Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Seretide Evohaler, Viani Evohaler, Aliflus Evohaler, Fluticasone propionate/salmeterol xinafoate

UK/W/0103/pdWS/001

Marketing Authorisation Holder: GSK

Rapporteur:	UK
Finalisation procedure (day 120):	09th July 2018

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Seretide Evohaler, Viani Evohaler, Aliflus Evohaler,
INN (or common name) of the active substance(s):	Fluticasone propionate/salmeterol xinafoate
MAH:	GSK
Currently approved Indication(s)	Asthma
Pharmaco-therapeutic group (ATC Code):	R03AK06
Pharmaceutical form(s) and strength(s):	Salmeterol 25/Fluticasone 50/ 125/ 250 mcg HFA inhalational aerosol

I. EXECUTIVE SUMMARY

Following the assessment of the clinical trial, 'Clinical assessment of fluticasone propionate/ salmeterol xinafoate HFA MDI in 6-month to 4-year-old Japanese patients with bronchial asthma.
SmPC changes are proposed in sections 4.2 and 5.1.

Summary of outcome

☐ No change

☒ New study data: <section 5.1>

☐ New safety information: <section(s) xxxx, xxxx>

☒ Paediatric information clarified: <section 4.2>

☐ New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION

The following SmPC changes are proposed (new text in bold and underlined):

4.2 Posology and method of administration

…

Paediatric population

…

~~There are no data available for use of Seretide inhaler in childern aged under 4 years.~~ **The safety and efficacy of Seretide inhaler in children aged under 4 years has not been established**.

…

5.1 Pharmacodynamic properties

…

Paediatric population:

…

A multi-centre 8-week, double-blind, study was conducted to evaluate the safety and efficacy of salmeterol-FP metred dose inhaler (50/25 micrograms, 1 or 2 inhalations twice daily) versus FP (50 micrograms, 1 or 2 inhalations twice daily) alone in Japanese paediatric (6-month to 4 years of age) patients with infantile bronchial asthma. The safety of long-term treatment with salmeterol-FP metred dose inhaler (50/25 micrograms, 1 or 2 inhalations twice daily) was evaluated in a 16-week, open-label, extension treatment period. Ninety-one percent (136/150) and eighty-eight percent (132/150) of randomised patients treated with salmeterol-FP and FP alone, respectively, completed the study. The study failed to meet its primary efficacy endpoint of mean change from baseline in total asthma symptom score (double blind period). No statistically significant superiority in favour of salmeterol-FP to FP was demonstrated (95% CI [-2.47; 0.54], p=0.206). No clinically significant differences were noted in the safety profile between salmeterol-FP and FP alone (8-week double-blind period); moreover, no new safety signals were

identified with administration of salmeterol-FP in the 16-week open-label extension period. There were no patient deaths. It is difficult to make a confident diagnosis of asthma in children 4 years and younger, therefore conclusive data is difficult to obtain. Salmeterol-FP is not approved in children under 4 years old.

…

III. INTRODUCTION

On 3rd April 2017, GSK submitted a notification of completion of a Japanese paediatric study entitled *Clinical assessment of fluticasone propionate/ salmeterol xinafoate HFA MDI in 6-month to 4-year-old Japanese patients with bronchial asthma* (Study number 200680) under Article 46 of the Regulation 1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

The pharmaceutical formulations used in the study included Fluticasone propionate (FP) /Salmeterol Xinafoate(SLM) 50/25 mcg pMDI and FP 50 mcg pMDI. Study medicines were provided by the applicant.

Study Drug	FP/SLM 50/25 µg	FP 50 µg
Dosage form	pMDI	pMDI
Content	Metered-dose aerosol product containing 50 µg of fluticasone propionate, 25 µg of salmeterol per inhalation	Metered-dose aerosol product containing 50 µg of fluticasone propionate per inhalation.
Physical description	An inhaler formulation delivering metered doses of the aerosol of the drug solution	An inhaler formulation delivering metered doses of the aerosol of the drug solution
Additive	1, 1, 1, 2-tetrafluoroethane (HFA134a)	1, 1, 1, 2-tetrafluoroethane (HFA134a)
Route of administration	Inhalation	Inhalation

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report(s) for:

Study Number: 200860
Title: Clinical assessment of fluticasone propionate/salmeterol xinafoate HFA MDI in 6-month to 4-year-old Japanese patients with bronchial asthma

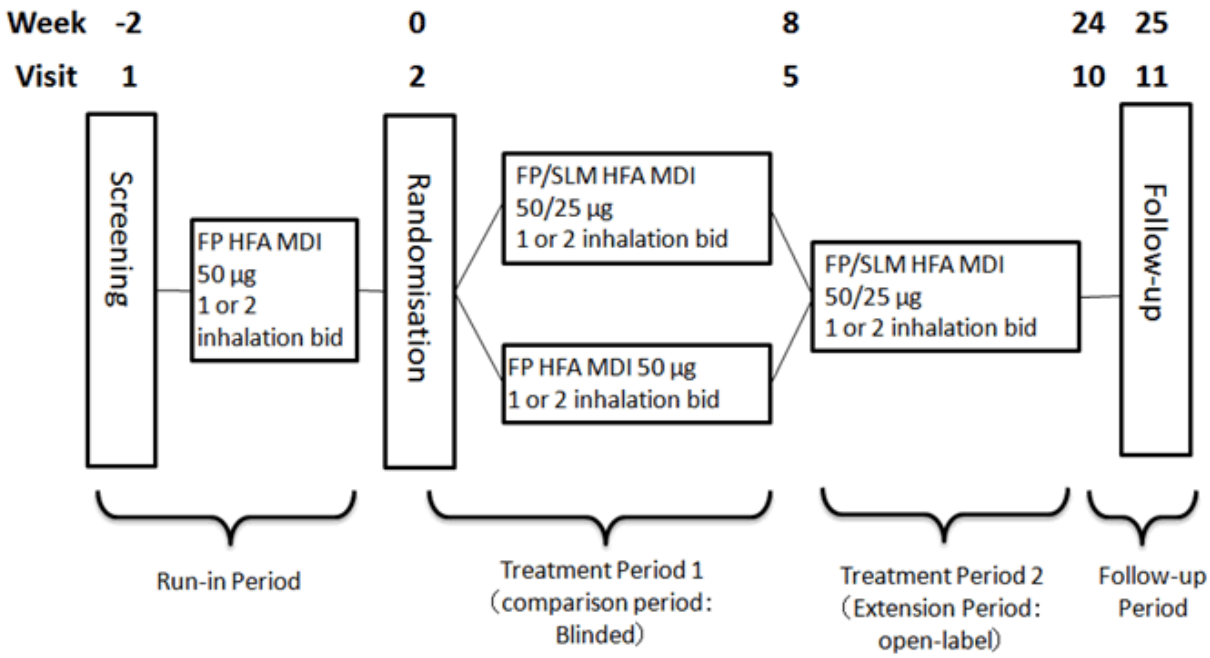
2. Clinical study(ies)

- **Description**

- **Methods**

  - Objective:
    The objective of this study was to evaluate the efficacy and safety of fluticasone propionate/salmeterol xinafoate Hydro fluoro alkane (HFA) Metered dose inhaler (MDI) (FP/SLM) 50/25 mcg 1 or 2 inhalations twice daily for 8 weeks in comparison with FP HFA MDI (FP) 50 mcg 1 or 2 inhalations twice daily in 6-month to 4-year-old Japanese patients with infantile bronchial asthma. In addition, the safety of long term treatment with FP/SLM 50/25 mcg 1 or 2 inhalations twice daily was evaluated in the 16 weeks of extension period.

