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<b>Study No.:</b> SFA100062
<b>Title:</b> A Randomized, Parallel Group, Double-Blind, Comparative Trial Assessing Lung Function and Other Measures of Asthma Control in Adults and Adolescents, at least 12 Years of Age, with Asthma, Who Have Either a B16-Arg/Arg, a B16-Gly/Gly or a B16-Arg/Gly Genotype and are Treated With Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50mcg or Salmeterol DISKUS 50mcg BID
<b>Rationale:</b> It is unclear whether genetic variations at position 16 of the $\beta_2$ -adrenergic receptor gene ( <i>ADRB2</i> ) modulate treatment responses of long-acting $\beta_2$ -agonists. Therefore, this clinical study was conducted to investigate whether the phenotypic responses to salmeterol and salmeterol plus ICS were altered by genotypic variation at the B16 position.
<b>Phase:</b> IV
<b>Study Period:</b> 25 October 2004 – 21 January 2007
<b>Study Design:</b> This was a multi-center, randomized, double-blind, parallel group, active comparator controlled design.
<b>Centres:</b> 63 sites in the US, two sites in Peru, and two sites in Kenya
<b>Indication:</b> Asthma
<b>Treatment:</b> During the open-label albuterol period, eligible subjects used only albuterol 90mcg <i>prn</i> to relieve asthma symptoms for 8 weeks. After the 8-week open-label albuterol treatment period, subjects entered an 8-week open-label ipratropium bromide treatment period, (18mcg <i>prn</i> ) to relieve asthma symptoms. Subjects also received open-label albuterol 90mcg for <i>prn</i> use in the event that asthma symptoms responded incompletely to ipratropium bromide, in which case albuterol would be used as a superceding medication.  After completing the open-label ipratropium bromide period, subjects were randomized to double-blind treatment for 16 weeks. Each subject received a supply of study medication via the DISKUS for one of two possible treatment groups, fluticasone propionate/salmeterol combination product (FSC) 100/50mcg BID or salmeterol 50mcg BID. All eligible subjects were given open-label ipratropium 18mcg for use as needed throughout the double-blind period of the trial. Subjects also received open-label albuterol (SM) 90mcg for <i>prn</i> use in the event that asthma symptoms respond incompletely to ipratropium, in which case albuterol would be used as a superceding medication for acute relief.  All subjects who completed 16 weeks of double-blind treatment entered a final wash-out period during which double-blind treatment was terminated and subjects managed their asthma with only open-label ipratropium 18mcg. Subjects also received open-label albuterol 90mcg for <i>prn</i> use in the event that asthma symptoms responded incompletely to ipratropium, in which case albuterol was to be used as a superceding medication for acute relief.
<b>Objectives:</b> The primary objective of this study was to evaluate lung function as assessed by AM PEF AUC relative to baseline [AUC(bl)] in subjects who have the B16 Arg/Arg genotype compared with that of subjects who have the B16 Gly/Gly genotype over 16 weeks of treatment with FSC DISKUS 100/50mcg BID.
<b>Primary Outcome/Efficacy Variable:</b> The primary measure of efficacy was area under the curve describing AM PEF relative to baseline [AUC(bl)] over the 16 week double-blind treatment period. The primary comparison of interest was between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group.
<b>Secondary Outcome/Efficacy Variable(s):</b> Secondary measures of efficacy included area under the curve describing PM PEF relative to baseline [AUC(bl)] and pre-dose FEV <sub>1</sub> . Other secondary measures were change from baseline in percent of symptom free days, and supplemental ipratropium bromide use.
<b>Statistical Methods:</b> The sample size calculation for this study was based on the primary efficacy measure of AM PEF, recorded by subjects in daily diaries over the course of the study. It was estimated that the standard deviation of mean change from baseline in AM PEF over the 16-week double-blind treatment period in subjects randomized to the FSC treatment group would be 50 L/min. Using 28.5 L/min as the non-inferiority criterion bound (lower confidence interval limit of -28.5 L/min), a sample size of 82 subjects per group (per genotype per treatment group) would provide >90% power to demonstrate non-inferiority of the Arg/Arg genotype to the Gly/Gly genotype within the FSC treatment group in terms of AM PEF mean change from baseline over the 16-week treatment period, based on a 2-sided significance level of 0.05.
The Intent-to-Treat (ITT) population included all subjects who were randomized to blinded study drug. The ITT population was the primary analysis population for summaries and analyses of demographic/background, efficacy and safety data. During the conduct of the study, one investigative site (018742) was closed due to significant deviations in

