Rapporteur's Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Salmeterol + Fluticasone propionate

(Seretide®)

DE/W/047/pdWS/001

Rapporteur:	Germany
Finalisation procedure (Day 120):	25.05.2013
Date of finalisation of PAR:	25.06.2013

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VIII
INN (or common name) of the active substance(s):	Salmeterol / Fluticasone propionate
MAH (s):	See section VIII
Pharmaco-therapeutic group (ATC Code):	R03AK06
Pharmaceutical form(s) and strength(s):	Inhalation powder

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 5.1, 5.2 (SmPC) and 3 (PL).

<Summary of outcome>

☐ No change

X Change

- ☐ New study data: <section(s) xxxx, xxxx>
- ☐ New safety information: <section(s) xxxx, xxxx>
- X Paediatric information clarified: sections 5.1, 5.2 and 3
- ☐ New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION

Based on the studies submitted for this paediatric worksharing procedure an update of Section 5.1, 5.2 of the SPC and 3 of the PL is proposed.

III. INTRODUCTION

Salmeterol/fluticasone propionate Diskus/Accuhaler is approved via the mutual recognition procedure in Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden and UK. The SmPC is the same in these countries. For the nationally salmeterol/fluticasone propionate Diskus SmPCs Bulgaria, Cyprus, Czech Republic, Hungary, Iceland, Lithuania, Malta and Slovakia also have the same text. Minor differences exist in the SmPCs of Estonia, Poland, Romania and Slovenia. Latvia and Norway are more aligned with GSK's company global datasheet.

Please note that comments and recommendations in this document are based on the MRP version of the SmPC.

GSK submitted 12 completed paediatric study(ies) for the combination product salmeterol /fluticasone propionate, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. In addition Study SAS30019 was included. This study has been reviewed in the majority of the EU MSs except for Cyprus, Latvia, Romania and Slovakia.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study(ies) do not influence the benefit risk for Seretide and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- An annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product.

IV. SCIENTIFIC DISCUSSION

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

Seretide is a combination product containing salmeterol and fluticasone propionate. It is marketed in two formulations:
Diskus (Accuhaler): A multi-dose dry powder inhaler (DPI) containing 50mcg salmeterol and 100mcg, 250mcg or 500mcg fluticasone propionate.
Evohaler: A metered dose inhaler (MDI) emitting salmeterol xinafoate equivalent to 25 mcg of salmeterol and 50,125,250 mcg of fluticasone propionate per actuation.

A worksharing procedure under Article 46 has been completed in January 2010 and variations to implement the outcome of this procedure have been submitted across the EU.

IV.2 Non-clinical aspects

Not applicable as no non-clinical studies have been submitted.

IV.3 Clinical aspects

1. Introduction

The MAH submitted 12 studies/ extended synopses which are displayed below:

Study Code: SAM40101
Study Title: A pilot single centre, randomised, double-blind crossover study to demonstrate the superiority of Salmeterol/fluticasone propionate combination product 50/100mcg bd versus fluticasone propionate 100mcg bd when treated for two weeks with respect to activity levels in children aged 7-15 years.
GSK Study Report Number: GM2003/00237/00

Study Code: SFA100314
Study Title: A Stratified, Multicenter, Randomized, Double-Blind, Parallel Group, 4-Week Comparison of Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50mcg BID versus Fluticasone Propionate DISKUS 100/50mcg BID in Pediatric and Adolescent Subjects with Activity-Induced Bronchospasm.
GSK Study Report Number: RM2005/00343/00

Study Code: SFA100316
Study Title: A Stratified, Multicenter, Randomized, Double-Blind, Parallel Group, 4- Week Comparison of Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50mcg BID versus Fluticasone Propionate DISKUS 100mcg in Pediatric and in adolescent Subjects with Activity-Induced Bronchospasm.
GSK Study Report Number: RM2005/00345/00

Study Code: SAM40012
Study Title: A Multicentre, Randomised, Double-blind, Double-dummy, Parallel Group Comparison of Three Treatments: 1) Seretide 50/100 mcg bd via Diskus/Accuhaler Inhaler, 2) Fluticasone Propionate 200 mcg bd via Diskus Inhaler, 3) Fluticasone Propionate 100mcg bd via Diskus/Accuhaler Inhaler in Children Aged 4-11 Years with Asthma.
GSK Study Report Number: BP1999/00102/00

Study Code: SAS30021
Study Title: A Stratified, Randomized, Double-Blind, Placebo-Controlled, Parallel- Group, 12-Week Trial Evaluating the Safety and Efficacy of the Fluticasone Propionate/Salmeterol Diskus Combination Product 100/50mcg Once Daily Versus Fluticasone Propionate Diskus 100mcg Once Daily and Placebo in Symptomatic Pediatric Subjects (4-11 Years) With Asthma.
GSK Study Report Number: RM2004/00007/00

Study Code: SAS30031
Study Title: A Randomized, Double-Blind, 12-Week Trial Evaluating the Safety of the Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50mcg BID Versus Fluticasone Propionate DISKUS 100mcg BID in Symptomatic Pediatric Subjects (4-11 Years) With Asthma.
GSK Study Report Number: RM2002/00268/00

Study Code: SAM40100

Study Title: Single centre, randomised, double-blind, comparator study to demonstrate he superiority of salmeterol/fluticasone propionate combination DISKUS/ACCUHALER 50/100mcg bd over fluticasone propionate DISKUS/ACCUHALER 200mcg bd with respect to airway physiology in asthmatic children treated for 6 weeks
GSK Study Report Number: GM2006/00205/00

Study Code: ADERE PEDIATRIC 1
Study Title: Prospective, parallel-group, randomized, open label study to evaluate the impact of additional guidance from the health professionals team on treatment compliance of children aged between 6 and 14 years old with persistent moderate or severe asthma, receiving the combination salmeterol/fluticasone propionate 50/250 mcg (Seretide) twice a day.
GSK Study Report Number: ICH E3 Summary

Study Code: SAS30018
Study Title: Comparison of stepwise treatment of asthmatic children with salmeterol/fluticasone propionate (FP) combination product (Seretide) and/or fluticasone propionate (Flixotide) based on PD20 methacholine plus symptoms or based on symptoms only (Children Asthma Therapy Optimal - CATO)
GSK Study Report Number: ICH E3 Summary

Study Code: SAM 3802
Study Title: An observational study to assess the health related quality of life impact of treating poorly controlled asthmatic children with Seretide 50/100mcg
GSK Study Report Number: ICH E3 Summary

Study Code: SAM40121
Study Title: Summary of the efficacy and safety and safety of salmeterol 50mcg and fluticasone propionate 100mcg administered in Diskus Dry Powder Inhaler twice daily in steroid experienced children with reversible airways obstruction
GSK Study Report Number: ICH E3 Summary

Study Code: SAS10016
Study Title: A 2-week, randomized, double-blind, parallel-group study in pediatric subjects with asthma aged 4 to11 years to examine the pharmacokinetics of fluticasone propionate (FP) and salmeterol (SALM) from the FP/SALM combination product administered twice daily via the Diskus (FP 100mcg/SALM 50mcg) and the FP Diskus (FP 100mcg).
GSK Study Report Number: RM2004/00114/00

In addition Study SAS30019 which has been reviewed before has been submitted:
Study Code: SAS30019
Study Title: A multicentre, randomised, double-blind, double-dummy, parallel group study to compare the salmeterol/fluticasone propionate combination (SERETIDE*/VIANI*/ADVAIR*) delivered via either a dry powder inhaler (DISKUS*/ACCUHALER*) or via a non-chlorofluorocarbon (CFC) metered-dose inhaler (MDI), both at a dose of 50/100mcg twice daily for 12 weeks, in the treatment of children aged 4-11 years with asthma.
GSK Study Report Number: GM2003-00011-01

2. Clinical study(ies)

SAM40101 A pilot single centre, randomised, double blind crossover study to demonstrate the superiority of Salmeterol/Fluticasone propionate combination product

50/100mcg bd versus fluticasone propionate 100 mcg bd when treated for two weeks with respect to activity levels in children aged 7-15 years (2004)

- **Objective(s)**

To demonstrate superiority of salmeterol/formeterol combination product 50/100 mcg over fluticasone propionate 100mcg bd with respect to increased physical activity in children with mild asthma.

- **Study design**

Single centre (Denmark), two-way cross over randomised pilot study with a three week single blind placebo run-in followed by a two week double blind active period. The study included a three week single blind placebo wash-out period.

- **Study population /Sample size**

Male and female asthma patients receiving 400 mcg of beclomethasone dipropionate or equivalent with physician documented activity induced symptoms and/or impaired involvement in activities due to asthma were eligible.
The between subject variability of the data generated with the foot pod device was not known and a formal sample size calculation was not possible. The planned sample size was 30 patients.

- **Treatments**

Fluticasone propionate/Salmeterol 50/100 mcg bid via Diskus inhaler
Or
Fluticaosne propionate 100 mcg bid via Diskus inhaler

Outcomes/endpoints

Primary endpoint: total distance recorded by the foot pod during set physical activities which was recorded on the daily record card by subjects.