  - Study design:
    This was a multicentre, stratified, randomized, active control, double-blind, parallel group comparative study with an open-label uncontrolled extension period. The study had four periods: a run-in period of 2 weeks, a treatment period 1 of 8 weeks (double-blind phase), a treatment period 2 of 16 weeks (open-label phase), and a follow-up period of 1 week. Japanese patients with infantile bronchial asthma aged 6-months to 4-years were enrolled in the run-in period and received FP. Following the run-in period, the eligible subjects were randomized to FP/SLM 50/25 mcg or FP 50 mcg at the ratio of 1:1. The treatments were stratified by age (<2 years, >=2 years) and by daily inhalation group (2 puffs per day, 4 puffs per day) for >=2 years old. In treatment period 1, the efficacy and safety of FP/SLM was evaluated in comparison with FP. The primary efficacy endpoint was mean change from baseline in total asthma symptom score (daytime plus night-time) in patient diary at the end of treatment period 1. The subjects who completed treatment period 1 entered treatment period 2 and received FP/SLM 50/25 mcg. In treatment period 2, the safety of long-term treatment with FP/SLM 50/25 mcg was evaluated. The duration of participation in the study was 10 weeks for completion of treatment period 1 and 27 weeks for completion of the whole study.



- Study population /Sample size

  Study participants:
  Inclusion criteria: Main criterion for inclusion was Japanese male and female aged 6-month to 4-year-old at Visit 1 and outpatients who were diagnosed with infantile bronchial asthma by reference to the JPGL 2012 for whom Inhaled corticosteroid (ICS)/Long-acting beta 2 agonist (LABA) treatment was considered necessary.

  Patients who had confirmatory diagnosis of upper or lower respiratory tract infection were excluded.

  The randomization criterion was patients with the asthma symptom score (daytime plus night-time) totalling ≥6 over the last 7 days of the run-in period and additionally having daily symptom score of ≥ 1 on at least 3 of the last 7 days of the run-in period, and those patients who were not using systemic glucocorticosteroids during the run-in period.

Number of subjects:

Population	FP/SLM	FP	Total
All Subjects Enrolled (ASE)			370
Randomized [1]	150	150	300
Intent-to-Treat (ITT)	150	150	300
Intent-to-Treat 2 (ITT2), n (%)	147 (98)	141 (94)	288 (96)
Per-protocol (PP), n (%)	148 (99)	147 (98)	295 (98)
Plasma Cortisol (PC), n (%)	149 (>99)	150 (100)	299 (>99)
Plasma Cortisol 2 (PC2), n (%)	146 (97)	141 (94)	287 (96)

ASE: All subjects screened and for whom a record exists on the study database.
ITT: All randomized subjects who received at least a single dose of trial medication for Period 1.
ITT2: All subjects who received at least a single dose of study drug for Period 2.
PP: All subjects in the Intent-to-Treat population who do not have any full protocol deviations.
PC: All subjects in the Intent-to-Treat population excluding a subject who has received systemic glucocorticosteroids, Ritonavir-containing drugs within four weeks prior to PC collection and outside the collection time (from 8 am to 11 am) at screening.
PC2: All subjects in the PC population who received at least a single dose of study drug for Period 2.
Note: Percentages for ITT2, PP, PC and PC2 are out of ITT population.
[1] Randomized population is not a defined population and consists of all subjects who were randomized and given a randomization number.

Sample size:
The sample size for this study was determined in reference to the overseas clinical studies of PULMICORT Respules (AstraZeneca K.K., JAN: budesonide) in children including infants (04-3100, 04-3072, 04-3069) and the data from overseas clinical study of FP/SLM in children (SAS30019). The percentage improvement with FP/SLM in infants was conservatively set at 50% in view of the fact that percentage improvements with FP/SLM, an ICS/LABA combination, was expected to be greater than those with PULMICORT Respules (approximately 30-38%), an ICS, and that the percentage improvement noted in the overseas clinical study of FP/SLM in children was approximately 62%.
The percentage improvement in the FP group that remained on the same study drug as the run-in period was conservatively set at 20% on the basis of the percentage improvement with PULMICORT Respules relative to placebo (which is approximately 8-18%), and the difference in the percentage improvement between FP/SLM and FP was set at 30% (equivalent to daily total symptom scores of 1.8). The standard deviation (SD) was estimated to be a little smaller than baseline on the basis of the clinical study of PULMICORT Respules; and the estimated SD was calculated to be 5-6 in the overseas clinical study of FP/SLM. Consequently, SD of changes in this study was set to 5.0 which is a little smaller than 6, an anticipated baseline of this study. It was estimated that 123 subjects per group would give 80% power to detect difference between FP/SLM and FP at the two-sided 5% level of significance. In consideration of 20% subjects who were not to be included in the analysis population, it was determined that a total of 296 subjects (148 subjects per group) would need to be randomized.

- Treatments

The subjects were to receive the study drug (FP/SLM 50/25 mcg or FP 50 mcg) with the following dosage and administration. The study drugs (FP/SLM 50/25 mcg and FP 50 mcg) were started in the morning of the first dosing day. The parent or legally acceptable representative was instructed to make the subject take the investigational drug,

comparator or run-in FP twice daily in the morning and at night at intervals of about 12 hours.

Run-in period (2 weeks):
FP 50 mcg (1 or 2 inhalations twice daily)
The number of FP inhalations was judged by the investigator (or sub investigator) in accordance with the subject's condition: 1 or 2 inhalations twice daily (FP 100 or 200 mcg/day), except for subjects younger than 2 years who were limited to 1 inhalation (FP 100 mcg/day).

Treatment period 1 (8weeks):
The subjects were stratified according to their age (<2 years, >=2 years) at Visit 1 and randomized to one of the following two treatment groups at the ratio of 1:1.
FP/SLM 50/25 mcg (1 or 2 inhalations twice daily)
FP 50 mcg (1 or 2 inhalations twice daily)
The subjects inhaled the same number of puffs as they did in the run-in period, so that the amount of ICS would be the same as that of FP in the run-in period.
Treatment period 2 (16 weeks):
FP/SLM 50/25 mcg (1 or 2 inhalations twice daily)
The subject started inhaling the same number of puffs as they did in treatment period 1. FP/SLM dosage could be decreased or increased (2 or 4 inhalations per day) depending on the condition of the subject (including subjects younger than 2 years at Visit 1) at the discretion of the investigator (or sub investigator).

Treatment Assignment
At the start of treatment period 1, subjects were stratified by age at Visit 1 (<2 years, >=2 years) and randomly assigned to one of the following two treatment groups at the ratio of 1:1 according to the randomization schedule.
 FP/SLM 50/25 mcg
 FP HFA 50 mcg
Subjects were allocated to the following group at the beginning of treatment period 2.
 FP/SLM 50/25 mcg

This was a double-blind (treatment period 1) study with a subsequent unblinded phase (treatment period 2). None of the patients, parents or legally acceptable representatives or the investigator (or sub investigator) was notified of the content of the study medication the subject was receiving during the double-blind phase.

