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<b>Study No:</b> B2F104300		
<b>Title :</b> A randomised, double blind, placebo controlled study to examine the safety, tolerability, pharmacodynamics and pharmacokinetics of single inhaled dry powder doses of a novel long acting $\beta$ -2-receptor agonist in healthy male subjects and asthmatics		
<b>Rationale:</b> The present study tested the safety, tolerability, pharmacodynamics and pharmacokinetics of a new chemical entity (NCE) as single inhaled doses in healthy male subjects and asthmatic male subjects, compared to salmeterol 50 $\mu$ g and placebo.		
<b>Phase:</b> I		
<b>Study Period:</b> 24 Aug 2005 - 06 July 2006		
<b>Study Design:</b> Cohort 1: double blind, placebo controlled, ascending, dose study in healthy subjects. Cohort 2 and 3: double-blind, placebo-controlled, 4-way crossover in mild to moderate asthmatics.		
<b>Centres:</b> Two centres in the UK		
<b>Indication:</b> Mild to moderate asthma and chronic pulmonary disease (COPD).		
<b>Treatment:</b> The study comprised of the following: Cohort 1: Subjects were randomised to a dose-ascending sequence in which they received four out of five doses of the NCE. Placebo replacement doses were randomly seeded in the sequence. Cohorts 2 and 3: Subjects were randomised to a 4-way crossover sequence including: two doses of the NCE, salmeterol 50 $\mu$ g and placebo.		
<b>Primary Objective:</b> To investigate the safety and tolerability of single inhaled doses of the NCE in healthy subjects and mild to moderate asthmatics.		
<b>Statistical Methods:</b> The population 'All Subjects' which consisted of all available data from all subjects who received at least one dose of study treatment was used for all statistical analyses.		
<b>Safety:</b> The safety and tolerability profile of single inhaled doses of the NCE in healthy subjects and asthmatic patients was analysed through the examination of individual patient data and the estimation of treatment effects determined using descriptive statistics.		
<b>Efficacy:</b> Cohorts 2 and 3 were combined to provide >90% power to detect a 0.25 L difference in FEV1 at 24h post-dose between any of the active doses and placebo. The primary endpoint was FEV1 at 24h post dose. The primary treatment comparison was between the NCE and placebo.		
<b>Pharmacokinetics (PK) and pharmacodynamics (PD):</b> All PK and PK/PD modelling was exploratory and an estimation approach was adopted.		
<b>Study Population:</b> Cohort 1: Healthy adult males aged between 18 and 45 years. Cohorts 2 and 3: Male asthmatic subjects aged between 18 to 70 years with mild to moderate asthma and no other significant pulmonary diseases. Data regarding the NCE will be provided in the event the NCE is marketed. Data regarding salmeterol is provided at this time.		
<b>Number of Subjects:</b>	<b>Cohort 2</b>	<b>Cohort 3</b>
Planned N	16	14
Dosed N	28	
Completed n (%)	27 (96%)	
Total Number Subjects Withdrawn N (%)	1 (4%)	
Withdrawn due to Adverse Events n (%)	1 (4%)	
Withdrawn due to Lack of Efficacy n (%)	0	
Withdrawn for Other Reasons n (%)	0	
<b>Demographics</b>	<b>Cohorts 2/3</b>	
N	28	
Females: Males	Male only	
Mean Age in Years (sd)	38.8 (13.51)	
Mean Weight in Kg (sd)	83.2 (10.13)	
White n (%)	28 (100%)	

