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<b>Study No.:</b> SAS110099
<b>Title:</b> Clinical Assessment of GW815SF (SLM/FP) HFA MDI in Paediatric Patients With Bronchial Asthma – A Study to Compare GW815SF HFA MDI With Concomitant Treatment With Salmeterol Xinafoate Dry Powder Inhaler (DPI) Plus Fluticasone Propionate DPI and to Assess Long-Term Safety of GW815SF HFA MDI
<b>Rationale:</b> One inhalation of GW815SF HFA MDI 25/50mcg twice daily is applicable for salmeterol (SLM) and fluticasone propionate (FP) both at the usual paediatric dose (50/100mcg/day), and two inhalations of GW815SF HFA MDI 25/50mcg twice daily, SLM and FP both at the maximum approved paediatric dose (100/200mcg/day) in Japan. The present study assesses the efficacy and safety of one inhalation of GW815SF HFA MDI 25/50mcg twice daily for 4 weeks relative to the concurrent treatment with SLM and FP both at the usual dose, i.e., one inhalation of SLM Dry Powder Inhaler (DPI) 25mcg twice daily plus one inhalation of FP DPI 50mcg twice daily. The study also assesses the long-term safety of the treatment in the 20-week extension period following the crossover period as there is no experience with the product in paediatric subjects in Japan.
<b>Phase:</b> III
<b>Study Period:</b> 2 April 2007 -1 9 January 2008
<b>Study Design:</b> A multicentre, randomised, open-label, two-period crossover study followed by an extension treatment period
<b>Centres:</b> A total of 8 medical institutions in Japan At all centres, subjects were randomised to treatments.
<b>Indication:</b> Paediatric Asthma
<b>Treatment:</b> During the 2-week run-in period, subjects continue to take the antiasthma medication containing inhaled corticosteroid [ICS; fluticasone propionate (FP) 100mcg/day or equivalent] which has been started before the run-in period. When a subject has been taking other ICS, the medication should be switched to FP 100mcg/day before the start of run-in period. After the run-in period, subjects enter the crossover period and are randomised to one of the two treatment groups which are different in the sequence of the following two treatments: GW815SF HFA MDI 25/50mcg and SLM DPI 25mcg+FP DPI 50mcg. During the crossover period, each subject ceases the ICS and takes two treatments (one inhalation of GW815SF HFA MDI 25/50mcg twice daily, one inhalation of SLM DPI 25mcg twice daily plus one inhalation of FP DPI 50mcg twice daily) for 4 weeks with an interval for wash-out. During the washout period, the study medication is switched to the antiasthma drug used during the run-in period. Subjects completing the two periods of treatment enter the extension period. During the extension period, subjects take one inhalation of GW815SF HFA MDI 25/50mcg twice daily for 20 weeks.
<b>Objectives:</b> To determine the equivalence by morning Peak Expiratory Flow (PEF), of one inhalation of GW815SF HFA MDI 25/50mcg twice daily to one inhalation of SLM DPI 25mcg twice daily plus one inhalation of FP DPI 50mcg twice daily in paediatric subjects with bronchial asthma in a crossover manner. To determine the long-term safety of one inhalation of GW815SF HFA MDI 25/50mcg twice daily in paediatric subjects with bronchial asthma in the extension period following the crossover period.
<b>Primary Outcome/Efficacy Variable:</b> Mean change from baseline in morning PEF over Weeks 1-4 in each treatment period (Treatment Periods 1 and 2) during the crossover period.
<b>Secondary Outcome/Efficacy Variable(s):</b> <b>Efficacy Endpoints</b> Percent predicted morning PEF, percent personal best morning PEF, evening PEF, circadian variation in PEF, percentage of subjects with symptom-free nights and days, percentage of subjects with rescue medication-free nights and days

**Safety Endpoints**

Adverse events (AEs)

**Statistical Methods:** The standard deviation for the treatment difference in the change from baseline in morning PEF during the 4-week treatment period (Weeks 1-4) was assumed to be 30 L/min based on past clinical data. Assuming an equivalence margin ( $\Delta$ ) of 15 L/min, 36 subjects are needed to declare the equivalence of GW815SF HFA MDI 25/50mcg to SLM DPI 25mcg+FP DPI 50mcg at a two-sided 5% significance level with 80% power. Therefore, 36 subjects completing the crossover period are required as the Per Protocol Set (PPS) population. Based on this estimation, the target number for randomisation was set at 45 assuming a 20% attrition due to withdrawal or dropout during the crossover period.