Only salbutamol inhaler was permitted as a rescue medication in case of deterioration of asthma.

- Outcomes/endpoints

Primary Efficacy Endpoint
 Mean change from baseline in total asthma symptom score (daytime plus night-time) at the end of treatment period 1 derived from the patient diary of the subjects who had completed 8 weeks of treatment.
The asthma symptoms that were used in the overseas clinical trials in infant asthma patients with other ICS were used [Kemp, 1999; Baker, 1999]. Daytime and night-time asthma symptoms were rated on a 4-point scale:
0 = none: no symptoms of asthma
1 = mild symptoms: awareness of asthma symptoms and/or signs that were easily tolerated

2 = moderate symptoms: asthma symptoms and/or signs with some discomfort, causing some interference of daily activities or sleeping
3 = severe symptoms: incapacitating asthma symptoms and/or signs, with inability to perform daily activities or sleeping
The baseline value was the score over the last 7 consecutive days of the run-in period (excluding the day of Visit 2). The endpoint value (at the end of treatment 1) was the score over the last 7 days of treatment period 1 (excluding the last day of treatment period 1). The total asthma symptom score (daytime plus night-time) over 5 days or more is acceptable if some data were missing

Secondary Efficacy Endpoints

- Mean change from baseline in night-time asthma symptom score
- Mean change from baseline in daytime asthma symptom score
- Frequency of asthma exacerbations
- Use of rescue medication (number of occasions of use during a 24-hour period and percentage of days with rescue-free 24-hour period)
- Quality of Life (QOL): Mean change from baseline in JPAC score

Safety Assessments
The safety assessments were the monitoring of adverse events, clinical laboratory tests, height, vital signs, 12-lead ECGs and oropharyngeal examination. The adverse events were graded as mild, moderate, or severe according to their intensity.

- Statistical Methods

Four subject populations were defined: All Subjects Enrolled (ASE) Population, Intent-To-Treat (ITT) Population, Per Protocol (PP) Population, and Plasma Cortisol (PC) Population.
The ITT population (all subjects who have been randomized to treatment and received at least one dose of randomized study medication in treatment period 1) was the population of primary interest for all efficacy and safety endpoints.

Primary Comparisons of Interest
For the primary endpoint, estimation of mean treatment differences was performed for the following treatment comparisons:
 FP/ SLM 50/25 mcg vs. FP 50 mcg
Other Comparisons of Interest
For the secondary endpoints, estimation of mean treatment differences was performed for the following treatment comparisons:
 FP/ SLM 50/25 mcg vs. FP 50 mcg

Unless otherwise specified, continuous data were summarized using descriptive statistics of n, mean, SD, median, minimum and maximum. Categorical data were summarized using n and percentage.

➢ Results

- Recruitment/ Number analysed
The summary of subject disposition (Period 1 ITT population) is provided below:

	FP/SLM (N=150)	FP (N=150)	Total (N=300)
Completion Status			
Completed treatment period 1 [1]	148 (99)	142 (95)	290 (97)
Withdrawn	2 (1)	8 (5)	10 (3)
Primary/subreason for withdrawal			
Adverse event	0	1 (<1)	1 (<1)
Protocol deviation	0	1 (<1)	1 (<1)
Subject reached protocol-defined withdrawal criteria	2 (1)	5 (3)	7 (2)
Deterioration of asthma of original version	0	3 (2)	3 (1)
Deterioration of asthma without hospitalization of amendment 1	1 (<1)	1 (<1)	2 (<1)
Deterioration of asthma with an in-patient hospitalization or emergency department visit in treatment period 1 of Amendment 1	1 (<1)	1 (<1)	2 (<1)
Withdrew consent	0	1 (<1)	1 (<1)

The summary of subject disposition (Period 2 ITT2 population) is provided below:

	FP - FP/SLM (N=141)	FP/SLM - FP/SLM (N=147)	FP/SLM Total (N=288)
Completion Status			
Completed treatment period 2 [1]	132 (94)	136 (93)	268 (93)
Withdrawn	9 (6)	11 (7)	20 (7)
Primary/subreason for withdrawal			
Adverse event	4 (3)	5 (3)	9 (3)
Subject reached protocol-defined stopping criteria	2 (1)	5 (3)	7 (2)
Deterioration of asthma of original version	1 (<1)	3 (2)	4 (1)
Deterioration of asthma with an in-patient hospitalization or emergency department visit in treatment period 2 of Amendment 1	0	2 (1)	2 (<1)
Investigator discretion	2 (1)	0	2 (<1)
Withdrew consent	1 (<1)	1 (<1)	2 (<1)

Source: Table 5.0041

As per a list of important protocol deviations provided in the CSR for period 1, 7/150 patients and 9/150 patients in the FP/SLM and FP arms respectively have used a prohibited medicine or device. Similar figures for period 2 include 14/141 and 19/147

- Baseline data
  Demographic characteristics for the subjects were generally similar between the treatment groups.
  The majority of subjects were aged 2 years or older for both treatment groups (83% each). The mean age (SD) was 2.9 years (1.12) in the FP/SLM group and 2.7 years (1.14) in the FP group. The mean age in months (SD) was 40.5 months (14.07) in the FP/SLM group and 38.4 months (14.10) in the FP group. The percentage of male was higher in both treatment groups (FP/SLM group: 63%; FP group: 60%). Regarding the severity of asthma, the majority of subjects in both treatment groups had moderate

persistent asthma or severe persistent asthma: subjects with moderate persistent accounted for 49% and 48% in the FP/SLM and FP groups, respectively; the subjects with severe persistent accounted for 41% and 46% in the FP/SLM and FP groups, respectively. The duration of asthma was >= 1 year and <2 years in the majority of subjects for both treatment groups (FP/SLM group: 33%, FP group: 31%), with asthma duration being <3 years in >=89% of the subjects. Subjects with atopic-type asthma totalled 66% in the FP/SLM group and 54% in the FP group.

There were no obvious differences between the treatment groups relating to any baseline disease characteristics of subjects.
The mean asthma symptom score at baseline (SD) was 11.5 points (4.57) for the FP/SLM group and 11.4 points (4.57) for the FP group. More than 50% of the subjects had the asthma symptom score of >=10 points (60% in the FP/SLM group and 57% in the FP group). The mean JPAC score at baseline (SD) was 13.3 points (2.85) in the FP/SLM group and 12.8 points (3.33) in the FP group.
The majority of subjects (110 subjects [73%] in the FP/SLM group and 117 subjects [78%] in the FP group) had experienced asthma exacerbations that were managed without oral/systemic corticosteroids (and not involving hospitalization) within the last 12 months before Visit 1. More than 50% of subjects (81 subjects [54%] in the FP/SLM group and 87 subjects [58%] in the FP group) had experienced asthma exacerbations requiring oral/systemic corticosteroids (but not involving hospitalization) within the last 12 months before Visit 1. Of these, 35 subjects (23%) in the FP/SLM group and 24 subjects (16%) in the FP group had experienced 3 or more than 3 asthma exacerbations. Forty-four subjects (29%) in the FP/SLM group and 51 subjects (34%) in the FP group had experienced asthma exacerbations that required hospitalization within the last 12 months before Visit 1; of these, 4 subjects (3%) in the FP/SLM group and 10 subjects (7%) in the FP group experienced 3 or more than 3 asthma exacerbations.

