wilbraham MBBS, DCPSA

Study Center:
Quintiles Drug Research Unit at Guy's Hospital, Quintiles Ltd, 6 Newcomen Street, London SE1 1YR, United Kingdom

Publication (reference):
Not applicable

Study Period (years):		**Phase of Development:**
(Date of first enrollment)	16 March 2010	Phase I/IIa
(Date of last completed)	30 October 2010	

Objectives

Primary Objective:

To establish a model of dose-dependent bronchodilation that will be used to establish the pharmacodynamic equivalency of the long-acting beta adrenergic agonist (LABA) component of new combination asthma drug treatments. The intention to better characterize the time course of bronchodilation following a single treatment with 3 doses of Advair® 100/50 (1 puff, 2 puffs or 4 puffs, which is equivalent to 100/50, 200/100 and 400/200 µg fluticasone/salmeterol respectively).

Secondary Objective:

To investigate the effects of Advair® 100/50 (1 puff, 2 puffs or 4 puffs) on blood potassium and heart rate as potential pharmacodynamic markers. Also to measure the pharmacokinetics of salmeterol and fluticasone administered as a combination dry powder in this study to allow for pharmacokinetic/pharmacodynamic interrelationship. The pharmacokinetics of fluticasone

Name of Sponsor/Company: Oriel Therapeutics Inc, a Sandoz Company	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: Advair® Diskus® 100/50	**Volume:**	
Name of Active Ingredient: Fluticasone propionate/ salmeterol xinofoate	**Page:**	

were also to be measured to obtain data on the influence of co-administration of salmeterol on dose ranging fluticasone pharmacokinetics in the asthmatic population.

Methodology:

This was a single-center, single-dose, randomized, 3-period crossover study in patients with asthma. This exploratory pilot study investigated the pharmacodynamics (forced expiratory volume in 1 second [FEV_1], heart rate [HR] and blood potassium), pharmacokinetics and general safety of the salmeterol component of Advair® Diskus®, a combination drug for asthma, for the purposes of dose-scale model development. A single dose was administered by dry powder oral inhalation using Advair® Diskus® in each of 3 treatment periods. One, 2 and 4 puffs of 1 dosage strength of Advair® (100/50 µg) were administered via the Diskus® device in a randomized order. Lung function (including FEV_1, peak expiratory flow [PEF] and forced vital capacity [FVC]) were monitored frequently over 24 hours and blood samples for pharmacokinetic determination were taken. Heart rate was also monitored as a pharmacodynamic endpoint periodically up to 24 hours. Blood potassium was sampled at pre-defined time points from prior to each dose until 24 hours after each dose. Subjects were discharged from the clinic approximately 24 hours after the single dose (after last lung function assessment and pharmacokinetic blood draw). At the end of the study, all subjects were to be contacted by the clinic via telephone approximately 5 to 7 days after last dose for a safety follow-up.

Number of subjects (planned and analyzed):

It was anticipated that up to 30 subjects would be recruited to ensure a minimum of 24 complete datasets. A total of 22 subjects were enrolled and 21 completed the study per protocol, which was considered sufficient to achieve the objectives of the study.

Diagnosis and main criteria for inclusion:

Diagnosis:

Patients with asthma and compromised lung function (≥50% predicted).

Criteria for Inclusion:

1. Adult males and females ≥18 years with body mass index (BMI) 19 to 32 kg/m^2 (inclusive)

Name of Sponsor/Company: Oriel Therapeutics Inc, a Sandoz Company	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: Advair® Diskus® 100/50	**Volume:**	
Name of Active Ingredient: Fluticasone propionate/ salmeterol xinofoate	**Page:**	

and a body weight ≥50 kg.