Secondary assessment included mPEF and ePEF, FEV1, FeNO and PAQLQ.

- **Statistical Methods**

The study was designed to show superiority of the combination product over fluticasone propionate monotherapy. However the study was not powered to detect a specific treatment difference. The primary endpoint was compared between treatments using effects analysis of covariance model. The model included fixed effects for period, treatment and baseline.

➢ **Results**

- **Recruitment/ Number analysed**

32 patients were randomised and received both treatments. All subjects completed both arms of the study.

- **Efficacy results**

There was no difference between treatments as regards the primary parameter (combination: 2.27 km/h, monotherapy: 2.28 km/h (raw mean for both treatment periods)). The only statistically significant difference in secondary endpoints was seen for mPEF (combination-monotherapy: 11.67 l/min; p= 0.035) and ePEF (difference: 16.92 L/min; p=0.003).

- **Safety results**

22 subjects experienced a total of 38 adverse events. 14 subjects reported events during wash-out, when they were given placebo. 12 subjects reported events during Salmeterol/fluticasone propionate treatment (nasopharyngitis, headache, vomiting, pharyngolaryngeal pain). 3 subjects reported AEs during fluticasone propionate treatment (nasopharyngitis, headache). There were no SAEs or DAEs.

Conclusion:
No significant differences were seen with regard to the primary parameter, the total distance during set activities. No new safety signal was detected.

Assessor's comment: This was a small and rather short pilot study, which was inconclusive as regards the primary endpoint. MPEF as well as ePEF were significantly improved in the combination group compared to the monotherapy group. No new safety signal was detected.

SFA 100314 A Stratified, Multicenter, Randomized, Double-Blind, Parallel Group, 4-Week Comparison of Fluticasone Propionate/Salmeterol DISKUS® Combination Product 100/50mcg BID versus Fluticasone Propionate DISKUS 100mcg BID in Pediatric and Adolescent Subjects with Activity-Induced Bronchospasm (2003-2006)

Objective(s): The primary objective of this study was to demonstrate that the fluticasone propionate/salmeterol combination product (100/50mcg BID via DISKUS) provided superior long-term protection against bronchospasm induced by activity compared with fluticasone propionate 100mcg BID in pediatric and adolescent subjects aged 4 – 17 diagnosed with persistent asthma and who also experienced activity-induced bronchospasm.

- **Study design**

This was a stratified, randomized, double-blind, parallel group, multicenter (28 centres in the US) trial. During a 7 to 14-day run-in period, subjects received open-label fluticasone propionate 100mcg DISKUS BID. Qualified subjects were then randomized to receive a 4-week regimen of one of the following double-blind treatments: fluticasone propionate/salmeterol 100/50mcg DISKUS BID, or fluticasone propionate 100mcg DISKUS BID. Exercise challenge assessments were performed prior to randomization (Visit 2 – Eligibility Visit) and again after 4 weeks of treatment (Treatment Week 4 [Visit 5]).

- **Study population /Sample size**

Males and females aged 4 to 17 years with persistent asthma treated with ICS. All subjects were required to have a FEV1 of 70% to 95% of predicted normal. Each subject must have demonstrated a positive exercise challenge.
Based on data from previous studies, maximal percent fall in FEV1 following exercise challenge was assumed to be 11 percentage points. It was estimated that 103 subjects per treatment arm would provide 90% power to detect a difference of 5 percentage points in maximal percent fall in FEV1 between the two treatment groups.

- **Treatments**

Fluticasone propionate/Salmeterol 50/100 mcg bid via Diskus inhaler
Or
Fluticasone propionate 100 mcg bid via Diskus inhaler

Outcomes/endpoints
The primary efficacy endpoint was maximal percent fall in FEV1 following exercise challenge.

The secondary endpoints included 4-hour serial post-dose FEV1 AUC, mPEF, ePEF, and percentage of subjects who demonstrated a <10%, a ≥10% to <20%, and a ≥20% maximal fall in FEV1 following exercise challenge.

- **Statistical Methods**

The primary population for all statistical analyses was the intent-to-treat (ITT) population.
All statistical tests tested a two-sided hypothesis of no difference between treatment groups at a significance level of 0.05 unless specified otherwise.

➢ **Results**

- Recruitment/ Number analysed

248 patients were randomised. 111 subjects in the combination group and 102 subjects in the mono-therapy group completed the study. 2 patients in the salmeterol/ fluticasone propionate group compared to 7 subjects in the fluticasone propionate group withdrew due to an AE.

Baseline data:
Groups were balanced at baseline.

- **Efficacy results**

There was a statistically significant difference between treatments as regards the primary parameter maximal percent fall in FEV1 following exercise challenge (combination: -9.5 %, monotherapy: -12.7 % , p=0.021). Except for FEV1 AUC over the course of four hours, which was significantly greater in the combination therapy treatment group when compared to the FP treatment group, no statistically significant differences were seen in the secondary endpoints.

- **Safety results**

30% of the subjects in the salmeterol/fluticasone propionate group and 28% of the subjects in the fluticasone propionate group experienced adverse events. The most common AEs were headache and respiratory infection. No serious AEs were reported during double blind treatment. 2 subjects in the salmeterol/fluticasone propionate group and 7 subjects in the fluticasone propionate group were withdrawn due to an AE.

Conclusion:
At Treatment Week 4, the mean maximal percent fall in FEV1 observed after exercise challenges conducted approximately 8.5 hours post-dose, was significantly less in the combination therapy group when compared to the FP group in the ITT population. No new safety signal was detected.

Assessor's comment: This study showed that bronchoprotection measured as the percent fall in FEV1 after exercise challenge was significantly better with salmeterol/fluticasone propionate compared to fluticasone propionate monotherapy while most other secondary measures of efficacy did not show significant benefits. The clinical relevance is questionable. The significant improvement in FEV1AUC can be expected as fluticasone propionate monotherapy does not have a bronchodilatatory effect.

SFA 100316 A Stratified, Multicenter, Randomized, Double-Blind, Parallel Group, 4-Week Comparison of Fluticasone Propionate/Salmeterol DISKUS® Combination Product 100/50mcg BID versus Fluticasone Propionate DISKUS 100mcg BID in Pediatric and Adolescent Subjects with Activity-Induced Bronchospasm (2003-2005)

Objective(s): The primary objective of this study was to demonstrate that the fluticasone propionate/salmeterol combination product (100/50mcg BID via DISKUS) provided superior long-term protection against bronchospasm induced by activity compared with fluticasone propionate 100mcg BID in pediatric and adolescent subjects aged 4 – 17 diagnosed with persistent asthma and who also experienced activity-induced bronchospasm.

- **Study design**

This was a stratified, randomized, double-blind, parallel group, multicenter (31 centres in the US) trial. During a 7 to 14-day run-in period, subjects received open-label fluticasone propionate 100mcg DISKUS BID. Qualified subjects were then randomized to receive a 4-week regimen of one of the following double-blind treatments: fluticasone propionate/salmeterol 100/50mcg DISKUS BID, or fluticasone propionate 100mcg DISKUS BID. Exercise challenge assessments were performed prior to randomization (Visit 2 – Eligibility Visit) and again after 4 weeks of treatment (Treatment Week 4 [Visit 5]).

- **Study population /Sample size**

Males and females aged 4 to 17 years with persistent asthma treated with ICS. All subjects were required to have a FEV1 of 70% to 95% of predicted normal. Each subject must have demonstrated a positive exercise challenge.
Based on data from previous studies, maximal percent fall in FEV1 following exercise challenge was assumed to be 11 percentage points. It was estimated that 103 subjects per treatment arm would provide 90% power to detect a difference of 5 percentage points in maximal percent fall in FEV1 between the two treatment groups.

- **Treatments**

Fluticasone propionate/Salmeterol 50/100 mcg bid via Diskus inhaler
Or
Fluticasone propionate 100 mcg bid via Diskus inhaler

Outcomes/endpoints
The primary efficacy endpoint was maximal percent fall in FEV1 following exercise challenge. The secondary endpoints included 4-hour serial post-dose FEV1 AUC, mPEF, ePEF, and percentage of subjects who demonstrated a <10%, a ≥10% to <20%, and a ≥20% maximal fall in FEV1 following exercise challenge.

- **Statistical Methods**

The primary population for all statistical analyses was the intent-to-treat (ITT) population.
All statistical tests tested a two-sided hypothesis of no difference between treatment groups at a significance level of 0.05 unless specified otherwise.

➢ **Results**

- **Recruitment/ Number analysed**

231 patients were randomised. 106 subjects in the combination group and 108 subjects in the mono-therapy group completed the study. 1 patient in each group withdrew due to an AE.

Efficacy data for one investigator were removed from efficacy analyses due to significant deviations in Good Clinical Practice. A total of 15 (6%) subjects (7 and 8 subjects in the FSC and FP groups, respectively) were randomized to blinded study drug at this site. Removal of the efficacy data for these subjects did not affect the efficacy conclusions from the study.

Baseline data:
MPEF, ePEF and rescue free days were slightly higher in the fluticasone propionate group.