Baseline disease characteristics by age group
The baseline disease characteristics are summarized by age group (<2 years, >=2 years)
There were no obvious differences in baseline disease characteristics between the treatment groups in either age group. Furthermore, there was no obvious difference in baseline disease characteristics between the subgroups.

Prior medication:
The most frequently used pre-screening asthma medications were similar between the treatment groups and were leukotriene receptor antagonists (81% in the FP/SLM group, 85% in the FP group) and inhaled corticosteroids (80% in the FP/SLM group, 83% in the FP group). The types of inhaled corticosteroids used by the subjects prior to screening were ICS alone (81% in the FP/SLM group, 73% in the FP group) and ICS+LABA (any patch, oral or inhaler) (19% in the FP/SLM group, 27% in the FP group).

The most frequently used concomitant asthma medications during the run-in period were similar between the treatment groups: montelukast sodium (53% in the FP/SLM group, 49% in the FP group), pranlukast (25% in the FP/SLM group, 32% in the FP group), and carbocisteine (10% in the FP/SLM group, 13% in the FP group).

The extent of exposure in the two groups is shown in the table below:

	FP/SLM (N=150)	FP (N=150)
Daily Dose		
<2 year-old and 2 puffs per day, n (%)	25 (17)	26 (17)
≥2 year-old and 2 puffs per day, n (%)	67 (45)	58 (39)
≥2 year-old and 4 puffs per day, n (%)	58 (39)	66 (44)

Treatment compliance during treatment period 1 was high in both treatment groups. The mean treatment compliance (SD) was 98.93% (2.889) in the FP/SLM group and 99.03% (4.461) in the FP group. Most of the subjects in each treatment group had >=95% compliance (FP/SLM group: 91%, FP group: 97%).

Treatment compliance during treatment period 2 was high in the FP/SLM group, with most subjects having >=95% compliance.

- Efficacy results

Primary Efficacy Results (Total Asthma Symptom Score)
The primary endpoint was the mean change from baseline in total asthma symptom scores (daytime plus night-time) over the last 7 days of treatment period 1. Subjects received 8 weeks of treatment during treatment period 1.

Table 19 Statistical Analysis of Mean Change from Baseline in Total Asthma Symptom Score (Daytime plus Night-time) Over the Last 7 Days of Treatment Period 1 (ITT Population)

	FP/SLM N=150	FP N=150
Change from baseline to Endpoint, n	148	142
LS Means (SE)	-3.97 (0.534)	-3.01 (0.545)
LS Means Difference vs FP	-0.97	-
95% CI	(-2.47, 0.54)	-
p-value	0.206	-

The results in the per protocol population were consistent with the results in the ITT Population. The results of sensitivity analyses using LOCF were consistent with those from the primary efficacy analysis.

Table 20 Weekly Total Asthma Symptom Score (Daytime plus Night-time): Mean Change from Baseline to Endpoint by Age Group (Period 1, ITT Population)

		FP/SLM	FP
< 2 years	Baseline, n	25	26
	Mean (SD)	10.52 (4.194)	12.77 (4.844)
	Endpoint, n	24	25
	Mean change (SD)	-3.96 (5.729)	-2.88 (5.380)
>=2 years	Baseline, n	125	124
	Mean (SD)	11.70 (4.632)	11.09 (4.474)
	Endpoint, n	124	117
	Mean change (SD)	-3.97 (6.665)	-3.04 (7.074)
Overall of ITT population	Baseline, n	150	150
	Mean (SD)	11.50 (4.570)	11.38 (4.568)
	Endpoint, n	148	142
	Mean change (SD)	-3.97 (6.504)	-3.01 (6.790)

Period 2: The mean change from baseline in weekly total asthma symptom scores at the end of treatment period 2 (Week 24) was -3.98 points in the <2 year-old group and -5.99 points in the >= 2 year-old group for the FP/SLM total group. By treatment during period 1, the mean change from baseline in weekly total asthma symptom scores at Week 24 was -1.33 points (<2 year-old subgroup) and -7.03 points (>=2 year-old subgroup) for the FP/SLM-FP/SLM group and was -7.03 points (<2 year-old subgroup) and -5.01 points (>=2 year old subgroup) for the FP- FP/SLM group.

Secondary Efficacy Results

Night-time Asthma Symptoms Score
Period 1 (double-blind phase)
Statistical analysis of mean changes from baseline in night-time asthma symptom scores over the last 7 days of treatment period 1 is presented below

The mean change from baseline in weekly night-time asthma symptom scores at the end of treatment period 2 (Week 24) was -2.93 points in the FP/SLM total group. By treatment during treatment period 1, the mean change from baseline in weekly night-time asthma symptom scores at Week 24 was -3.04 points in the FP/SLM-FP/SLM group and -2.83 points in the FP-FP/SLM group.

Table 23 Statistical Analysis of Mean Change from Baseline in Night-time Asthma Symptom Score Over the Last 7 Days of Treatment Period 1 (ITT Population)

	FP/SLM N=150	FP N=150
Change from baseline to Endpoint, n	148	142
LS Means (SE)	-2.10 (0.286)	-1.61 (0.292)
LS Means Difference vs FP	-0.49	-
95% CI	(-1.29, 0.32)	-
p-value	0.235	-

Period 2: The mean change from baseline in weekly night-time asthma symptom scores at the end of treatment period 2 (Week 24) was -2.93 points in the FP/SLM total group. By treatment during treatment period 1, the mean change from baseline in weekly night-time asthma symptom scores at Week 24 was -3.04 points in the FP/SLM-FP/SLM group and -2.83 points in the FP-FP/SLM group.

Daytime Asthma Symptoms Score
Period 1 (double-blind phase)
Statistical analysis of mean changes from baseline in daytime asthma symptom scores over the last 7 days of treatment period 1 is presented

Table 25 Statistical Analysis of Mean Change from Baseline in Daytime Asthma Symptom Score Over the Last 7 Days of Treatment Period 1 (ITT Population)

	FP/SLM N=150	FP N=150
Change from baseline to Endpoint, n	148	142
LS Means (SE)	-1.87 (0.281)	-1.39 (0.287)
LS Means Difference vs FP	-0.48	-
95% CI	(-1.27, 0.31)	-
p-value	0.236	-

Period 2: The mean change from baseline in weekly daytime asthma symptom scores at the end of treatment period 2 (Week 24) was -2.76 points in the FP/SLM total group. By treatment during period 1, the mean change from baseline in weekly daytime asthma symptom scores at Week 24 was -3.06 points in the FP/SLM-FP/SLM group and -2.47 points in the FP-FP/SLM group.