Good Clinical Practice (GCP) identified at the site. Subjects randomized at this site (10 subjects) were not included in the ITT efficacy analyses.

The primary comparison of interest was that of non-inferiority between the Arg/Arg and Gly/Gly genotypes in the FSC treatment group assessed in terms of overall mean AM PEF change from baseline for the 16-week double-blind treatment period. Other comparisons included Arg/Arg versus Gly/Gly in the salmeterol treatment group and Arg/Arg versus Arg/Gly and Arg/Gly versus Gly/Gly in both the FSC and salmeterol treatment groups. These comparisons also assessed non-inferiority with 95% 2-sided confidence intervals and the same non-inferiority criterion bound as the primary comparison in terms of overall mean AM PEF change from baseline for the 16-week double-blind treatment period. An analysis of covariance (ANCOVA) model, including terms for genotype, ethnicity stratum and baseline, was used to assess non-inferiority in AM PEF mean change from baseline for the overall 16-week double-blind treatment period.

**Study Population:** Each subject had a diagnosis of persistent asthma as defined by the American Thoracic Society for at least 3 months prior to Visit 1. At the screening visit (Visit 1), the subject had a best FEV<sub>1</sub> that was  $\geq 70\%$  and  $\leq 100\%$  of predicted normal. Predicted FEV<sub>1</sub> was based on the National Health and Nutrition Examination Survey (NHANES III) predicted normal values for ages 8 years and older.

**Number of Subjects:**

FSC 100/50mcg, n=270	Arg/Arg	Gly/Gly	Arg/Gly
Planned, n	90	90	90
Randomised, n=272	89	91	92
Completed, n (%)	78 (88%)	79 (87%)	82 (89%)
Total Number Subjects Withdrawn, n (%)	11 (12%)	12 (13%)	10 (11%)
Withdrawn due to Adverse Events n (%)	3 (3%)	1 (1%)	2 (2%)
Withdrawn due to Lack of Efficacy (Exacerbation), n (%)	2 (2%)	1 (1%)	0
Withdrawn for other reasons n (%)	6 (7%)	10 (11%)	8 (9%)
SM 50mcg, n=270	Arg/Arg	Gly/Gly	Arg/Gly
Planned, n	90	90	90
Randomised, n=272	90	92	90
Completed, n (%)	68 (76%)	76 (83%)	73 (81%)
Total Number Subjects Withdrawn, n (%)	22 (24%)	16 (17%)	17 (19%)
Withdrawn due to Adverse Events n (%)	1 (1%)	3 (3%)	6 (7%)
Withdrawn due to Lack of Efficacy (Exacerbation), n (%)	3 (3%)	3 (3%)	1 (1%)
Withdrawn for other reasons n (%)	18 (20%)	10 (11%)	10 (11%)

**Demographics:**

FSC 100/50mcg	Arg/Arg	Gly/Gly	Arg/Gly
N (ITT)	89	91	92
Females: Males	62/27	55/36	59/33
Mean Age, years (SD)	33.8 (13.31)	33.3 (14.33)	31.0 (14.40)
Race, n (%)			
White	44 (49%)	59 (65%)	57 (62%)
Black	29 (33%)	18 (20%)	17 (18%)
Other	16 (18%)	14 (15%)	18 (20%)
SM 50mcg	Arg/Arg	Gly/Gly	Arg/Gly
N (ITT)	90	92	90
Females: Males	57/33	51/41	58/32
Mean Age, years (SD)	30.0 (12.02)	35.2 (16.34)	32.8 (14.17)
Race, n (%)			
White	45 (50%)	57 (62%)	54 (60%)
Black	32 (36%)	19 (21%)	15 (17%)
Other	13 (14%)	16 (17%)	21 (23%)