<b>Efficacy:</b> Data regarding the NCE will be provided in the event the NCE is marketed. Data regarding salmeterol is provided at this time.					
<b>Salmeterol-Placebo</b>					
<b>Relative Time</b>	<b>Change from Baseline Serial FEV<sub>1</sub> (L) Data (95%CI) Salmeterol - Placebo</b>				
2 h	0.257 (0.153, 0.362)				
4 h	0.199 (0.083, 0.315)				
6 h	0.221 (0.102, 0.339)				
12 h	0.164 (0.022, 0.307)				
22 h	0.079 (-0.081, 0.238)				
23 h	-0.098 (-0.276, 0.080)				
24 h	0.006 (-0.148, 0.161)				
26 h	-0.035 (-0.180, 0.111)				
30 h	-0.046 (-0.213, 0.121)				
48 h	-0.172 (-0.345, 0.001)				
<b>Pharmacodynamic (PD) Endpoints:</b> Data regarding the NCE will be provided in the event the NCE is marketed. Data regarding salmeterol is provided at this time.					
<b>Salmeterol-Placebo</b>					
<b>Relative Time</b>	<b>2 h</b>	<b>4 h</b>	<b>6 h</b>	<b>12 h</b>	<b>22 h</b>
sGaw treatment ratio	1.269 (1.164, 1.384)	1.279 (1.167, 1.401)	1.200 (1.089, 1.322)	1.148 (1.015, 1.297)	1.060 (0.921, 1.221)
<b>Relative Time</b>	<b>23 h</b>	<b>24 h</b>	<b>26 h</b>	<b>30 h</b>	<b>48 h</b>
sGaw treatment ratio	0.941 (0.837, 1.059)	0.936 (0.833, 1.052)	0.932 (0.829, 1.049)	0.902 (0.789, 1.032)	0.918 (0.811, 1.040)
<b>Salmeterol-Placebo</b>					
<b>Parameters</b>		<b>Change from Baseline Weighted Mean (95% CI)</b>	<b>Parameters</b>	<b>Change from Baseline Min or Max<sup>1</sup> (95% CI)</b>	
<b>ECG</b>	QTc(F)- (0-8h) msec	3.24 (-0.67, 7.14)	QTc(F) maximum - (0-8h) msec	2.55 (-3.49, 8.58)	
	QTc(I) - (0-8h) msec	-9.97 (-17.38, -2.56)	QTc(I) maximum - (0-8h) msec	-13.50 (-24.35, -1.95)	
	QTc(B) - (0-8h) msec	6.51 (1.29, 11.73)	QTc(B) maximum - (0-8h) msec	3.33 (-4.36, 11.02)	
<b>Vital Signs</b>	Supine HR (0-8h) bpm	1.80 (0.33, 3.27)	Supine HR maximum (0-8h) bpm	1.12 (-2.80, 5.04)	
	Supine HR (0-4h) bpm	2.81 (1.27, 4.34)	Supine HR maximum (0-4h) bpm	3.70 (-1.09, 8.49)	
	Supine DBP (0-8h) mmHg	-0.95 (-2.60, 0.69)	Supine DBP minimum (0-8h) mmHg	-0.65 (-3.13, 1.84)	
	Supine SBP (0-8h) mmHg	0.34 (-1.69, 2.36)	Supine SBP maximum (0-8h) mmHg	1.26 (-1.98, 4.50)	
<b>Blood Levels</b>	Glucose (0-4h) mmol/L	0.09 (0.01, 0.18)	Glucose maximum (0-4h) mmol/L	0.10 (-0.02, 0.23)	
	Potassium (0-4h) mmol/L	-0.06 (-0.18, 0.06)	Potassium minimum (0-4h) mmol/L	-0.05 (-0.14, 0.04)	

1. For further clarification please refer to appropriate parameter heading	
<b>Safety results:</b> Adverse events (AEs) were elicited by the investigators, using non-leading questions throughout the study and at the follow-up visit. Data regarding the NCE will be provided in the event the NCE is marketed. Data regarding salmeterol is provided at this time.	
<b>Adverse Events:</b>	<b>Cohorts 2/3</b>
N (All subjects)	28
No. subjects with AEs n (%)	17 (61)
Most Frequent AEs n (%)	
Fatigue	3 (11)
Headache	5 (18)
Chest Discomfort	4 (15)
Pharyngolaryngeal pain	2 (7)
Dizziness	2 (7)
Diarrhoea	2 (7)
Blurred Vision	2 (7)
Blood creatine phosphokinase increased	2 (7)
<b>Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:</b>	Ventricular Tachycardia 1 (2.3) [1]
<b>Publications:</b> No Publication	

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