Asthma Exacerbations
Period 1 (double-blind phase)
The number of subjects who experienced asthma exacerbations over the 8 weeks of treatment period 1 was greater for the FP group (8 subjects, 5%) than for the FP/SLM group (4 subjects, 3%). The odds ratio of FP/SLM vs. FP group was 0.47 (95% CI: 0.14, 1.60)

Period 2:
The number of subjects who experienced asthma exacerbations over the 16 weeks of treatment period 2 was 15 (5%) in the FP/SLM total group. By treatment during treatment period 1, the number of subjects who experienced asthma exacerbations over treatment period 2 was 11 (7%) in the FP/SLM-FP/SLM group and 4 (3%) in the FPFP/SLM group.

Use of Rescue Medication
The rescue medication was salbutamol inhaler only in case of deterioration of asthma.

Table 30 Statistical Analysis of Mean Change from Baseline in Percentage of Days with Rescue-free 24 Hours over the Last 7 Days of Treatment Period 1 (ITT Population)

	FP/SLM N=150	FP N=150
Change from baseline to Endpoint, n	148	142
LS Means (SE)	-0.3 (2.11)	-2.9 (2.16)
LS Means Difference vs FP	2.6	-
95% CI	(-3.3, 8.6)	-
p-value	0.389	-

Period 2: The mean change from baseline in the percentage of days with rescue-free 24 hours at the end of treatment period 2 (Week 24) was 1.9% in the FP/SLM total group. By treatment during period 1, the mean change from baseline in the percentage of days with rescuefree 24 hours at Week 24 was 1.7% in the FP/SLM-FP/SLM group and 2.2% in the FPFP/ SLM group.

JPAC Score
Period 1 (double-blind phase)
With the JPAC questionnaire, the control status of asthma and interference with daily activities in the last month of treatment period 1 were assessed.

At baseline, the mean JPAC score was higher in the FP/SLM group (13.3 points) than that in the FP group (12.8 points). The LS mean change from baseline in JPAC scores at Visit 5 in the FP/SLM group (0.4 points) was greater than in the FP group (-0.3 points), and the treatment difference was statistically significant (p=0.041).

Period 2 The mean change from baseline in JPAC scores at visit 10 (Week 24) was 1.1 points in the FP/SLM total group. By treatment during period 1, the mean change from baseline in JPAC scores at Visit 10 was 1.1 points in the FP/SLM-FP/SLM group and 1.2 points in the FP-FP/SLM group.

- Safety results

Period 1: The incidence of on-treatment AEs was similar between the treatment groups, with 74% (111 subjects) in the FP/SLM group and 73% (110 subjects) in the FP group. The incidence of drug-related AEs was <1% (1 subject) in the FP group, while there were no drug-related AEs reported in the FP/SLM group.
No deaths were reported. The incidence of on-treatment SAEs was low in both treatment groups, with <1% (1 subject) in the FP/SLM group and 3% (5 subjects) in the FP group. None of the SAEs were considered to be related to the study drug.

Table 36 Overview of On-Treatment Adverse Events (Period 1, ITT Population)

	FP/SLM (N=150)	FP (N=150)	Total (N=300)
Any AE	111 (74)	110 (73)	221 (74)
AEs related to study drug	0	1 (<1)	1 (<1)
AEs leading to permanent discontinuation of study drug	0	4 (3)	4 (1)
AE leading to dose reduction	0	0	0
AE leading to dose interruption/delay	0	1 (<1)	1 (<1)
Any SAE	1 (<1)	5 (3)	6 (2)
SAEs related to study drug	0	0	0
Fatal SAEs	0	0	0
Fatal SAEs related to study drug	0	0	0

Period 2: The incidence of on-treatment AEs in the FP/SLM group was 91% (262 subjects). The incidence of drug-related AEs was <1% (2 subjects).
No deaths were reported. The incidence of on-treatment SAEs was 7% (20 subjects). None of the SAEs were considered by the investigator to be related to FP/SLM.
The incidence of post-treatment AEs was 28% (81 subjects). Of these, 4 subjects were considered related to the study drug (blood cortisol decreased).

Summary of On-treatment adverse events (≥2%)

Table 37 Overview of On-Treatment Adverse Events (Period 2, ITT2 Population)

	FP/SLM Total (N=288)
Any AE	262 (91)
AEs related to study drug	2 (<1)
AEs leading to permanent discontinuation of study drug	13 (5)
AE leading to dose reduction	1 (<1)
AE leading to dose interruption/delay	2 (<1)
Any SAE	20 (7)
SAEs related to study drug	0
Fatal SAEs	0
Fatal SAEs related to study drug	0

Table 39 Summary of On-Treatment Common Adverse Events (>=2% in Any Treatment Group) (Period 1, ITT Population)

System Organ Class Preferred Term	FP/SLM (N=150)	FP (N=150)	Total (N=300)
ANY EVENT	111 (74)	110 (73)	221 (74)
Infections and infestations	87 (58)	87 (58)	174 (58)
Upper respiratory tract infection	28 (19)	18 (12)	46 (15)
Nasopharyngitis	18 (12)	24 (16)	42 (14)
Bronchitis	15 (10)	13 (9)	28 (9)
Gastroenteritis	11 (7)	14 (9)	25 (8)
Pharyngitis	11 (7)	9 (6)	20 (7)
Hand-foot-and-mouth disease	9 (6)	4 (3)	13 (4)
Impetigo	5 (3)	3 (2)	8 (3)
Herpangina	3 (2)	4 (3)	7 (2)
Influenza	3 (2)	4 (3)	7 (2)
Otitis media	3 (2)	4 (3)	7 (2)
Sinusitis	3 (2)	4 (3)	7 (2)
Molluscum contagiosum	1 (<1)	3 (2)	4 (1)
Conjunctivitis	3 (2)	0	3 (1)
Respiratory, thoracic and mediastinal disorders	22 (15)	33 (22)	55 (18)
Upper respiratory tract inflammation	10 (7)	18 (12)	28 (9)
Asthma	4 (3)	13 (9)	17 (6)
Rhinorrhea	4 (3)	0	4 (1)
General disorders and administration site conditions	6 (4)	7 (5)	13 (4)
Pyrexia	6 (4)	7 (5)	13 (4)
Skin and subcutaneous tissue disorders	14 (9)	12 (8)	26 (9)
Urticaria	5 (3)	2 (1)	7 (2)
Miliaria	2 (1)	4 (3)	6 (2)
Gastrointestinal disorders	15 (10)	10 (7)	25 (8)
Diarrhoea	5 (3)	1 (<1)	6 (2)
Vomiting	2 (1)	4 (3)	6 (2)
Eye disorders	4 (3)	2 (1)	6 (2)
Conjunctivitis allergic	3 (2)	1 (<1)	4 (1)
Injury, poisoning and procedural complications	7 (5)	8 (5)	15 (5)
Arthropod sting	0	3 (2)	3 (1)

Table 40 Summary of On-Treatment Common Adverse Events (>=2%) (Period 2, ITT2 Population)