Crossover Period:

The primary efficacy population was the PPS population, defined as a subset of the Full Analysis Set (FAS) population who complied with the protocol. Safety analyses were performed on the Safety Population (SP), defined as all subjects who entered the treatment period and received at least one dose of the study medication.

For the primary efficacy endpoint "change from baseline in morning PEF during the 4-week treatment period (Weeks 1-4)," two-sided 95% confidence intervals for treatment difference were estimated using a Mixed effect model that has "treatment group," "period" and "drug" as fixed effects and "subjects" as a random effect. Equivalence of GW815SF HFA MDI 25/50mcg to SLM DPI 25mcg+FP DPI 50mcg was declared when the confidence interval for treatment difference lay entirely within the equivalence margin ( $\pm 15$  L/min).

For the secondary efficacy endpoints "morning and evening PEF," "percent predicted morning PEF," "percent personal best morning PEF," and "circadian variation in PEF," two-sided 95% confidence intervals for the mean treatment difference in the change from baseline was estimated using the same Mixed effect model as for the primary efficacy analysis. For nighttime and daytime asthma symptoms and the use of rescue medication, two-sided 95% confidence intervals for the mean treatment difference in the change from baseline were estimated using the same Mixed effect model as for the primary efficacy analysis.

Extension Period:

Efficacy analyses were performed on the FAS, defined as all randomised subjects excluding all those who received no dose of the study medication (for extension period) or who had no efficacy data after entering the extension period. The SP was defined as all subjects who received at least one dose of the study medication (for extension period) after entering the extension period. For all efficacy endpoints, summary statistics were calculated. No statistical hypothesis testing was performed.

**Study Population:**

**Main Inclusion Criteria:** Paediatric outpatients,  $\geq 5$  and  $\leq 14$  years of age, with bronchial asthma who have been treated with ICS (FP 100mcg/day or equivalent) for at least 4 weeks prior to the start of run-in period (Visit 1); and who have a mean morning PEF measurement in the last 7 days of the run-in period (excluding the first day of Treatment Period 1)  $\leq 90\%$  of his/her best PEF measurement.

**Main Exclusion Criteria:** Subjects who were admitted to the hospital due to asthma exacerbation within 8 weeks prior to Visit 1; who used systemic steroid within 4 weeks prior to Visit 1; who received antibacterials or antivirals for treatment of upper or lower respiratory tract infection within 2 weeks prior to Visit 1; who have a past or current history of a disease or require medical or other treatments, that may affect the safety of subjects or the efficacy or safety evaluation of the study medication; who were admitted to the hospital due to asthma exacerbation during the run-in or wash-out period; who had an upper or lower respiratory tract infection during the 2 weeks just before the start of study treatment (Visit 2); or who used prohibited drugs during the 2 weeks just before Visit 2.