**Primary Efficacy Results:**

FSC 100/50mcg
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<b>AM PEF (L/min) -</b>			
Subjects, n	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	87	90	91
Baseline, n	84	89	91
Mean (SE)	352 (10.3)	371 (10.0)	373 (9.6)
Double-blind Period (Weeks 1-16), n	86	89	91
Mean (SE)	382.6 (10.1)	394.3 (9.7)	399.3 (11.1)
Mean change (SE)	32.6 (4.7)	24.9 (5.9)	25.9 (4.8)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	7.9	0.8	7.1
95% Confidence Interval	-6.3, 22.1	-13.0, 14.6	-7.1, 21.3
p-value	0.276	0.910	0.325
<b>SM 50mcg</b>			
<b>AM PEF (L/min)</b>			
Subjects, n	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	86	91	89
Baseline, n	80	91	86
Mean (SE)	387 (11.5)	373 (10.2)	362 (9.4)
Double-blind Period (Weeks 1-16), n	81	89	86
Mean (SE)	403.1 (11.9)	385.1 (9.8)	388.9 (11.0)
Mean change (SE)	19.4 (3.9)	12.4 (3.1)	24.6 (5.4)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	9.8	11.1	-1.2
95% Confidence Interval	-1.7, 21.4	-0.2, 22.3	-13.0, 10.6
p-value	0.095	0.054	0.836
<b>Secondary Outcome Variables:</b>			
<b>FSC 100/50mcg</b>			
<b>PM PEF (L/min)</b>			
Subjects, n	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	87	90	91
Baseline, n	84	89	91
Mean (SE)	370 (10.6)	380 (10.0)	381 (9.8)
Double-blind Period (Weeks 1-16), n	86	89	91
Mean (SE)	394.7 (10.5)	400.2 (9.7)	405.8 (11.2)
Mean change (SE)	26.8 (4.8)	22.4 (5.8)	25.0 (4.6)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	5.6	2.5	3.0
95% Confidence Interval	-8.4, 19.6	-11.1, 16.1	-10.9, 17.0
p-value	0.433	0.714	0.667
<b>SM 50mcg</b>			
<b>PM PEF (L/min)</b>			
Subjects, n	Arg/Arg	Gly/Gly	Arg/Gly
Subjects, n	86	91	89
Baseline, n	80	90	87
Mean (SE)	398 (12.6)	386 (10.7)	373 (10.2)
Double-blind Period (Weeks 1-16), n	81	89	86
Mean (SE)	414.1 (13.0)	395.7 (10.1)	399.6 (11.6)
Mean change (SE)	19.3 (3.9)	10.5 (3.2)	26.2 (5.9)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	11.7	14.6	-2.9
95% Confidence Interval	-0.6, 24.0	2.7, 26.5	-15.4, 9.6
p-value	0.062	0.017	0.648
<b>FSC 100/50mcg</b>			