System Organ Class Preferred Term	FP/SLM Total (N=288)
ANY EVENT	262 (91)
Infections and infestations	220 (76)
Nasopharyngitis	68 (24)
Upper respiratory tract infection	56 (19)
Gastroenteritis	44 (15)
Bronchitis	43 (15)
Pharyngitis	39 (14)
Influenza	38 (13)
Sinusitis	20 (7)
Otitis media	17 (6)
Pneumonia	12 (4)
Tonsillitis	11 (4)
Conjunctivitis	10 (3)
Hand-foot-and-mouth disease	9 (3)
Molluscum contagiosum	8 (3)
Impetigo	7 (2)
Streptococcal infection	7 (2)
Adenovirus infection	6 (2)
Otitis media acute	6 (2)
Varicella	6 (2)
Respiratory syncytial virus infection	5 (2)
Respiratory, thoracic and mediastinal disorders	78 (27)
Asthma	35 (12)
Upper respiratory tract inflammation	34 (12)
Rhinorrhoea	7 (2)
Rhinitis allergic	5 (2)
Skin and subcutaneous tissue disorders	53 (18)
Eczema	12 (4)
Urticaria	10 (3)
Dermatitis diaper	6 (2)
Miliaria	6 (2)
Rash	6 (2)
Gastrointestinal disorders	47 (16)
Diarrhoea	14 (5)
Constipation	11 (4)
Vomiting	11 (4)
Injury, poisoning and procedural complications	25 (9)
Arthropod sting	7 (2)
Arthropod bite	5 (2)
General disorders and administration site conditions	12 (4)

Pyrexia	10 (3)
Eye disorders	19 (7)
Conjunctivitis allergic	9 (3)

Table 41 Summary of On-Treatment Common Adverse Events (>=2%) (Period 1 + Period 2, ITT Population)

System Organ Class Preferred Term	FP/SLM - FP/SLM (N=150)
ANY EVENT	139 (93)
Infections and infestations	125 (83)
Upper respiratory tract infection	44 (29)
Nasopharyngitis	40 (27)
Gastroenteritis	30 (20)
Bronchitis	27 (18)
Pharyngitis	26 (17)
Influenza	24 (16)
Hand-foot-and-mouth disease	15 (10)
Sinusitis	13 (9)
Conjunctivitis	10 (7)
Impetigo	10 (7)
Otitis media	10 (7)

Molluscum contagiosum	7 (5)
Pneumonia	7 (5)
Herpangina	5 (3)
Adenovirus infection	4 (3)
Otitis media acute	4 (3)
Streptococcal infection	4 (3)
Beta haemolytic streptococcal infection	3 (2)
Croup infectious	3 (2)
Exanthema subitum	3 (2)
Respiratory, thoracic and mediastinal disorders	51 (34)
Asthma	26 (17)
Upper respiratory tract inflammation	17 (11)
Rhinorrhoea	7 (5)
Epistaxis	3 (2)
Rhinitis allergic	4 (3)
Gastrointestinal disorders	36 (24)
Diarrhoea	11 (7)
Constipation	6 (4)
Vomiting	5 (3)
Cheilitis	3 (2)
Skin and subcutaneous tissue disorders	38 (25)
Eczema	9 (6)
Urticaria	8 (5)
Dermatitis diaper	6 (4)
Miliaria	5 (3)
Rash	4 (3)
Injury, poisoning and procedural complications	18 (12)
Arthropod bite	5 (3)
Eye disorders	16 (11)
Conjunctivitis allergic	8 (5)
Eye discharge	3 (2)
General disorders and administration site conditions	12 (8)
Pyrexia	10 (7)

On treatment AEs by age subgroup:
Period 1: The incidence of on-treatment AEs in the <2 year-old age subgroup was 80% in the FP/SLM group and 81% in the FP group. In the >=2 year-old subgroup, the incidence was 73% in the FP/SLM group and 72% in the FP group. There was no obvious difference in the incidence of on-treatment AEs between the subgroups.

A drug-related AE was reported in only 1 subject (stomatitis) of the FP group in the <2 year old subgroup

Period 2: The incidence of on-treatment AEs in the <2 year-old age subgroup was 98%. In the >=2 year-old subgroup, the incidence was 90%. No difference in the incidence of on treatment
AEs was evident between the subgroups.

Drug-related AEs occurred in 2 subjects (both with blood cortisol decreased) in the >=2 year-old subgroup

The AEs leading to discontinuation of the study drug were reported in 4 subjects (1 subject each of pneumonia, skull fracture, subdural haemorrhage, asthma and electrocardiogram QT prolonged) in the <2 year-old subgroup and in 9 subjects (7 subjects: asthma; 3 subjects: pneumonia; 1 subject: Henoch-Schonlein purpura) in the >=2 year-old subgroup.

On-Treatment Adverse Events by Number of Daily inhalations in >=2 Year-old Group

In the 2 puffs/day subgroup, the incidence of on-treatment AEs was 72% in the FP/SLM group and 76% in the FP group. In the 4 puffs/day subgroup, the incidence was 74% in the FP/SLM group and 68% in the FP group. There was no substantial difference between the two daily inhalation groups.

No drug-related AEs occurred in either subgroup

Adverse Events by Time of Onset

The AEs occurred at a similar incidence of 74% during >=Week 0 and <=Week 8, 76% during >Week 8 and <=Week 16, and 78% after >Week 16.

SAEs

No deaths were reported during the study.

None of the on-treatment SAEs were considered by the investigator to be related to the study drug. SAEs leading to discontinuation of the study drug were reported in 3 subjects (all with asthma) in the FP group.

Period 1

Table 46 Summary of On-Treatment Serious Adverse Events (Period 1, ITT Population)

System Organ Class Preferred Term	FP/SLM (N=150)	FP (N=150)	Total (N=300)
ANY EVENT	1 (<1)	5 (3)	6 (2)
Respiratory, thoracic and mediastinal disorders	0	4 (3)	4 (1)
Asthma	0	4 (3)	4 (1)
Infections and infestations	1 (<1)	1 (<1)	2 (<1)
Bronchitis	1 (<1)	0	1 (<1)
Gastroenteritis	0	1 (<1)	1 (<1)
Upper respiratory tract infection	0	1 (<1)	1 (<1)

Period 2: On-treatment SAEs were reported in 20 subjects, with asthma (8 subjects) and pneumonia (7 subjects) being the most frequently reported SAEs. None of the SAEs were considered by the investigator to be related to the study drug. SAEs that led to discontinuation of the study drug were reported in 12 subjects

Haematology and Clinical Chemistry:

Period 1: None of the haematology or clinical chemistry parameters showed any clear changes from baseline at Visit 5 in either treatment group.

Period 2: None of the haematology/ clinical chemistry parameters showed any clear changes from baseline at Visit 10.

Plasma cortisol:
Although there was some inter-subject variability, no apparent decrease from baseline in the plasma cortisol level was noted at Visit 5 in either the FP/SLM or the FP group. For period 2, although there was some inter-subject variability, no apparent decrease from baseline in the plasma cortisol level was noted at Visit 10.

12 lead ECG
Period 1:
At Visit 2, no clear changes from baseline (at screening) were observed in the ECG values nor in the ECG values after 5 to 10 minutes of dosing with the study drug (FP/SLM or FP) in any ECG parameter for either the FP/SLM or FP group. No clinically significant abnormal ECG findings were observed in any subject for either the FP/SLM or FP group. Similarly, no noteworthy shift in ECG findings from baseline to 5 to 10 minutes after dosing with the study drug was observed with no difference seen between the FP/SLM and FP groups.
There were no AEs related to 12-lead ECG during treatment period 1.
No marked differences were noted between the <2 year-old and >=2 year-old subgroups nor between the 2 puffs/day and 4 puffs/day subgroups at Visit 2.