	Crossover Period	Extension Period
Number of Subjects:		
Planned, N	45	

Randomised, N (Entered for extension period)	51	50
Completed, n (%) (as subjects completing extension period)	50 (98.0)	50
Total Number Subjects Withdrawn, N (%)	1 (2.0)	0
Withdrawn due to Adverse Events n (%)	0	0
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for other reasons n (%)	1 (2.0)	0
<b>Demographics</b>	<b>Crossover Period (PPS)</b>	<b>Extension Period (FAS)</b>
N	48	50
Females: Males	16: 32	17: 33
Mean Age, years (SD)	8.4 (2.45)	8.4 (2.42)
Race, n (%)		
Asian – Japanese Heritage	48 (100)	50 (100)
<b>Primary Efficacy Results: Mean Change from Baseline in Morning PEF (L/min) over Weeks 1-4 (PPS Population)</b>		
	<b>SFC 50/100mcg/day (N=48)</b>	<b>SLM 50mcg + FP 100mcg/day (N=48)</b>
Baseline, Mean (SD)	232.3 (77.78)	234.3 (74.21)
Adjusted Mean Change from Baseline (SE)	14.3 (4.53)	17.1 (4.53)
Difference between treatments [(SLM+FP)-SFC] (SE)	2.8 (5.91)	
95% CI	-9.10, 14.69	
p-value	0.6383	
<b>Secondary Outcome Variable(s):</b>		
For the extension period, each day of treatment is expressed as the day relative to the baseline (defined as the 7 days just before the start of extension treatment).		
<b>Crossover Period (PPS)</b>		
Mean Morning PEF (L/min)	<b>SFC 50/100mcg/day (N=48)</b>	<b>SLM 50mcg + FP 100mcg/day (N=48)</b>
Baseline, Mean (SD)	232.3 (77.78)	234.3 (74.21)
Weeks 1-4, Mean (SD)	246.9 (83.50)	251.3 (82.10)
Change from Baseline during Weeks 1-4 (SD)	14.6 (32.21)	17.0 (30.41)
p-value (Based on paired t-test within Treatment Group)	0.0030	0.0003
Percent Predicted Morning PEF (%)	<b>SFC 50/100mcg/day (N=48)</b>	<b>SLM 50mcg + FP 100mcg/day (N=48)</b>
Baseline, Mean (SD)	90.10 (15.588)	91.08 (14.050)
Adjusted Mean Change from Baseline during Weeks 1-4 (SE)	5.38 (1.543)	6.73 (1.543)
Difference between treatments [(SLM+FP)-SFC] (SE)	1.35 (2.069)	
95% CI	-2.811, 5.519	
Percent Personal Best Morning PEF (%)	<b>SFC 50/100mcg/day</b>	<b>SLM 50mcg + FP 100mcg/day</b>
Baseline, Mean (SD)	85.72 (11.550)	86.65 (8.902)
Adjusted Mean Change from Baseline during Weeks 1-4 (SE)	5.01 (1.480)	6.46 (1.480)
Difference between treatments [(SLM+FP)-SFC] (SE)	1.44 (2.017)	
95% CI	-2.617, 5.504	
Evening PEF (L/min)	<b>SFC 50/100mcg/day</b>	<b>SLM 50mcg + FP 100mcg/day</b>

Baseline, Mean (SD)	240.3 (77.21)	244.6 (75.63)
Adjusted Mean Change from Baseline during Weeks 1-4 (SE)	16.3 (3.74)	15.8 (3.74)
Difference between treatments [(SLM+FP)-SFC] (SE)	-0.6 (5.29)	
95% CI	-11.07, 9.95	
Circadian Variation in PEF (%)	<b>SFC 50/100mcg/day</b>	<b>SLM 50mcg + FP 100mcg/day</b>
Baseline, Mean (SD)	7.50 (4.941)	7.81 (4.269)
Adjusted Mean Change from Baseline during Weeks 1-4 (SE)	0.06 (0.638)	-0.08 (0.638)
Difference between treatments [(SLM+FP)-SFC] (SE)	-0.14 (0.902)	
95% CI	-1.932, 1.650	
Percentage of Subjects with Symptom-Free Nights and Days (%)	<b>SFC 50/100mcg/day</b>	<b>SLM 50mcg + FP 100mcg/day</b>
Baseline, Subjects n/N (%)	35/48 (72.9)	39/48 (81.3)
Week 4, Subjects n/N (%)	44/48 (91.7)	39/48 (81.3)
Percentage of Subjects with Rescue Medication-Free Nights and Days (%)	<b>SFC 50/100mcg/day</b>	<b>SLM 50mcg + FP 100mcg/day</b>
Baseline, Subjects n/N (%)	42/48 (87.5)	42/48 (87.5)
Week 4, Subjects n/N (%)	45/48 (93.8)	42/48 (87.5)
<b>Extension Period (FAS)</b>	<b>SFC 50/100mcg/day (N=50)</b>	
Morning PEF (L/min)		
Baseline, Mean (SD)	257.2 (83.09)	
Change from Baseline during Weeks 1-20 (SD)	3.0 (24.56)	
Percent Predicted Morning PEF (%)		
Baseline, Mean (SD)	99.69 (101.13)	
Adjusted Mean Change from Baseline during Weeks 1-20 (SD)	1.46 (9.568)	
Percent Personal Best Morning PEF (%)		
Baseline, Mean (SD)	94.97 (12.983)	
Adjusted Mean Change from Baseline during Weeks 1-20 (SD)	1.29 (8.541)	
Evening PEF (L/min)		
Baseline, Mean (SD)	268.3 (81.42)	
Adjusted Mean Change from Baseline during Weeks 1-20 (SD)	2.7 (23.43)	
Circadian Variation in PEF (%)		
Baseline, Mean (SD)	7.56 (5.144)	
Adjusted Mean Change from Baseline during Weeks 1-20 (SD)	-0.37 (3.568)	
Percentage of Subjects with Symptom-Free Nights and Days (%)	42/50 (84.0)	
Baseline, Subjects n/N (%)		
Week 20, Subjects n/N (%)	39/46 (84.8)	
Percentage of Subjects with Rescue Medication-Free Nights and Days (%)		
Baseline, Subjects n/N (%)	45/50 (90.0)	
Week 20, Subjects n/N (%)	41/46 (89.1)	
<b>Safety Results (Safety Population):</b>		
Crossover Period:		
On-therapy adverse events (AEs) and serious adverse events (SAEs) were defined as those occurring during the crossover period (including wash-out period).		