- **Efficacy results**

There was no statistically significant difference between treatments as regards the primary parameter maximal percent fall in FEV1 following exercise challenge (combination: -9.9 , monotherapy: -11.1 , p=0.158). The statistical analysis plan for this study designated specific step-down rules for the testing of the secondary efficacy measure. Comparison of treatment differences for the secondary measure of 4-hour serial post-dose FEV1 AUC on Treatment Day 1 was contingent upon obtaining a significant treatment difference for the primary measure of mean maximal percent fall in FEV1 following the exercise challenge test at Treatment Week 4. Since a significant treatment difference was not observed for analysis of the primary measure, all comparisons for the secondary and related secondary measures were not considered statistically significant.

- **Safety results**

18% of the subjects in the salmeterol/fluticasone propionate group and 21% of the subjects in the fluticasone propionate group experienced adverse events. The most common AEs were headache, gastroenteritis, pharyngeal pain and respiratory infection. No serious AEs were reported during double blind treatment. 1 subject in each group withdrew due to an AE.

Conclusion:
At Treatment Week 4, the mean maximal percent fall in FEV1 observed after exercise challenges conducted approximately 8.5 hours post-dose, was not significantly different in the combination therapy group when compared to the FP group in the ITT population. No new safety signal was detected.

Assessor's comment: This study was inconclusive as regards the primary endpoint.

SAM40012 A Multicenter, Randomized, Double-Blind, Parallel Group, Comparison of Three Treatments: 1.) Seretide ™ (100/50mcg strength) bid via Diskus™/Accuhaler™ Inhaler, 2.) Fluticasone Propionate 200 mcg bid via Diskus™ inhaler, 3.) Fluticasone Propionate 100mcg bid via Diskus™/Accuhaler™ Inhaler in children aged 4-11 years with asthma (2000-2001)

Objective(s): The primary objective of this study was to demonstrate that Seretide 100/50mcg BID is a more effective treatment than either fluticasone propionate 100mcg BID or fluticasone propionate 200mcg bid in asthmatic subjects aged 4 – 17 years.

- **Study design**

This was an international, multicenter, randomised, double-blind, double-dummy, parallel group, 24 week, Phase IV study.

- **Study population /Sample size**

Males and females aged 4 to 11 years with persistent asthma symptomatic on 400 to 500 mcg budesonide, beclomethasone dipropionate or equivalent daily.
It was anticipated that a sample size of 157 subjects per group would give at least 80 % power to detect a 10% difference between treatment groups in the mean percentage of combined symptom free days and nights using a Mann Whitney U test with a 5% two-sided significance level.

- **Treatments**

Fluticasone propionate/Salmeterol 100/50 mcg bid via Diskus inhaler
Or
Fluticasone propionate 100 mcg bid via Diskus inhaler
Or
Fluticasone propionate 200 mcg bid via Diskus inhaler

Outcomes/endpoints
The primary efficacy endpoint was percentage of combined symptom free days and nights as recorded in subjects' electronic daily record cards (MiniDoc eDRC) over the whole treatment period.
Secondary endpoints included mPEF, ePEF incidence of exacerbations, percentage of symptom-free days and nights.

- **Statistical Methods**

Each pairwise treatment comparison of the percentage of symptom-free 24-hour periods was undertaken using the Van Elteren extension to the Wilcoxon Rank Sum test, stratified by country. The Hodges-Lehmann estimator was used to estimate each pairwise treatment difference.

➢ **Results**

- **Recruitment/ Number analysed**

The ITT population included 176 patients in the combination therapy group, 175 patients in the fluticasone propionate 100mcg group and 180 patients in the fluticasone propionate 200mcg group. 173 patients in the combination group, 165 patients in the fluticasone propionate 100 mcg group and 175 patients in the fluticasone propionate 200 mcg group completed the study. Audit of one site raised concerns regarding GCP and protocol compliance and this site's participation in the study was terminated. Data for the 17 subjects randomised at this site were therefore listed separately and not included in the efficacy analyses for the ITT population, except for an analysis of the primary efficacy parameter performed on the safety population. The centre's 26 subjects were included in the safety analysis. Whilst the study was underway, it became evident that in a number of cases data had been entered incorrectly in the MiniDoc eDRC by the parent/subject or that the MiniDoc eDRC had failed. Therefore, a procedure was written for investigators to replace MiniDoc eDRCs. This process was termed Jump to Treatment (JTT) and the term was also applied to events where the MiniDoc eDRC failed during treatment and had to be replaced. Investigators were to fully document all JTT cases in the subjects'. notes and in a JTT events log, which was signed and dated by the investigator. Quintiles reviewed each JTT case and checked the JTT log against the subject's notes. Data from the first MiniDoc eDRC were only corrected where source data verification could be performed i.e. corrections for the data recorded in the MiniDoc eDRC had been documented in the subject's notes. This review was performed before unblinding. Furthermore, before unblinding, an independent check of subject eligibility was made of all the calculations made in the MiniDoc eDRCs by Quintiles and GSK. Overall, there were 251 JTT cases, (in 190 subjects), 167 occurred at Visit 2/2A and 84 during treatment.

Baseline data:
PEF (L/min) at baseline was higher in the comparator groups. The median value of symptom-free days and nights was 38.5%, 33.3% and 37.4% for the combination group, fluticasone propionate 100 mcg group and fluticasone propionate 200 mcg group, respectively.

- **Efficacy results**

During Weeks 1-24, each of the three groups showed an increase in the percentage of symptom-free combined days and nights with median values of 88.6%, 86.3% and 87.5% for the SFC50/100, FP100 and FP200 groups, respectively, for the ITT population. There were no statistically significant differences between the treatments for any of the comparisons made. During the 24-week treatment period, 12% of subjects were completely symptom-free for combined days and nights in the SFC50/100 group, in comparison with 3% and 8% in the FP100 and FP200 groups, respectively. During the run-in period, subjects required no relief medication for the majority of days and nights; during the treatment period there was a slight increase from the run-in values in the % of days with no relief medication. PEF (morning, evening and clinic) demonstrated steadily rising increases in each treatment group throughout the study, to the extent that all groups had a mean value of >100% predicted clinic PEF at the end of the treatment period. During the 24-week treatment period, 60%, 54% and 53% subjects in the SFC50/100, FP100 and FP200 groups, respectively, had no exacerbations. The three treatment groups were similar with regard to the results obtained from the health outcomes questionnaires and number of unscheduled asthma-related healthcare contacts. Because of the unexpectedly high number of JTT subjects, additional analyses were performed on the ITT population excluding JTT subjects. In contrast to the ITT population, where the JTT subjects were excluded there was a significant difference in favour of SFC50/100 compared with the FP100 group during weeks 1-24 (p=0.009) but no other statistically significant differences were observed. The results of these additional analyses provide support for a lack of confidence in the integrity of the ITT efficacy data in this study. For this reason, definitive conclusions regarding treatment-related differences cannot be made.

- **Safety results**

The incidence of AEs was generally similar across treatment groups. The SFC50/100 group had the lowest incidence of AEs which started during treatment, with 99 (55%) subjects in the SFC50/100 group, 111 (61%) in the FP100 group and 112 (60%) in the FP200 group reporting at least one event. The most common AEs (occurring in 5% or more subjects in any group) were: influenza, cough, fever, headache, common cold, viral infection, rhinitis, acute nasopharyngitis and pharyngitis. The incidence of these events was similar in each treatment group. The incidence of serious adverse events (SAEs) was low with two (1%) subjects in the SFC50/100 group reporting abdominal penetrating injury, left lung injury and hands lacerated (one patient) and hospitalisation for coeliac disease, one (<1%) in the FP100 group reporting pneumonia and four(2%) in the FP200 group reporting salmonella, acute laryngitis and viral infection, head contusion and multiple fractures. One further subject in the FP200 group has two SAEs reported on the safety database, which are not included in the study database because of the termination of centre 26 subjects'. participation in the study. Changes in urinary cortisol corrected for creatinine and uncorrected for creatinine showed no statistically significant differences between the treatments for any of the comparisons made. A subset analysis excluding incomplete samples (cortisol population) also showed no statistically significant differences between treatments. The withdrawal rates were generally low with three subjects (2%) in the SFC50/100 group, 10 (6%) in the FP100 group and five (3%) in the FP200 group withdrawing from the study. For only two subjects, both in the FP100 group, the reason for withdrawal was an AE which started during treatment (pneumonia and cough respectively).

Conclusion: No statistically significant differences were detected between the treatments for any of the comparisons made during Weeks 1-24. However, issues relating to Minidoc eDRC data integrity meant that no reliable efficacy conclusions regarding differences among treatments were possible. No safety signal was detected.

Assessor's comment. This study showed no statistically significant differences between treatments. The patient's rather mild nature of asthma might have played a role here. However, problems with the MiniDoc eDRC in a large number of patients render this study unanalysable anyway. No new safety signal was identified.