Period 2:
At Visit 5, overall, no clear changes from baseline (at screening) were observed in the ECG value nor in the ECG value after 5 to 10 minutes of dosing with the study drug (ie, FP/SLM, the study drug for treatment period 2). Furthermore, no clear changes from baseline were observed in the ECG values at either Visit 8 or Visit 10.

Electrocardiogram QT prolonged was reported as an AE in 2 subjects [both aged 1 year]) during treatment period 2. Both of these events were reported in ECG results at Visit 5, were considered mild in intensity, and deemed unrelated to the study drug.

Furthermore, no clinically significant abnormal ECG findings were observed at either Visit 8 or Visit 10.
No major differences were noted between the <2 year-old and >=2 year-old subgroups nor between the 2 puffs/day and 4 puffs/day subgroups at Visit 5. No major differences were noted between the <2 year-old and >=2 year-old subgroups at either Visit 8 or Visit 10.

3. Discussion on clinical aspects

Although FP/SLM was approved for treatment of paediatric bronchial asthma in Japan, no safety or efficacy data are available in any appropriate and well-planned clinical studies in infants and young children aged <=4 years. Therefore, safety of FP/SLM in these young children has not been established. The JPGL2012 recommends that, in the long term management of paediatric bronchial asthma in children aged <=5 years, an ICS/LABA combination including FP/SLM should be considered as a treatment choice for children with highly severe bronchial asthma requiring treatment with LABA.

However, the JPGL2012 warrants that further assessments are necessary to establish its safe use. Accordingly, this study was conducted with the aim of evaluating efficacy and safety of FP/SLM in Japanese patients aged <=4 years with infantile bronchial asthma.

This study evaluated the efficacy and safety of FP/SLM compared with FP over the 8 weeks of treatment period 1 in Japanese asthmatic children aged 6 months to 4 years. Additionally, the study assessed the long-term safety of FP/SLM by extending the treatment duration for another 16 weeks. Three hundred subjects who entered treatment period 1 were randomized to receive the study drug, 150 subjects to the FP/SLM group and 150 subjects to the FP group. The demographic characteristics were generally similar between the two treatment groups.

Regarding the randomized subjects aged <2 years, 25 subjects (17%) were in the FP/SLM group and 26 subjects (17%) were in the FP group. With regard to the randomized subjects aged >=2 years, 125 subjects (83%) were in the FP/SLM group and 124 subjects (83%) in the FP group. The dose of study drug for treatment period 1 was 2 puffs/day for the subjects aged <2 years for the sake of safety, and either 2 puffs/day or 4 puffs/day as judged by the investigator for the subjects aged >=2 years. A total of 288 subjects who completed treatment period 1 entered treatment period 2. In treatment period 2, subjects started receiving FP/SLM with the same number of puffs as they did during treatment period 1. The FP/SLM dose could be increased or decreased (2 puffs/day or 4 puffs/day) depending on the condition of subjects at the discretion of the investigator (or sub investigator). FP/SLM was administered for up to 175 days.

In the double-blind phase (treatment period 1), the mean change from baseline in the total asthma symptom score (daytime plus night-time), the primary efficacy endpoint, showed a numerical improvement in both the FP/SLM and FP groups, with a mean change of - 3.97 in the FP/SLM group and -3.01 in the FP group; however, no statistically significant difference in favour of FP/SLM was observed (95% Cl [-2.47; 0.54], p=0.206) between the treatment groups. Unlike with older children and adults, it is difficult to conduct an objective assessment using pulmonary-function testing with infants and young children, and therefore, the symptom score rated by the parent was selected as the primary efficacy endpoint.

However, high intersubject variability was observed and no superiority of FP/SLM to FP was demonstrated for the primary endpoint. The outcomes of assessment by age group (<2 years, >=2 years) and by daily inhalation group in subjects aged >=2 years (2 puffs/day, 4 puffs/day) showed a similar trend between the subgroups. The number of subjects who experienced asthma exacerbations during the 8 weeks of treatment period 1, the secondary endpoint, was 4 in the FP/SLM group and 8 in the FP group, indicating that the risk of developing asthma exacerbations in the FP/SLM group was numerically approximately 0.5-fold that in the FP group (odds ratio: 0.47; 95% Cl [0.14, 1.60]) although confidence intervals were too wide to provide certainty.
The mean change from baseline in the JPAC score was 0.4 in the FP/SLM group and -0.3 in the FP group. The estimated difference reached statistical significance in favor of the FP/SLM group (95% Cl [0.0, 1.4], p=0.041). However the clinical significance of the magnitude of difference is questionable.
The percentage of days with rescue-free 24 hours at baseline was high in both treatment groups, 87.9% in the FP/SLM group and 87.7% in the FP group, and consequently, there was little change from baseline at the end of the 8 weeks of treatment period 1 (FP/SLM: -0.3, FP: -2.9).

Although FP/SLM demonstrated no clear superiority to FP for most of the efficacy endpoints, there was a trend in terms of exacerbation and JPAC scores favouring FP/SLM. However this is not confirmed.

During treatment period 2, further reductions in the total asthma symptom score were observed for both FP/SLM-FP/SLM and FP-FP/SLM groups. The reduction from baseline (the last seven days in run-in period) was 6.10 points and 5.29 points for the FP/SLM-FP/SLM and FP-FP/SLM groups, respectively. Improvement with administration of FP/SLM was also observed in terms of other endpoints during treatment period 2.

In the double-blind phase (treatment period 1), the overall incidence of AEs during the 8-week treatment period was 74% in the FP/SLM group and 73% in the FP group. The most frequently reported AEs in the FP/SLM group were upper respiratory tract infection (19%), nasopharyngitis (12%), and bronchitis (10%); while in the FP group, nasopharyngitis (16%), upper respiratory tract infection (12%), and upper respiratory tract inflammation (12%) were most frequently reported. There were no major differences between the two treatment groups. Comparable results were demonstrated between the two treatment groups for SAEs and AEs of special interest. These AE profiles were generally consistent with the known safety profile of FP/SLM reported in adults or children aged >=5 years, with no new issues of clinical concern with FP/SLM treatment identified.
With respect to plasma cortisol measurements, plasma cortisol decrease was reported as an AE in 1 subject of the FP group during treatment as well as in 1 subject of the FP/SLM group during post-treatment in treatment period 1. However, on the whole, no substantial change was noted in either of the treatment groups over the 8 weeks of treatment period 1.
Regarding the 12-lead ECG values, no AEs were observed. In addition, no clinically significant changes were observed in other laboratory assessments, with no substantial differences noted between the treatment groups.
Although these measurements had some variations due to the subjects being infants and young children, no marked differences were noted between the age groups (<2 year-old and >=2 year-old subgroups) or between the daily inhalation groups (2 puffs/day and 4 puffs/day subgroups). Moreover, no major differences associated with age, FP dose, and coadministration with SLM were observed for the safety profile between the FP/SLM and FP groups.