2. Subjects with a clinical diagnosis of mild to moderate asthma (defined as satisfying the Global Initiative in Asthma [GINA] definition of asthma or has satisfied in the past and have a pre-bronchodilator FEV_1 >50% at screening. Note that subjects who had been intubated for ventilation in the past 5 years or were considered to have very severe asthma were excluded from the study.
3. Subjects demonstrating ≥15% reversibility (and a ≥200 mL difference) from prebronchodilator FEV_1 within 15 to 30 minutes of receiving up to 400 µg salbutamol by metered-dose inhaler (MDI) with spacer or up to 5 mg salbutamol by nebulizer at screening.
4. Subjects who if female, were not currently pregnant or breast feeding and were using medically acceptable methods of contraception.
5. Subjects whose clinical laboratory test results were not clinically relevant and were acceptable to the Investigator.
6. Subjects who were negative for hepatitis B surface antigen (HBsAg), hepatitis C antibody and human immunodeficiency virus (HIV) I and II test at screening.
7. Subjects who were negative for drugs of abuse and alcohol tests at screening and admission.
8. Subjects who were non-smokers for at least 3 months prior to screening.
9. Subjects with a <10 pack-year smoking history.
10. Subjects who were able and willing to give written informed consent.
11. Subjects who were able to use an inhaled medical device, as demonstrated by the use of a flow loop assessment.
12. Medical history was verified by either a personal physician or medical practitioner as appropriate.

Inhaled short-acting beta adrenoceptor stimulants (e.g. salbutamol) were to be withheld for at least 6 hours prior to dosing. All long-acting beta adrenoceptor stimulants (e.g. salmeterol)

Name of Sponsor/Company: Oriel Therapeutics Inc, a Sandoz Company	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: Advair® Diskus® 100/50	**Volume:**	
Name of Active Ingredient: Fluticasone propionate/ salmeterol xinofoate	**Page:**	

and all other bronchodilators (e.g. theophylline) were to be withheld for 1 week prior to dosing. Subjects were permitted to continue normal treatment with inhaled corticosteroids, anti-leukotrienes and antihistamines, at a constant dose, throughout the study.

Criteria for exclusion:

1. Subjects who did not conform to the above inclusion criteria.
2. Subjects with a clinically relevant history or presence gastrointestinal, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, dermatological, connective tissue diseases or disorders which would preclude participation in the opinion of the Investigator.
3. Subjects with a clinically relevant medical or surgical history that would preclude the administration of inhaled corticosteroids as indicated in the patient information leaflet for Seretide® Accuhaler® or Advair® Diskus®.
4. Subjects with a QTc of >500 ms.
5. Subjects with a history of relevant drug hypersensitivity.
6. Subjects with a history of alcoholism.
7. Subjects with a history of drug abuse.
8. Subjects receiving oral or parenteral corticosteroid treatment within 4 weeks of randomization for exacerbation of their asthma or who have been intubated for ventilation in the past 5 years or are considered to have very severe asthma.
9. Subjects taking inhibitors of Cytochrome P450 3A4 (CYP3A4) such as ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, or telethromycin.
10. Subjects consuming more than 28 units (male)/ 21 units (female) of alcohol a week. Unit = 1 (125 mL) glass of wine = 1 measure of spirits = ½ pint of beer.
11. Subjects with a significant infection or known inflammatory process on screening.
12. Subjects with acute gastrointestinal symptoms at the time of screening and/or

Name of Sponsor/Company: Oriel Therapeutics Inc, a Sandoz Company	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: Advair® Diskus® 100/50	**Volume:**	
Name of Active Ingredient: Fluticasone propionate/ salmeterol xinofoate	**Page:**	

admission (e.g. nausea, vomiting, diarrhea, heartburn).

13. Subjects with an acute respiratory infection such as influenza at the time of screening and/or admission.
14. Female subjects who were pregnant, trying to become pregnant, breast feeding, or not using an acceptable method of contraception.
15. Subjects who had used any investigational drug in any clinical trial within 3 months of receiving the last dose.
16. Subjects who have received the last dose of investigational medicinal product (IMP) greater than 3 months ago but who were on extended follow-up requiring blood sampling.
17. Subjects using medication, which in the opinion of the Investigator would affect the outcome of the study.
18. Subjects who had donated and/or received any blood or blood products within the 3 months prior to first dosing (reviewed on a case by case basis).
19. Subjects who could not communicate reliably with the Investigator.
20. Subjects who were unlikely to co-operate with the requirements of the study.

Test product, dose and mode of administration, batch number:
Advair® Diskus® 100/50: fluticasone 100 µg/puff, salmeterol 50 µg/puff (1, 2 or 4 puffs) administered as a dry powder by oral inhalation (lot number 9ZP6113).