SAS30021 A Stratified, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 12-Week Trial Evaluating the Safety and Efficacy of the Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50mcg Once Daily Versus Fluticasone Propionate DISKUS 100mcg Once Daily and Placebo in Symptomatic Pediatric Subjects (4-11 Years) With Asthma (2001-2004)

Objective(s): The primary objective of this study was to demonstrate superior efficacy and comparable safety of fluticasone propionate/salmeterol DISKUS combination product 100/50mcg once daily compared with fluticasone propionate DISKUS 100mcg once daily in pediatric subjects ages 4 to 11 years with asthma.

- **Study design**

This was a 12-week, randomized, double-blind, placebo-controlled, parallel group, multicenter (108 centres in the US and 10 centres in Latin America) trial.

- **Study population /Sample size**

Symptomatic male or female subjects 4 to 11 years of age with a diagnosis of asthma who were treated with short-acting beta2-agonists only or non-ICS controller medications for at least one month prior to Screening. All subjects were required to have an AM PEF of 50-85% of predicted normal and ≥15% reversibility within 30 minutes following 2 puffs of albuterol at Screening. Using a two-sample, two-sided t-test, with a 0.05 significance level, 285 subjects per treatment group provided at least 90% power to detect a difference of 4% in mean change from baseline over Weeks 1-12 in percent of predicted PM PEF between any two treatment groups (based on a standard deviation of 12%).

- **Treatments**

Fluticasone propionate/Salmeterol 50/100 mcg QD via Diskus inhaler
Or
Fluticasone propionate 100 mcg QD via Diskus inhaler
Or
Placebo QD via Diskus inhaler

Outcomes/endpoints

The primary efficacy measure was change from Baseline in % predicted ePEF over Weeks 1-12. Secondary efficacy measures included: change from Baseline in % predicted mPEF over Weeks 1-12, change from Baseline at Endpoint in 24-hour albuterol use, change from Baseline at Endpoint in 24-hour asthma symptom scores and 2-hour PEF after the first dose of study drug.

- **Statistical Methods**

All statistical tests performed tested two-sided hypotheses of no treatment difference between treatment groups. Investigator sites were pooled into geographic regions for the efficacy analyses. All analyses were performed using ANCOVA, with the exception of analyses of albuterol use, which were performed using non-parametric ANOVA.
The primary treatment comparison for the primary efficacy endpoint served as a gatekeeper for the interpretation of all other treatment comparisons and efficacy endpoints. To control for multiplicity across the four secondary efficacy endpoints for the treatment comparison of primary

interest, tests of H01 were performed in a sequential manner to control the Type I error rate at 0.05. To control for multiplicity across other related efficacy endpoints, step-down rules were used for interpretation of results.

- **Results**

- **Recruitment/ Number analysed**

908 patients were randomized. Of the 304 subjects who received fluticasone propionate/salmeterol 100/50mcg QD, 248 (82%) completed the study, 304 subjects received fluticasone propionate 100mcg QD and 241 (79%) completed the study, and 300 subjects received placebo and 226 (75%) completed the study.

Baseline data:
Groups were balanced at baseline.

- **Efficacy results**

There were no statistically significant differences between the FSC 100/50mcg QD and FP 100mcg QD treatment groups for any parameter with the exception of the secondary efficacy measure of 2-hour post-dose PEF and the other efficacy measure of AM PEF.

- **Safety results**

The pattern and type of adverse events were similar across treatment groups. The frequency of adverse events was 71 % in the placebo group, 73 % in the salmeterol/fluticasone propionate group and 70% in the fluticasone propionate group. The most AEs were headache and nasopharyngitis. Eight subjects reported serious adverse events during the treatment period. Of these serious adverse events, four subjects (three in the placebo group and one in the FP group) were hospitalized for an asthma exacerbation. A total of 15 subjects were withdrawn from the study due to an adverse event (four in the placebo group, six in the FSC group, and five in the FP group). Hematology and clinical chemistry analytes that were outside the threshold range were few and similar across treatment groups. Geometric mean 24-hour urinary cortisol excretion was unchanged at Week 12 relative to Baseline in the placebo and FSC groups. A decrease in geometric mean 24-hour urinary cortisol excretion at Week 12 relative to Baseline was noted in the FP group.

Conclusion:
Treatment with FSC 100/50mcg QD did not result in significantly greater improvements in percent predicted PM PEF over Weeks 1-12 compared with FP 100mcg QD. No new safety signal was detected.

Assessor's comment: This study tested salmeterol/fluticasone propionate once daily dosing as initial maintenance treatment. This posology has so far not been licensed. The study was inconclusive as regards the primary and most of the secondary endpoints.

SAS30031 A Randomized, Double-Blind, 12-Week Trial Evaluating the Safety of the Fluticasone Propionate/Salmeterol DISKUS. Combination Product 100/50mcg BID Versus Fluticasone Propionate DISKUS 100mcg BID in Symptomatic Pediatric Subjects (4-11 Years) With Asthma (2002-2003)

Objective(s): The objective of this study was to evaluate the safety of the fluticasone propionate/ salmeterol **DISKUS** combination product 100/50mcg BID compared with fluticasone

propionate **DISKUS** 100mcg BID in symptomatic paediatric subjects 4 to 11 years of age with asthma.

- **Study design**

This was a randomized, double-blind, parallel-group, multicenter (79 centres in the US and in Canada) study consisting of a 2-week run-in period (baseline ICS therapy continued) and a 12-week treatment period.

- **Study population /Sample size**

Symptomatic male and female subjects 4-11 years of age diagnosed with asthma, who required physician-prescribed treatment for at least 2 months, were eligible. Subjects 6-11 years of age were required to have an FEV1 of 50-95% of the Polgar predicted value and subjects 4 and 5 years of age were required to have a clinic AM PEF of 50- 95% of the Polgar predicted value at the Screening Visit.
No power calculations were performed for determining the sample size for the study. However, a sample size of 200 subjects was judged to provide sufficient safety data (with 100 subjects per treatment arm) for this study.

- **Treatments**

Fluticasone propionate/Salmeterol 100/50 mcg BID via Diskus inhaler
Or
Fluticasone propionate 100 mcg BID via Diskus inhaler

Outcomes/endpoints
Safety measures included assessment of adverse events, laboratory tests, 24-hour urine cortisol excretion, 12-lead electrocardiograms (ECGs), vital signs, physical and oropharyngeal examinations, and asthma exacerbations/worsening asthma. Other assessments included clinic pulmonary function (serial FEV1 for subjects 6-11 years of age and serial PEF for subjects 4 and 5 years of age) and daily diary records (AM and PM PEF, daytime asthma symptom scores, and supplemental albuterol use).

- **Statistical Methods**

No power calculations were performed for determining the sample size for the study. Since no power calculations were performed, there were no statistical analyses conducted for the safety and other measures included in this study; only summary statistics were provided.

➢ **Results**

- **Recruitment/ Number analysed**

203 subjects were randomized to receive double-blind treatment. Of the 101 subjects who received the DISKUS combination product, 82 (81%) completed the study and of the 102 who received FP 100mcg DISKUS, 86 (84%) completed the study.

Baseline data:
Groups were balanced at baseline.

- **Safety results**

The adverse event profile with the DISKUS Combination Product was comparable to FP 100 mcg DISKUS alone. 59% of the patients in the combination group compared to 57% of the patients in the mono-therapy group reported at least one AE. Headache and upper respiratory tract infection were the most common AEs. There were no SAEs during treatment. Withdrawals due to adverse events were three in subjects receiving the DISKUS Combination Product and

none in the FP 100mcg DISKUS group. No subjects had clinically significant abnormal ECGs during treatment. Laboratory abnormalities occurred at a low incidence, were generally minor in nature, and were similar between treatment groups. The values for 24-hour urinary cortisol excretion at Baseline and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the two groups, and no subject in either treatment group had a value below the lower limit of the normal range.

- **Efficacy results**

Overall, subjects in the DISKUS Combination Product group had comparable or greater improvements in individual measures of overall asthma control (lung function, albuterol requirements and asthma symptom scores) than subjects in the FP 100 mcg DISKUS group. After 12 weeks of treatment, improvements in FEV1 were greater in the DISKUS Combination Product group than in the FP 100mcg DISKUS group (change from baseline: combination:0.16 L, fluticasone propionate: 0.10 L) . Subjects in the DISKUS Combination Product group had greater improvements in FEV1 and PEF than subjects in the FP 100mcg DISKUS group at all timepoints during the 2-hour serial measurements after the first dose of study medication. Improvements in asthma symptom scores and albuterol use were comparable between treatment groups.

Conclusion:
The DISKUS Combination Product had a comparable safety profile as FP 100mcg DISKUS alone**.**

Assessor's comment: This study shows an acceptable safety profile of Seretide. No new safety signal was detected.

SAM40100 Randomised, double-blind, comparator study to demonstrate the superiority of salmeterol/fluticasone propionate combination DISKUS™ 50/100mcg bd over fluticasone propionate DISKUS™/ACCUHALER™ 200mcg bd with respect to airway physiology in asthmatic children treated for 6 weeks (2003-2005).