<b>Pre-Dose FEV<sub>1</sub> (L)</b>	<b>Arg/Arg</b>	<b>Gly/Gly</b>	<b>Arg/Gly</b>
Baseline, n	87	90	91
Mean (SE)	2.76 (0.08)	2.86 (0.07)	2.87 (0.07)
Double-blind Period (Weeks 1-16), n	81	88	89
Mean (SE)	2.95 (0.08)	3.05 (0.08)	3.09 (0.08)
Mean change (SE)	0.22 (0.03)	0.21 (0.03)	0.22 (0.03)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference (L)	0.02	0.02	0.00
95% Confidence Interval	-0.07, 0.10	-0.07, 0.10	-0.08, 0.09
p-value	0.679	0.714	0.953
<b>SM 50mcg</b>			
<b>Pre-Dose FEV<sub>1</sub> (L)</b>	<b>Arg/Arg</b>	<b>Gly/Gly</b>	<b>Arg/Gly</b>
Baseline, n	86	91	89
Mean (SE)	2.89 (0.08)	2.88 (0.08)	2.84 (0.08)
Double-blind Period (Weeks 1-16), n	79	84	84
Mean (SE)	3.07 (0.09)	2.97 (0.09)	3.00 (0.08)
Mean change (SE)	0.21 (0.03)	0.08 (0.03)	0.13 (0.03)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference (L)	0.13	0.05	0.08
95% Confidence Interval	0.04, 0.21	-0.03, 0.13	-0.01, 0.16
p-value	0.003	0.218	0.076
<b>FSC 100/50mcg</b>			
<b>Percent of Symptom Free Days (%)</b>	<b>Arg/Arg</b>	<b>Gly/Gly</b>	<b>Arg/Gly</b>
Subjects, n	87	90	91
Baseline, n	81	89	90
Mean (SE)	31.5 (4.63)	32.2 (3.70)	34.6 (4.39)
Double-blind Period (Weeks 1-16), n	86	89	91
Mean (SE)	43.5 (4.41)	50.6 (4.20)	48.6 (4.21)
Mean change (SE)	9.9 (2.83)	18.2 (2.88)	14.6 (3.19)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	-7.7	-3.2	-4.5
95% Confidence Interval	-15.8, 0.4	-11.0, 4.6	-12.6, 3.6
p-value	0.061	0.419	0.271
<b>SM 50mcg</b>			
<b>Percent of Symptom Free Days (%)</b>	<b>Arg/Arg</b>	<b>Gly/Gly</b>	<b>Arg/Gly</b>
Subjects, n	86	91	89
Baseline, n	80	90	87
Mean (SE)	34.4 (4.63)	36.1 (4.31)	35.4 (4.31)
Double-blind Period (Weeks 1-16), n	81	89	86
Mean (SE)	44.9 (4.14)	43.6 (4.18)	44.9 (4.31)
Mean change (SE)	9.6 (3.21)	8.2 (2.69)	9.1 (2.69)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	2.1	1.0	1.1
95% Confidence Interval	-5.4, 9.5	-6.3, 8.2	-6.4, 8.6
p-value	0.583	0.795	0.768
<b>FSC 100/50mcg</b>			
<b>Supplemental Ipratropium Bromide Use (puffs/day)</b>	<b>Arg/Arg</b>	<b>Gly/Gly</b>	<b>Arg/Gly</b>
Subjects, n	87	90	91