Extension Period: On-therapy adverse events (AEs) and serious adverse events (SAEs) were defined as those occurring during the extension period (from the day after the last dose of crossover period until the day of last dose of extension period).		
<b>Crossover Period</b>	<b>SFC 50/100mcg/day (N=51)</b>	<b>SLM 50mcg + FP 100mcg/day (N=50)</b>
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>n (%)</b>	<b>n (%)</b>
Subjects with any AE(s), n(%)	17 (33.3)	16 (32.0)
The most frequent 10 events in each treatment group (all AEs)		
Upper respiratory tract inflammation	7 (13.7)	3 (6.0)
Nasopharyngitis	2 (3.9)	4 (8.0)
Stomatitis	2 (3.9)	0
Gastroenteritis	1 (2.0)	2 (4.0)
Headache	0	2 (4.0)
Laryngotracheo bronchitis	1 (2.0)	1 (2.0)
Enteritis infectious	1 (2.0)	0
Hand foot & mouth disease	0	1 (2.0)
Varicella	0	1 (2.0)
Otitis media	0	1 (2.0)
Molluscum contagiosum	1 (2.0)	0
Impetigo	0	1 (2.0)
Hordeolum	1 (2.0)	0
Asthma	1 (2.0)	1 (2.0)
Epistaxis	1 (2.0)	0
Rhinalgia	1 (2.0)	0
Abdominal pain	1 (2.0)	1 (2.0)
Nausea	0	1 (2.0)
Diarrhoea	0	1 (2.0)
Toothache	1 (2.0)	0
Contusion	1 (2.0)	0
Arthropod sting	1 (2.0)	0
Forearm fracture	1 (2.0)	0
Myalgia	1 (2.0)	0
Decreased appetite	1 (2.0)	0
Heat rash	0	1 (2.0)
<b>Extension Period</b>	<b>SFC 50/100mcg/day (N=51)</b>	
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>n (%)</b>	
Subjects with any AE(s), n(%)	41 (82.0)	
The most frequent 10 events		
Upper respiratory tract inflammation	17 (34.0)	
Gastroenteritis	7 (14.0)	
Nasopharyngitis	7 (14.0)	
Asthma	5 (10.0)	
Eczema	4 (8.0)	
Stomatitis	3 (6.0)	
Influenza	2 (4.0)	
Enterocolitis infectious	2 (4.0)	
Impetigo	2 (4.0)	
Urticaria	2 (4.0)	
Conjunctivitis allergic	2 (4.0)	
Liver function test abnormal	2 (4.0)	

<b>Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]</b>		
<b>Crossover Period</b>	<b>SFC 50/100mcg/day (N=51)</b>	<b>SLM 50mcg + FP 100mcg/day (N=50)</b>
Subjects with non-fatal SAEs, n (%)	0	0
Subjects with fatal SAEs, n (%)	0	0
<b>Extension Period</b>	<b>SFC 50/100mcg/day (N=51)</b>	
Subjects with non-fatal SAEs, n (%)	0	
Subjects with fatal SAEs, n (%)	0	

**Conclusion:**

Crossover Period  
See publication below.

## Extension period

In paediatric subjects,  $\geq 5$  and  $\leq 14$  years of age, with mild persistent or moderate persistent bronchial asthma, improvements in lung function observed at the end of crossover period (start of extension treatment) were maintained through the 20-week extension treatment by one inhalation of GW815SF HFA MDI 25/50mcg twice daily.

**Publications:**

Nishima S, Nishimuta T, Morikawa A. Salmeterol/Fluticasone propionate Combination: A Comparison with Concurrent Salmeterol and Fluticasone propionate in Japanese Children with Asthma. (interim result) Jpn. J. Pediatr. Allergy Clin. Immunol. 2008; 22 (2) : 293-96 [Japanese]

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