Please note that only a summary has been provided for this study

Objective(s): The primary objective was to demonstrate superiority of SFC 50/100mcg bd over FP 200mcg bd with respect to improvements in sRAW in children with moderate to severe asthma. Secondary objectives included the assessment of the effects of SFC compared with FP on bronchial hyperreactivity (determined by Eucapnic Voluntary Hyperventilation Challenge) and other measures of asthma control and to compare the safety of SFC with FP.

- **Study design**

This was a 6-week, randomized, double-blind, active-controlled, parallel group, two-center (UK, New Zealand) trial.

- **Study population /Sample size**

Male or female children aged 4-8 years with asthma currently receiving a daily dose of 200-800µg /day BDP or equivalent were eligible. Subjects were also required to have a sRAW value of ≥1.3kPa.s for entry into the screening and treatment period.
The standard deviation of log-transformed sRAW was estimated to be 0.117 kPa.s. A clinically relevant difference in sRAW was taken to be a decrease of 10% comparing SFC to FP, based on clinical judgment. This is equivalent to a difference of -0.105 on natural log-transformed sRAW data. A sample size of 28 evaluable subjects per group would have 90% power to detect

a difference of 10% between treatment groups in sRAW pre-study medication at 6 weeks of treatment, assuming a common standard deviation of 0.117 kPa.s of natural log sRAW, at a 5% two-sided significance level.

Treatments
Fluticasone propionate/Salmeterol 100/50 mcg BID via Diskus inhaler
Or
Fluticasone propionate 200 mcg BID via Diskus inhaler

Outcomes/endpoints
Specific airway resistance (sRAW) assessed by body plethysmography.

- **Statistical Methods**

The primary endpoint was the pre-study medication sRAW at Week 6, using LOCF. sRAW values were transformed using natural logarithms prior to analysis. sRAW LOCF values were analysed at Week 6 using analysis of covariance (ANCOVA) with covariates of age, sex, natural log baseline (Day 0) and treatment group. Least squares means for the treatments were transformed back to the original scale and presented as geometric means. The treatment difference was exponentiated to express it as a geometric mean ratio. Interactions of treatment with sex, age and log baseline were tested in separate analysis models for statistical significance at the 10% level. If an interaction was considered meaningful, the effects of treatment were also presented separately for each subgroup factor level.

Results

- **Recruitment/ Number analysed**

24 patients were randomized. Of the 12 subjects who received fluticasone propionate/salmeterol 100/50mcg BID, 11 completed the study, 12 subjects received fluticasone propionate 200mcg BID and 11 completed the study.

Baseline data:
Information on this issue is too sparse for firm conclusions.

- **Efficacy results**

Combination treatment with SFC in children with moderate to severe asthma resulted in a statistically significant greater reduction in airway resistance than FP after 6 weeks of treatment. For some of the secondary endpoints the fluticasone propionate group did better than the combination group (e.g. % of symptom free days, daytime rescues use). However no statistical analysis is given.

- **Safety results**

The frequency of adverse events was 75 % in the salmeterol/fluticasone propionate group and 50% in the fluticasone propionate group. AEs encompassed pharyngolaryngeal pain, upper respiratory tract infection, ear infection asthma and injection site pain. No serious adverse event was reported.

Conclusion:
Salmeterol/fluticasone propionate combination therapy was statistically significant superior as regards the primary endpoint compared to fluticasone monotherapy No safety signal was detected

Assessor's comment This study tested the combination therapy compared to a higher dose of fluticasone propionate. Recruitment was below expectations. Anyhow, this study was positive as regards the primary end-point. However, with regard to some secondary endpoints the fluticasone propionate group did at least numerically better than the combination therapy. No firm conclusions can be drawn because a statistical analysis is missing.

ADERE PEDIATRIC 1 Prospective, parallel-group, randomized, open label study to evaluate the impact of additional guidance from the health professionals team on treatment compliance of children aged between 6 and 14 years old with persistent moderate or severe asthma, receiving the combination salmeterol/fluticasone propionate 50/250 mcg *(Seretide)* twice a day. ADERE PROJECT (Pediatric) (2004)

Please note that only a summary has been provided for this study

Objective(s): To evaluate the impact of education/guidance provided by health professional team on treatment compliance of children with persistent moderate or severe asthma.

Study design: This was a single centre (Brazil**),** prospective, controlled, parallel group, open, 90 day, Phase IV study

- **Study population /Sample size**

The study enrolled 6-14 year old children with a diagnosis of persistent moderate or severe asthma, according to the SBPT III Brazilian Consensus on Asthma Management.
It was planned to enrol 236 patients per group

Treatments
Fluticasone propionate/Salmeterol 50/100 mcg BID via Diskus inhaler with or without guidance (telephone call every 15 days)

Outcomes/endpoints
Primary Outcome/Efficacy Variable: Level of compliance defined as a percentage of the actual number of doses of salmeterol/fluticasone propionate administered by the Diskus device used divided by the number of doses expected for the time under consideration.

Secondary Outcome/Efficacy Variable(s): Disease control, evaluated by information acquired from a 5-point questionnaire including: use of emergency room visits, hospitalization due to asthma, use of reliever medication, night-time awakenings, co-morbidity symptoms (cough, wheeze, dyspnoea). 2) Improvement in the quality of life using SF-36 Questionnaire.

- **Statistical Methods**

Subjects from the no guidance group were not followed up as defined by the protocol: Information on compliance (primary endpoint) and adverse events were not obtained from these subjects. Therefore the planned statistical testing on the primary endpoint could not be conducted. The statistical analysis for efficacy and safety was done on the population of subjects that concluded the study (per protocol population).

Results

- **Recruitment/ Number analysed**

298 patients were randomized. 108 patients in the group with guidance and 109 patients in the group without guidance completed the study.

Baseline data:
Information is too sparse for final conclusions.

- **Efficacy results**

Subjects from the no guidance group were not followed up as defined by the protocol: Information on compliance (primary endpoint) and adverse events were not obtained from these subjects. Therefore the planned statistical testing on the primary endpoint could not be conducted. With regard to the secondary endpoints, generally speaking patients in the group with guidance did at least numerically better (p-values and CIs for comparisons not given) than those in the group without guidance.

- **Safety results**

Information of subjects from the group without guidance is reported as “not available”. In the group with guidance 20 subjects reported at least one AE. The most common AEs were leg pain and headache. No SAEs or DAEs were reported.

Conclusion: This study was not conducted as *per protocol*. Subjects from the no guidance group were not followed up as defined by the protocol. Therefore no conclusions can be drawn.

Assessor’s comment: This study primarily evaluated the benefit of professional guidance during asthma therapy. Both groups administered Seretide. It was not conducted as per protocol. No conclusions can be drawn.

SAS30018 Comparison of stepwise treatment of asthmatic children with salmeterol/fluticasone propionate (FP) combination product (Seretide) and/or fluticasone propionate (Flixotide) based on PD20 methacholine plus symptoms or based on symptoms only (Children Asthma Therapy Optimal”) (1999-2003)

Please note that only a summary has been provided for this study

Objective(s): To evaluate if, in children with asthma, a stepwise treatment (five levels varying from once daily fluticasone propionate 100 µg to twice daily a fixed combination of salmeterol and fluticasone propionate 50/250 µg) based on cumulative symptom scores alone results in sub-optimal treatment when compared to treatment based on cumulative symptom scores and PD20 methacholine.

- **Study design**

This was a 2-year, randomized, double-blind, parallel group, multi-centre (15 centres in the Netherlands) trial.

- **Study population /Sample size**

Symptomatic male and female subjects aged 6-16 years (inclusive) with asthma treated with FP 500 µg BD possibly in combination with long-acting ß2 agonists, or. FP 250 µg BD or beclomethasone dipropionate (BDP) 400 µg BD or budesonide (BUD) 400 µg BD or BDP 2x250µg BD possibly in combination with long-acting ß2 agonists, or FP 100 µg BD or BDP 200 µg BD or BUD 200 µg BD BDP 250 µg BD possibly in combination with long-acting ß2 agonists were eligible.
To demonstrate an increase of the mean percentage of asthma-free days to 75%, 86 patients are required (two-sided alpha=5%, power=80%) in each group. To allow for approximately 10% dropouts in each group, 200 patients (2x100) were to enter the randomised phase. It was assumed that for study duration of two years, the same number of subjects would suffice.

Treatments
FP 100 mcg once daily or twice daily or salmeterol/ FP 50/100 mcg BD or salmeterol/ FP 50/250 mcg BD or salmeterol/FP 50/500 mcg BD (device not mentioned). Data on treatment groups is sparse. It seems that in one group step-up and step-down was managed based on symptom scores only, while in the other group PD20 was also evaluated.

Outcomes/endpoints
Primary Outcome: Asthma symptom-free days (during the last 12 weeks) of the treatment period.

Secondary Outcome/Efficacy Variable(s):
Bronchial hyperresponsiveness, determined by PD20 methacholine
Lung function measured in the clinic.
Frequency of asthma exacerbations.

- **Statistical Methods**

Pre-planned subgroup analyses were done for 3 subgroups of patients (subgroup included on airway hyper responsiveness (AHR) alone, subgroup included on symptoms alone and subgroup included on both symptoms and AHR).