In the open-label phase (treatment period 2), the overall incidence of AEs was 91% in the FP/SLM group. The most frequently reported AEs were nasopharyngitis (24%), upper respiratory tract infection (19%), gastroenteritis (15%), bronchitis (15%), pharyngitis (14%), influenza (13%), asthma (12%), and upper respiratory tract inflammation (12%). These events were also reported in the FP/SLM and FP groups during treatment period 1.
The incidence of drug-related AEs was low, <1%. No deaths were reported. The overall incidence of SAEs was 7%. None of the SAEs were considered to be related to the study drug.
In subjects who received FP/SLM throughout periods 1 and 2, AEs occurred at a similar incidence during each of the three 8-week periods.
With respect to plasma cortisol measurements, shifts in plasma cortisol from the normal range to low values were observed. Of these, shifts deemed as AEs were reported in 3 subjects during treatment period 2 in the FP/SLM group and in 11 subjects during the post-treatment period. No substantial changes were observed with 24 weeks of treatment throughout treatment periods 1 and 2 in the FP/SLM-FP/SLM group.

Electrocardiogram QT prolonged was reported as an AE in 2 subjects during treatment period 2. Both of these events were reported in ECG results at Visit 5 (5 to 10 minutes post-dose with the study drug); both were considered mild in intensity and deemed unrelated to the study drug. One of these subjects discontinued the study drug due to the event. In addition, no clinically significant changes were observed in other laboratory assessments.
In summary, no new safety signals were identified with administration of FP/SLM in the 16-week extension period.

Conclusion: In this study, FP/SLM (2 puffs/day, 4 puffs/day) did not show superior efficacy to FP (2 puffs/day, 4 puffs/day); no clear add-on effect of SLM (LABA) was demonstrated in this study. There was a trend in infants and young children in terms of exacerbation and JPAC scores favouring FP/SLM, which was not confirmed. No clinically significant difference was noted in the safety profile over the 8 weeks of treatment period 1 between the FP/SLM and FP groups.
After week 8, further reductions in the symptom score were seen during administration of FP/SLM. In addition, no new safety signals were identified with 24-week treatment with FP/SLM.
Although further evaluation will be necessary, as no efficacy or safety data for FP/SLM on infants and young children are available, the results from this study are likely to become one of useful findings for the efficacy and safety of FP/SLM in infants and young children.

V. ASSESSMENT OF RESPONSE TO QUESTIONS RAISED AT DAY 89

1. CMS proposed to replace "*There are no data available for use of X in children aged under 4 years*." in Section 4.2 by "*The safety and efficacy of X in children aged under 4 years has not been established.*" The RMS which had intially suggested deletion, agrees with this recommendation.

   MAH response:
   GSK agrees to the proposal by the CMS to replace the current sentence "There are no data available for use of X in children aged under 4 years." with "The safety and efficacy of X in children aged under 4 years has not been established".

   Assessor's comment:

   The requested change in section 4.2 has been made. This is now acceptable

2. The paediatric information in Section 5.1 of the SPC should be updated to reflect the results of the study, the applicant is asked to give a proposal. The following points were raised by CMSs:
   (a) Present the efficacy and safety results.
   (b) With regard to efficacy, the study failed to meet its objective. No superiority of FP/SLM to FP was demonstrated for the primary endpoint (95% CI [-2.47; 0.54], p=0.206) in 6-month to 4-year-old children.
   (c) With regard to data conclusivity: Difficult to make a confident diagnosis of asthma in children 4 years and younger, therefore conclusive data is difficult to obtain.
   (d) Include statement on the safety findings.

   MAH response:
   GSK proposes to add the following paragraph to section 5.1 of the SmPC:-

A multi-centre 8-week, double-blind, study was conducted to evaluate the safety and efficacy of salmeterol-FP metred dose inhaler (50/25 micrograms, 1 or 2 inhalations twice daily) versus FP (50 micrograms, 1 or 2 inhalations twice daily) alone in Japanese paediatric (6-month to 4 years of age) patients with infantile bronchial asthma. The safety of long-term treatment with salmeterol-FP metred dose inhaler (50/25 micrograms, 1 or 2 inhalations twice daily) was evaluated in a 16-week, open-label, extension treatment period. Ninety-one percent (136/150) and eighty-eight percent (132/150) of randomised patients treated with salmeterol-FP and FP alone, respectively, completed the study. The study failed to meet its primary efficacy endpoints of mean change from baseline in total asthma sympton score (double blind period). No statistically significant superiority in favour of salmeterol-FP to FP was demonstrated (95% CI [-2.47; 0.54], p=0.206). No clinically significant differences were noted in the safety profile between salmeterol-FP and FP alone (8-week double-blind period); moreover, no new safety signals were identified with administration of salmeterol-FP in the 16-week open-label extension period. There were no patient deaths. It is difficult to make a confident diagnosis of asthma in children 4 years and younger, therefore conclusive data is difficult to obtain. Salmeterol-FP is not approved in children under 4 years old. (See Module 1.3.1).

Assessor's comment:

The proposed text presents a summary of the efficacy and safety results and clearly states that the study failed to meet its objective and that no superiority of FP/SLM to FP was demonstrated for the primary endpoint. Ten proposed text acknowledges that it is difficult to make a confident diagnosis of asthma in children 4 years and younger, therefore conclusive data is difficult to obtain. The safety results including the lack of new safety signals is presented. Language edit – the last phrase in brackets This text is acceptable

VI. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Although the above trial did not establish superiority of FP/SLM over FP in children 6m-4y, changes in the SPC are merited (sections 4.2 and 5.1).

- **Recommendation**

Type IB variation concerning amendments to Section 4.2 and 5.1 of the SPC as detailed above to be requested from the MAH.

4.2 Posology and method of administration

…

Paediatric population

…

~~There are no data available for use of Seretide inhaler in childern aged under 4 years.~~ **The safety and efficacy of Seretide inhaler in children aged under 4 years has not been established**.

…

5.1 Pharmacodynamic properties

…

Paediatric population:

…

A multi-centre 8-week, double-blind, study was conducted to evaluate the safety and efficacy of salmeterol-FP metred dose inhaler (50/25 micrograms, 1 or 2 inhalations twice daily) versus FP (50 micrograms, 1 or 2 inhalations twice daily) alone in Japanese paediatric (6-month to 4 years of age) patients with infantile bronchial asthma. The safety of long-term treatment with salmeterol-FP metred dose inhaler (50/25 micrograms, 1 or 2 inhalations twice daily) was evaluated in a 16-week, open-label, extension treatment period. Ninety-one percent (136/150) and eighty-eight percent (132/150) of randomised patients treated with salmeterol-FP and FP alone, respectively, completed the study. The study failed to meet its primary efficacy endpoint of mean change from baseline in total asthma symptom score (double blind period). No statistically significant superiority in favour of salmeterol-FP to FP was demonstrated (95% CI [-2.47; 0.54], p=0.206). No clinically significant differences were noted in the safety profile between salmeterol-FP and FP alone (8-week double-blind period); moreover, no new safety signals were identified with administration of salmeterol-FP in the 16-week open-label extension period. There were no patient deaths. It is difficult to make a confident diagnosis of asthma in children 4 years and younger, therefore conclusive data is difficult to obtain. Salmeterol-FP is not approved in children under 4 years old.

…