Reference product, dose and mode of administration, batch number:
Not applicable.

Duration of treatment:
Single dose followed for 24 hours in the clinical unit in each of 3 treatment periods.

Bioanalytical method:
Plasma samples were analyzed for fluticasone and salmeterol concentration at Tandem Labs (Salt Lake City, UT, USA) using LC/MS/MS methods with a quantitative range from 1.00 to 200 pg/mL for both analytes.

Name of Sponsor/Company: Oriel Therapeutics Inc, a Sandoz Company	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: Advair® Diskus® 100/50	**Volume:**	
Name of Active Ingredient: Fluticasone propionate/ salmeterol xinofoate	**Page:**	

Criteria for evaluation

Pharmacodynamics:

Lung function (FEV_1, FVC and PEF) were monitored up to 24 hours post-dose. Area under the FEV_1-time curve (expressed as % change from baseline, AUC-FEV_1) was the primary outcome derived from the dataset. In addition, maximum % and absolute change in FEV_1 from baseline (delta maximum FEV_1, delta max % FEV_1) were assessed. Other endpoints from the flow-volume loop, FVC and PEF, were also assessed and maximum percent change from baseline was calculated.

Heart rate was monitored as a pharmacodynamic endpoint using Lead II (2 leads) bedside monitoring. The following variables were assessed: area under the heart rate-time curve (expressed as change from baseline, AUC-HR, time 0-24 h), average change in HR (absolute) over time 0-24 h, maximum % change in HR from baseline over time 0-24 h.

Blood potassium was sampled at predefined time points up to 24 hours after each dose. The following variables were assessed: average change in blood potassium (absolute) over time 0-24 h and maximum % change in blood potassium from baseline over time 0-24 h.

Pharmacokinetics:

Following the single dose, area under the salmeterol plasma concentration-time curve (AUC_{0-24}), peak observed salmeterol concentration (C_{max}) and time of C_{max} (T_{max}) were estimated. PK parameters were also assessed for fluticasone. Additionally pharmacokinetic parameters were estimated as necessary for development of the pharmacokinetic/pharmacodynamic relationship.

Safety:

The safety evaluation included heart rate and FEV_1 (analyzed as part of the pharmacodynamic evaluation), vital signs (blood pressure, pulse rate and body temperature) and the monitoring and recording of adverse events.

Name of Sponsor/Company: Oriel Therapeutics Inc, a Sandoz Company	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: Advair® Diskus® 100/50	**Volume:**	
Name of Active Ingredient: Fluticasone propionate/ salmeterol xinofoate	**Page:**	

Statistical methods

Pharmacodynamic parameters:

FEV_1 was measured at pre-defined time points up to 24 hours yielding a time/response curve expressed as % change from baseline.

AUC-FEV_1 was analyzed by analysis of covariance (ANCOVA) for the effect of dose (1, 2 or 4 puffs) as was FVC and PEF with screening/baseline lung function as the covariate. Heart rate was measured pre-dose and at several time points post-dose to yield a time/response curve expressed as change from baseline. AUCHR was analyzed by ANCOVA for the effect of dose with baseline heart rate as the covariate. All pharmacodynamic data was summarized by the number of subjects, arithmetic mean, standard deviation and coefficient of variation. Additional summary parameters were calculated as appropriate. Due to the exploratory pilot nature of this study, several interpretations of the effects of Advair® on FEV_1 and heart rate may be analyzed for the purposes of model development.

Pharmacokinetic parameters:

The pharmacokinetic analysis population consisted of all subjects that had sufficient plasma concentration data for pharmacokinetic analysis. Pharmacokinetic parameters for salmeterol and fluticasone after inhalation were estimated by non-compartmental pharmacokinetic analysis. Actual sampling times were used for the calculation of pharmacokinetic parameters. All the below limit of quantification (BLQ) values were set to zero, with the exception that any BLQ value between 2 positive concentrations was set as missing. Missing concentrations were excluded from the calculation of descriptive statistics. Plasma concentrations and plasma pharmacokinetic parameters were listed and summarized using descriptive statistics. The plasma concentration data and the pharmacokinetic parameters were summarized by the number of subjects, arithmetic mean, standard deviation, median, minimum, maximum and coefficient of variation. In addition, geometric mean and geometric coefficient of variation were reported for all pharmacokinetic parameters except T_{max}.