Results

- **Recruitment/ Number analysed**

206 patients were randomized. 185 patients completed the study.

Baseline data:
Baseline data is sparse. There were imbalances with regard to the gender distribution.

- **Efficacy results**

Mean percentage of symptom-free days was 71% in the symptom score management group and 69% in the symptom score and PD20 management groups. Difference between groups as well as 95% CI and p-value are labelled “not applicable”.

- **Safety results**

The frequency of adverse events was 87 % in both groups. The most common AEs were upper respiratory tract infection and headache. 2 patients in the symptom score management group and 5 patients in the symptom score and PD20 management group reported SAEs.

Conclusion: With a statistical analysis missing, both treatments groups were numerically comparable as regards the mean percentage of symptom-free days.

Assessor’s comment: This study primarily evaluates two different ways to steer asthma therapy. No clear additional advantage of PD 20 evaluations was shown. The higher doses of the salmeterol/fluticasone propionate combination therapy are licensed for patients ≥12 years of age. It is not clear which population received this kind of treatment.

SAM3802 An observational study to assess the health related quality of life impact of treating poorly controlled asthmatic children with *Seretide* 50/100mcg (2002-2004)

Please note that only a summary has been provided for this study

Objective(s): To compare changes in the health related quality of life as measured by the Paediatric Asthma Quality of Life Questionnaire (PAQLQ) at baseline and week 16 of salmeterol/fluticasone propionate 50/100mcg bd treatment**.**

- **Study design**

This was a prospective, uncontrolled, 16-week, open labelled, observational Phase IV multicenter (13 centres in the Republic of Ireland) study.

- **Study population /Sample size**

Symptomatic asthma patients aged 7 -12 years of age with a PEFR ≥ 50% of predicted were eligible.
It was planned to enrol 150 patients.

Treatments
Fluticasone propionate/Salmeterol 50/100 mcg BID via Diskus inhaler

Outcomes/endpoints
Primary: Quality of life scores (overall and subscales) as measured by the PAQLQ at weeks 0,4 and 16. Changes in each scale score from baseline to week 4 and from baseline to week 16 were tested.
Secondary: Asthma control (peak expiratory flow rate [PEFR], use of short acting beta agonists, day and night time asthma symptoms, nocturnal awakenings due to asthma

- **Statistical Methods**

Descriptive analyses were performed on baseline data. Scoring of quality of life (PAQLQ) scales followed the guidelines and procedures laid down by the author. Changes in each scale score from baseline to week 4, and from baseline to week 16 were tested. The mean, standard deviation, 95% confidence intervals and p-values were calculated. All analysis was undertaken on the ITT population.

Results

- **Recruitment/ Number analysed**

35 patients were entered the study, 32 patients completed it.

- **Efficacy results**

Significant improvements were seen as regards the primary parameter (Change from baseline to week 16 in PAQLQ overall score 3.03, $p<0.01$). Generally secondary parameters also showed improvements.

- **Safety results**

14 subjects experienced at least one AE. The most common AE was cough. 1 subject experienced a SAE. No DAEs occurred.

Conclusion:
Salmeterol/fluticasone propionate statistically significantly improved quality of life as measured by the PAQLQ. No new safety signal was detected.

Assessor's comment: This study showed improvement with regard to quality of life. However due to the lack of a comparator it is of limited value.

SAM40121 Summary of the efficacy and safety and safety of salmeterol 50mcg and fluticasone propionate 100mcg administered in Diskus Dry Powder Inhaler twice daily in steroid experienced children with reversible airways obstruction (2004-2005)

Please note that the results of this study have only been provided as a summary.

Objective(s): To assess the efficacy of SAL 50mcg and FP 100mcg administered in Diskus Dry Powder Inhaler twice daily in children with reversible obstructive airway disease receiving inhaled corticosteroids.

Study design
This was a multicenter (11 centres in Hungary), uncontrolled, 12 week, Phase IV study.

- **Study population /Sample size**

Symptomatic male or female subjects aged 4-11 year with documented history of reversible obstructive airway disease with a PEFR or FEV1 > 60%-≤ 90% of predicted normal already treated with ICS, maximum daily dosage: budesonide 400mcg, BDP 500mcg, FP 200mcg were eligible.
265 subjects were planned to be included.

- **Treatments**

Fluticasone propionate/Salmeterol 50/100 mcg bid via Diskus inhaler

Outcomes/endpoints
Primary Outcome: mean morning peak flow rate measurement over the 12 week treatment period.

Secondary Outcomes included:
Mean evening PEFR, frequency and severity of daytime and night-time symptoms, average daily rescue salbutamol use, FEV1, number and severity of exacerbations.

- **Statistical Methods**

The primary population for all efficacy analyses was the intent-to-treat (ITT) population.
ITT principle was applied in the following way: The daily measurements of the efficacy parameters were averaged weekly, and these averages were used in the analysis. This method resulted in data from all subjects except one. In that exceptional case the missing value of the last week was substituted by the last measured value (Last observation carried forward). A repeated measurement ANOVA was used to evaluate the change of the primary efficacy parameter in time. In case of a significant time-effect, the mean difference of the visits from baseline was estimated and 95% confidence intervals were computed. The baseline value was defined as the mean peak expiratory flow of the last week of the run-in period. To test the effect of age, sex, and centre, a mixed model of ANOVA was applied with time (weeks) and sex as fix effects, centre as a random effect and age as covariate. The covariance structure was verified by the likelihood ratio test. A compound symmetry covariance structure was used. As a result, the mean change and the 95%CI was given, adjusting for age, sex, and centre.

➢ **Results**

- **Recruitment/ Number analysed**

139 subjects entered the study, 121 completed it.

- **Efficacy results**

The primary parameter PEFR significantly improved by 31,96 L/min (adjusted mean change, week 12-baseline, p<0.0001). secondary parameters also showed improvements.

- **Safety results**

43% of the patients reported at least one AE. Cough and tonsillitis were the most common AEs. No SAEs or DAEs occurred.

Conclusion:
Therapy with Seretide showed improvements in primary and secondary parameters. No new safety signal was detected.

Assessor's comment: This study showed positive effects of Seretide. However due to the lack of a comparator arm conclusions are limited.

SAS10016 A 2-week, randomized, double-blind, parallel-group study in pediatric subjects with asthma aged 4 to11 years to examine the pharmacokinetics (PK) of fluticasone propionate (FP) and salmeterol (SALM) from the FP/SALM combination product administered twice daily via the DISKUS (FP 100mcg/SALM 50mcg) and the FP DISKUS (FP 100mcg) (2003-2004)

Objective(s): The primary objective of the study was to characterize FP PK in children aged 4 to 11 years with asthma following twice daily administration of 1 inhalation from the ADVAIR DISKUS (FP/SALM 100/50mcg), or 1 inhalation from the FLOVENT DISKUS (FP 100mcg). Salmeterol PK data also were characterized following ADVAIR DISKUS administration.

Study design: This randomized, multi-centre (4 centres in the US), multiple-dose, double-blind, stratified (≈ one third ≤ 7 years old) parallel-group PK study.

- **Study population /Sample size**

Male and female subjects aged 4 to 11 years diagnosed with asthma according to the American Thoracic Society definition weighing at least 11kg with a BMI of 14 to 24kg/m2 were eligible.

Treatments
FLOVENT DISKUS Treatment: 1 inhalation FP 100mcg DISKUS BID for 14 to 17 days (200mcg total daily dose),
or
ADVAIR DISKUS Treatment: 1 inhalation FP/SALM 100/50mcg DISKUS BID for 14 to 17 days (200/100mcg total daily dose).

Outcomes/endpoints
Pharmacokinetics: Plasma samples taken on D14 were assayed for the determination of FP and SALM concentrations using LC-MS-MS methods.

- **Statistical Methods**

A total of 100 samples from 20 subjects were planned. These data were to be combined with data from a similar population in study SAS30031. Study SAS30031 was designed to collect the same number of samples as the present study. The combination of data from these 2 studies permits the estimation of parameters for a simple PK model. The structural PK model for FP in pediatrics have been shown to be similar to that in adults (linear, 1 compartment). Pharmacokinetic data were summarized by treatment. In general, categorical data were summarized using frequency counts and percentages, and continuous data were summarized

using descriptive statistics (ie, means, standard deviation [SD], medians, minima, and maxima). A 95% confidence interval was calculated for each treatment. Geometric means and SD for natural-log-transformed data also were provided if the data were natural-log-transformed. The 95% confidence intervals of the geometric mean were calculated by exponentiating the corresponding 95% confidence interval of the mean of the natural-log-transformed variables. Combined Plasma FP concentration – time data from SAS10016 and SAS30031 were analyzed using population PK with NONMEM and PREDPP subroutines (NONMEM Project Group, 1992 and 1998). Lognormal error model was fitted to estimate not quantifiable (NQ) values using maximum likelihood method. Basic structural model was fitted to the data which defined primary PK parameters. Several models were evaluated. The best fit model was chosen using established NONMEM criteria. Model predicted apparent clearance (CL/F), apparent volume of distribution (V/F) and duration of absorption (D1) were used to obtain FP systemic exposure in terms of area under the curve (AUC). Many demographic and baseline characteristics such as age, weight, gender, height, concomitant medications, were included in the base model one at a time as covariates to test their effects on FP PK parameters. Post-hoc individual parameters were predicted using the final model.