Baseline, n	82	87	87
Mean (SE)	0.98 (0.12)	1.15 (0.13)	1.15 (0.14)
Double-blind Period (Weeks 1-16), n	86	89	89
Mean (SE)	0.51 (0.07)	0.57 (0.07)	0.56 (0.07)
Mean change (SE)	-0.49 (0.11)	-0.60 (0.12)	-0.63 (0.11)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	-0.04	-0.03	-0.01
95% Confidence Interval	-0.22, 0.14	-0.21, 0.14	-0.19, 0.17
p-value	0.637	0.697	0.926
<b>SM 50mcg</b>			
<b>Supplemental Ipratropium Bromide Use (puffs/day)</b>	<b>Arg/Arg</b>	<b>Gly/Gly</b>	<b>Arg/Gly</b>
Subjects, n	86	91	89
Baseline, n	80	86	86
Mean (SE)	1.04 (0.12)	1.09 (0.13)	1.15 (0.14)
Double-blind Period (Weeks 1-16), n	81	89	85
Mean (SE)	0.66 (0.08)	0.71 (0.09)	0.68 (0.08)
Mean change (SE)	-0.36 (0.10)	-0.35 (0.08)	-0.45 (0.12)
Statistical Comparisons	Arg/Arg vs Gly/Gly	Arg/Gly vs Gly/Gly	Arg/Arg vs Arg/Gly
Double-blind Period (Weeks 1-16)			
LS means difference	-0.09	-0.08	-0.01
95% Confidence Interval	-0.26, 0.09	-0.25, 0.10	-0.19, 0.17
p-value	0.347	0.391	0.914
<b>Safety Results:</b> Study participation SAE's were collected from the time informed consent was obtained to Visit 2. Adverse events and serious adverse events were collected from Visit 2 through the last visit (Visit 11/or Discontinuation Visit).			
<b>FSC 100/50mcg</b>			
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>Arg/Arg</b>	<b>Gly/Gly</b>	<b>Arg/Gly</b>
Subjects with any AE(s), n(%)	n (%)	n (%)	n (%)
Headache	43 (48)	45 (49)	44 (48)
Nasopharyngitis	8 (9)	9 (10)	19 (21)
Pharyngolaryngeal pain	3 (3)	12 (13)	6 (7)
Upper respiratory tract infection	5 (6)	2 (2)	4 (4)
Cough	1 (1)	4 (4)	3 (3)
Influenza	1 (1)	1 (1)	6 (7)
Sinusitis	1 (1)	5 (5)	0
Nasal congestion	2 (2)	1 (1)	3 (3)
Back pain	1 (1)	3 (3)	1 (1)
Arthralgia	2 (2)	2 (2)	2 (2)
Pyrexia	1 (1)	1 (1)	3 (3)
Insomnia	3 (3)	2 (2)	0
	3 (3)	1 (1)	1 (1)
<b>SM 50mcg</b>			
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>Arg/Arg</b>	<b>Gly/Gly</b>	<b>Arg/Gly</b>
Subjects with any AE(s), n(%)	n (%)	n (%)	n (%)
Headache	39 (43)	44 (48)	37 (41)
Nasopharyngitis	6 (7)	12 (13)	12 (13)
Upper respiratory tract infection	6 (7)	9 (10)	3 (3)
Sinusitis	6 (7)	3 (3)	2 (2)
Pharyngolaryngeal pain	6 (7)	2 (2)	0
Back pain	1 (1)	3 (3)	3 (3)
Cough	0	6 (7)	1 (1)
Pain	0	3 (3)	3 (3)
Bronchitis	0	3 (3)	1 (1)
	3 (3)	1 (1)	0

Influenza	1 (1)	1 (1)	1 (1)
Pharyngitis	1 (1)	0	2 (2)
Viral infection	1 (1)	2 (2)	0
Sinus headache	1 (1)	2 (2)	0
Nasal congestion	1 (1)	2 (2)	0
Arthralgia	0	2 (2)	1 (1)
Musculoskeletal pain	1 (1)	0	2 (2)
Rash	0	2 (2)	1 (1)
<b>Serious Adverse Events - On-Therapy</b>			
<b>n (%), [n considered by the investigator to be related to study medication]</b>			
<b>FSC 100/50mcg</b>	<b>Arg/Arg</b>	<b>Gly/Gly</b>	<b>Arg/Gly</b>
Subjects with non-fatal SAEs, n (%)	0	0	0
<b>SM 50mcg</b>	<b>Arg/Arg</b>	<b>Gly/Gly</b>	<b>Arg/Gly</b>
Subjects with non-fatal SAEs, n (%)			
Rupture ovarian cyst	0	0	1 (<1%) [0]
<b>FSC 100/50mcg</b>			
Subjects with fatal SAEs, n (%)	0	0	0
<b>SM 50mcg</b>			
Asthma	0	0	1 (<1%) [0]
<b>Conclusion:</b> See publication below.			
<b>Publications:</b> Arginine 16 genotype does not modulate clinical response to salmeterol in subjects with asthma. Bleecker E, Yancey S, Ortega H, Anderson W. Chest 2007; pending.			

Date updated: 21-Sep-2007