Name of Sponsor/Company: Oriel Therapeutics Inc, a Sandoz Company	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: Advair® Diskus® 100/50	**Volume:**	
Name of Active Ingredient: Fluticasone propionate/ salmeterol xinofoate	**Page:**	

Safety parameters:

Individual and summary vital signs (blood pressure, pulse rate and body temperature) were presented in tabular form with mean, median, standard deviation and range (minimum and maximum) as appropriate.

Adverse events were tabulated and summarized according to version 13.1 of the Medical Dictionary for Regulatory Activities (MedDRA).

Results

Pharmacodynamic results:

After administration of 1 x 100/50 µg (1 puff), 2 x 100/50 µg (2 puffs), and 4 x 100/50 µg (4 puffs) of fluticasone propionate/salmeterol as Advair® Diskus® to patients with asthma there was an apparent dose-response in FEV_1 percent predicted and the suggestion of a possible dose-response in PEF percent change from baseline.

There were no apparent dose-response relationships for FEV_1 percent change from baseline, FVC percent change from baseline and percent predicted, PEF percent predicted, heart rate percent change from baseline or serum potassium percent change from baseline.

Exploratory pharmacokinetic/pharmacodynamic analysis indicated that a simple E_{max} model appeared to be consistent with the relationship between individual subject $AUEC_{(0.25-24)}$ and $AUC_{(4-12)}$ for FEV_1 percent predicted and the C_{max} and $AUC_{(0-t)}$ of fluticasone propionate and salmeterol.

Pharmacokinetic results:

After administration of 1 x 100/50 µg (1 puff), 2 x 100/50 µg (2 puffs), and 4 x 100/50 µg (4 puffs) of fluticasone propionate/salmeterol as Advair® Diskus® to patients with asthma there was a dose-related and but less than dose-proportional increase in the mean and individual subject plasma concentrations, C_{max}, and $AUC_{(0-t)}$ of fluticasone propionate and a dose-related and dose-proportional increase in the mean and individual subject plasma concentrations, C_{max}, and $AUC_{(0-t)}$ of salmeterol.

Name of Sponsor/Company: Oriel Therapeutics Inc, a Sandoz Company	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: Advair® Diskus® 100/50	**Volume:**	
Name of Active Ingredient: Fluticasone propionate/ salmeterol xinofoate	**Page:**	

Safety results:

Advair® 100/50 was well tolerated at doses up to and including the equivalent of 400 µg fluticasone/200 µg salmeterol (4 puffs using Advair® Diskus® 100/50). In total 14 treatment-emergent adverse events (TEAEs) were reported by 9 (41%) of the 22 subjects. Twelve TEAEs were mild intensity and 2 were moderate intensity (1 event of dysmenorrhoea and 1 event of headache). The most frequently reported TEAE was headache, which had the highest incidence (18% of subjects) at the lowest dose (1 puff of Advair® Diskus® 100/50). There were no clinically relevant findings in vital signs data.

Conclusions:

- There was an apparent dose-response in FEV_1 percent predicted.
- There was a suggestion of a possible dose response in PEF percent change from baseline.
- There were no apparent dose-response relationships for FEV_1 percent change from baseline, FVC percent change from baseline and percent predicted, PEF percent predicted, and heart rate percent change from baseline, and serum potassium percent change from baseline.
- There was a dose-related and but less than dose-proportional increase in the mean and individual subject plasma concentrations, C_{max}, and $AUC_{(0-t)}$ of fluticasone propionate.
- There was a dose-related and dose-proportional increase in the mean and individual subject plasma concentrations, C_{max}, and $AUC_{(0-t)}$ of salmeterol.
- Exploratory pharmacokinetic/pharmacodynamic analysis indicated that a simple E_{max} model appeared to be consistent with the relationship between individual subject $AUEC_{(0.25-24)}$ and $AUC_{(4-12)}$ for FEV_1 percent predicted and the C_{max} and $AUC_{(0-t)}$ of salmeterol.
- Advair® Diskus® 100/50 was well tolerated at doses up to and including the equivalent of 400 µg fluticasone/200 µg salmeterol (4 puffs).