Results

- **Recruitment/ Number analysed**

A total of 24 subjects were enrolled in the study, received at least 1 dose of study drug, and were included in the safety population. 22 subjects completed the study.

Baseline data:
There were imbalances with regard to gender distribution and ethnic origin.

- **PK results**

Pharmacokinetics:
FP PK following ADVAIR DISKUS in the pediatric (4 to 11 years) asthmatic population was best described by zero-order input, 1-compartment model with first order elimination. Population PK analysis demonstrated, on average, 1.5-times higher FP exposure following ADVAIR DISKUS compared with FLOVENT DISKUS in pediatric subjects with asthma.
Although 41% of the data for SALM was NQ, imputing NQ with highest and lowest possible integer indicated that geometric mean for SALM exposure following ADVAIR DISKUS 100/50 would range between 10.8 to 44.4pg/mL. None of the 13 covariates (weight, height, body mass index, lung functions in terms of PPFEV1, for children ≥6 years and PPPEF1 for children ≤5 years, race, gender, age, concomitant medications antihistamines, concomitant medications corticosteroids, age ≤7 years versus >7 years) showed any significant effect on FP PK parameters.
PD: No effect on change in urine cortisol from baseline was detected.

- **Safety results**

5 subjects in the mono-therapy group compared to 3 subjects in the combination therapy group experienced at least one AE. Headache was the most common AE reported
by subjects (2/24, 8%). No SAEs, or DAEs were reported.

Conclusion:
·Population PK analysis demonstrated higher FP exposure following ADVAIR DISKUS compared with FLOVENT DISKUS in paediatric subjects with asthma.
· Demographic and baseline characteristics in this paediatric asthmatic population did not appear to influence FP PK parameters. No safety signal was detected.

Assessor's comment: the applicant is asked to discuss the results of this study with respect to the statement in section 5.2 "When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately."

SAS30019 A multicentre, randomised, double-blind, double-dummy, parallel group study to compare the salmeterol/fluticasone propionate combination (SERETIDE*/VIANI*/ADVAIR*) delivered via either a dry powder inhaler (DISKUS*/ACCUHALER*) or via a non-chlorofluorocarbon (CFC) metered-dose inhaler (MDI), both at a dose of 50/100mcg twice daily for 12 weeks, in the treatment of children aged 4-11 years with asthma. (2002)

Please note that this study has been reviewed in the majority of the MSs except for Cyprus, Latvia, Romania and Slovakia.

Objective(s): The primary objective of this study was to demonstrate clinical equivalence between salmeterol/fluticasone propionate (FP) DISKUS (50/100 microgram [mcg], one inhalation twice daily) and salmeterol/FP MDI (25/50mcg, two inhalations twice daily) in children aged 4-11 years over a 12-week treatment period.

- **Study design**

This was a multicentre (63 centres in Europe), randomised, double-blind, double-dummy, 12 week parallel group study.

- **Study population /Sample size**

Symptomatic male and female children aged 4-11 years, with asthma, treated with ICS and a mPEF, of >50% and ≤85% of their PEF measured 15 minutes after administration of 400mcg of Ventolin.
A sample size of 266 patients (133 per treatment group) was required to demonstrate equivalence in mean morning PEF of salmeterol/FP DISKUS and salmeterol/FP MDI, with 85% power using a two-sided 95% confidence interval. This assumed a pooled standard deviation of 35L/min and used equivalence limits of ±15L/min.

Treatments
Salmeterol/FP 50/100mcg strength DISKUS inhaler containing 50mcg salmeterol xinafoate/100mcg FP per inhalation, one inhalation BID
or
Salmeterol/FP 25/50mcg strength pressurised MDI containing 25mcg salmeterol xinafoate/50mcg FP per inhalation, two inhalations BID

Outcomes/endpoints
The primary efficacy endpoint was the mPEF measurements over the12-week treatment period. Secondary efficacy endpoints included: ePEF; FEV1; daytime symptom scores, night-time symptom scores; percentage of symptom-free days; percentage of symptom-free nights; and incidence asthma exacerbations.

- **Statistical Methods**

For the interpretation of all PEF endpoints equivalence limits ±15L/min were used. Equivalence limits were not set for the other secondary endpoints. For these endpoints the assessment of equivalence of the two devices was based on the 95% confidence intervals including zero (for treatment differences) or one (for odds ratios) and where possible the clinical relevance of the range of the confidence interval.

Results

- **Recruitment/ Number analysed**

The Intent-To-Treat (ITT) population consisted of 428 subjects, 213 in the DISKUS group and 215 in the MDI group. The Per Protocol (PP) population consisted of 328 subjects, 160 in the DISKUS group and 168 in the MDI group.

Baseline data:
Pre-salbutamol and post-salbutamol FEV1 was slightly higher in the MDI group which used spacers compared to the other groups. Otherwise patients were balanced at baseline.

- **Efficacy results**

The treatment groups were statistically equivalent in terms of mean morning PEF, the primary efficacy endpoint, in the PP population (adjusted mean change from baseline: Diskus: 37.7 L/min; MDI: 38.6 L/min; difference: 0.9 L/min, 95% CI: -7.1; 5.4). Similar results for mean morning PEF over Weeks 1-12 were obtained in the ITT population. All of the secondary efficacy analyses demonstrated that there was no statistically or clinically significant difference between the DISKUS and MDI groups.

- **Safety results**

Treatment emergent AEs occurred in 91 subjects (43%) in the DISKUS group and 93 subjects (43%) in the MDI group. The most common TEAEs were nasopharyngitis, cough, rhinitis NOS and headache. Treatment emergent SAEs were experienced by four subjects, two (<1%) in each treatment group (DISKUS: concussion and asthma; MDI: forearm fracture and gastroenteritis NOS. Treatment emergent AEs that led to discontinuation from the study were experienced by four subjects (2%) in the DISKUS group and two subjects (<1%) in the MDI group. In the DISKUS group, AEs leading to discontinuation were: laboratory test abnormal NOS (low urinary cortisol/creatinine ratio); heart rate increased; headache; psychomotor hyperactivity; and asthma NOS (one subject experienced two AEs leading to discontinuation). In the MDI group, AEs leading to discontinuation were: laboratory test abnormal NOS (increased urinary cortisol/creatinine ratio); and muscle cramp. Both AEs of laboratory test abnormal NOS occurred pre-treatment, but were not reported until after treatment had commenced. There was little evidence of oral candidiasis. Eight subjects, three in the DISKUS group and five in the MDI group, had evidence of oral candidiasis at some point during the course of the study. Of the swabs taken, only two were positive (one from each treatment group). Urinary cortisol changes from Visit 2/2a to Visit 6, corrected for creatinine, were not statistically or clinically significantly different between treatment groups.
The only clinically relevant change in vital signs during the study occurred in one subject who withdrew from the study due to an increase in heart rate.

Conclusion: Clinical equivalence was demonstrated between salmeterol/FP DISKUS (50/100 mcg, one inhalation twice daily) and salmeterol/FP MDI (25/50 mcg, two inhalations twice daily) in asthmatic children aged 4-11 years over a 12-week treatment period.

Assessor's comment: This study compares Seretide Diskus and Seretide pMDI. It has been submitted and assessed before in most EU MSs. Both treatments similarly showed rather large improvements in mPEF. However, the sensitivity of the study does not seem to be optimal. The design should have included an additional comparator arm to test for superiority e.g. over ICS monotherapy.

3. Discussion on clinical aspects and conclusion

The applicant submitted altogether 13 studies. Most studies evaluated Seretide Diskus compared to Fluticasone propionate monotherapy. Study SAS 30019 compared Seretide Diskus to Seretide pMDI. This study has already been assessed by the majority of the MSs. Study SAM 40101 compared Seretide Diskus to fluticasone propionate monotherapy with regard to the activity level of the patients. It was inconclusive with this regard. SAF 100314 and SFA 100316 evaluated improvements in exercise challenge compared to fluticasone propionate monotherapy. While the combination was proven to be superior in SAF 100314, Study SFA 10016 was negative. Study SAM 40012 compared Seretide Diskus to two doses of fluticasone propionate monotherapy. It also was inconclusive due to methodical problems. SAS 30031 evaluated safety in comparison to fluticasone propionate monotherapy. No new safety signal was detected. SAM 40100 showed superior results in the combination therapy group as compared to the fluticasone propionate monotherapy group as regards sRAW. Study ADERE Paediatric 1 evaluated the impact of professional guidance during asthma therapy, while SAS30018 tested the use of PD20 methacholine challenge in steering asthma therapy. SAM3802, which evaluated health-related quality of life during Seretide Diskus therapy and SAM40121, which evaluated its effect on mPEF in children with reversible obstructive airway disease were uncontrolled which limits conclusions.
SAS 10016 was a PK study. The results of this study should be discussed in relation to the information given in Section 5.2 of the SPC, which partly is contradictory.
Almost all protocols evaluated doses which have already been licensed for paediatric asthma therapy. Study ADERE Paediatric 1 also evaluated higher doses. It is not clear, if these doses have also been administered to patients below 12 years of age. SAS30021 compared once daily dosing as initial maintenance treatment, which has not been licensed so far, to fluticasone propionate monotherapy OD and placebo. No differences were detected between both active treatments.
No study evaluated the efficacy and safety in children < 4 years of age.

In conclusion: The results of the studies submitted for this work sharing procedure are in line with what is known about salmeterol/fluticasone propionate combination therapy in children with asthma. However as Section 5.1 of the SPC does not contain any paediatric information, this section should be updated. The results of the PK study submitted by the applicant are contradictory to the statements given in Section 5.2 of the SPC. This should be explained.
In addition a statement indicating that children should administer Seretide under the supervision of an adult should be included in Section 4.2 of the SPC and Section 3 of the PIL.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Please see recommendation and List of Questions

- **Recommendation/List of Questions**

Based on the data submitted, the MAH should:

1.) update Section 5.1 of the SPC to include paediatric information. The applicant is asked to provide a concise proposal for the wording.
(Rapp supported by IE, NL, SE and UK)

2.) discuss the results of Study SAS10016 with respect to the statement in section 5.2 of the SPC *"When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately."* If the paediatric PK data are adequate, these should also be presented in SPC Section 5.2.
(Rapp supported by IE, NL,SE and UK)

3.) include a statement indicating that children should administer Seretide under the supervision of an adult in Section 4.2 of the SPC and Section 3 of the PIL.
(Rapp supported by IE, NL and UK, not supported by SE)

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

Question 1 (Rapporteur DE – supported by IE, NL, SE and UK)

Update Section 5.1 of the SPC to include paediatric information. The applicant is asked to provide a concise proposal for the wording.

Response

The pivotal paediatric studies to gain registration in under 12s in Europe were SFCB3020 (Diskus) and SAS30019 (Evohaler). These studies were submitted as part of the original applications to gain a paediatric indication (Diskus – SE/H/169/01-03 – initial application; Evohaler UK/H/0392/01-03/W10) and support the use of salmeterol/fluticasone propionate DISKUS and EVOHALER in the treatment of children ages 4-11 years with a diagnosis of asthma. Synopses for these studies are supplied again in Module 2.7.5 as reference.

SFCB3020 is a 12 week trial which randomised 257 children aged 4-11 years who were treated them with either salmeterol/fluticasone propionate 50/100mcg or salmeterol 50 mcg + fluticasone propionate (FP) 100mcg both twice daily after a 2 week run-in on their inhaled corticosteroid therapy. Both treatment arms experienced a 14% increase in peak expiratory flow rate as well as improvements in symptom score and rescue salbutamol use. There were no differences between the 2 treatment arms. There were no differences in safety parameters between the 2 treatment arms.

SAS30019 is a 12 week trial in children aged 4-11 years treated with salmeterol/FP combination delivered via either a dry powder inhaler (DISKUS) or via a non-chlorofluorocarbon (CFC) metered-dose inhaler (MDI) (EVOHALER), both at a dose of 50/100mcg twice daily. In this study which randomized 428 children aged 4-11 years, clinical equivalence was demonstrated between salmeterol/fluticasone propionate DISKUS (50/100mcg, one inhalation twice daily) and salmeterol/fluticasone propionate MDI (25/50mcg, two inhalations twice daily) over a 12-week treatment period. The adjusted mean change from baseline in mean morning peak expiratory flow over Weeks 1-12 was 37.7L/min in the DISKUS group and 38.6L/min in the MDI group. Improvements were also seen in both treatment groups on rescue and symptom free days and nights.

Additional safety data in children using the DISKUS device was generated in SAS30031 which was submitted as part of this Article 45 procedure. SAS30031 is a 12 week trial of children [n=203] 4-11 years of age randomized in a parallel-group study with persistent asthma and who were symptomatic on inhaled corticosteroid. Children received either salmeterol/FP (50/100 mcg) or FP (100 mcg) alone twice daily. This was a primary safety study. Two children on salmeterol/FP and 5 children on FP withdrew because of worsening asthma. After 12 weeks no children in either treatment arm had abnormally low 24-hour urinary cortisol excretion. There were no other differences in safety profile between the treatment arms.

GlaxoSmithKline propose the following text is added to Section 5.1 of the EU Summary of Product Characteristics (SmPCs) under the heading “Paediatric population”.

DISKUS

Paediatric population

In a 12 week trial of children aged 4-11 years [n=257] treated with either salmeterol/fluticasone propionate 50/100 or salmeterol 50 mcg + fluticasone propionate (FP) 100mcg both twice daily, both treatment arms experienced a 14% increase in peak expiratory flow rate as well as improvements in symptom score and rescue salbutamol use. There were no differences between the 2 treatment arms. There were no differences in safety parameters between the 2 treatment arms.

In a 12 week trial of children 4-11 years of age [n=203] randomized in a parallel-group study with persistent asthma and who were symptomatic on inhaled corticosteroid, safety was the primary objective. Children received either salmeterol/FP (50/100 mcg) or FP (100 mcg) alone twice daily. Two children on salmeterol/FP and 5 children on FP withdrew because of worsening asthma. After 12 weeks no children in either treatment arm had abnormally low 24-hour urinary cortisol excretion. There were no other differences in safety profile between the treatment arms.

EVOHALER

Paediatric population

In a trial which randomized children aged 4-11 years [n=428], clinical equivalence was demonstrated between salmeterol/fluticasone propionate DISKUS (50/100mcg, one inhalation twice daily) and salmeterol/fluticasone propionate MDI (25/50mcg, two inhalations twice daily) over a 12-week treatment period. The adjusted mean change from baseline in mean morning peak expiratory flow over Weeks 1-12 was 37.7L/min in the

DISKUS group and 38.6L/min in the MDI group. Improvements were also seen in both treatment groups on rescue and symptom free days and nights

GlaxoSmithKline has reviewed the results of the other paediatric studies which have been completed for salmeterol/fluticasone propionate and submitted under Article 45 and 46 paediatric procedures and concluded that no further update to Section 5.1 of the EU SmPCs is necessary.

Assessor's comment: the applicant proposes to describe the results of the pivotal studies submitted for the initial paediatric MAs in Chapter 5.1 of the SPC. This proposal is acceptable.

Question 2 (Rapporteur DE , IE, NL, SE and UK)

Discuss the results of Study SAS10016 with respect to the statement in section 5.2 of the SPC "*When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately*." If the paediatric PK data are adequate, these should also be presented in SPC Section 5.2.

Response

Study SAS10016

SAS10016 was a randomized, multiple-dose, double-blind, parallel group study in pediatric subjects with asthma, aged 4 to 11 years. Subjects were randomized to receive either fluticasone propionate (FP) DISKUS 100 or salmeterol/fluticasone propionate (Salmeterol/FP) propionate DISKUS 50/100mcg for a minimum of 14 days. The subject took 1 inhalation twice a day. The randomization was stratified for age groups 4-7 years and 8-11 years, in order that approximately one-third of the subjects were ≤ 7 years old. Study personnel directly observed the first and last doses. Subjects were allowed to use albuterol to relieve any asthma symptoms experienced by subjects, as needed.

Blood sampling (6ml each) for the determination of FP and salmeterol concentrations occurred on Day 14 relative to the time of the morning dose according to the following schedule:

- 0-15min post-dose, 0.5-1hr post-dose, 2-3hr post-dose, 4-6hr post-dose, and 7-9hr post-dose.

SAS10016 was conducted in order to obtain more serial pharmacokinetic (PK) samples in 4 to 11-year-old asthmatic children as a follow-up study to SAS30031 (also submitted as part of this Article 45 procedure DE/W/047/pdWS/001). SAS30031 was a 12-week study in 4 to 11-year-old asthmatic children to assess safety of salmeterol/fluticasone propionate DISKUS 50/100mcg BID versus FP DISKUS 100 BID. Only 144 of 203 subjects from SAS30031 provided viable samples for PK assessments of FP and salmeterol in this population. Of these only 13 subjects (4 in salmeterol/FP DISKUS and 9 in FP DISKUS) provided serial samples. As described in the SAS30031 protocol, a minimum of 20 subjects (10/group) providing 3 - 5 serial PK samples would be needed to perform an adequate population PK analysis. Therefore, GlaxoSmithKline

began a separate PK study (SAS10016) to obtain enough serial PK data for an adequate population PK analysis in the pediatric population. SAS10016 used the same population and serial sampling approach used for the PK sub-population in SAS30031.

Following completion of both studies a separate population PK analysis in paediatrics of the combined (SAS10016+SAS30031) data was performed but the results were inadequate and did not represent real PK in the paediatric population due to large number of BQL (below limit of quantitation) in the data. Therefore GlaxoSmithKline decided to undertake a meta-analysis using data of FP and salmeterol in 9 clinical studies including SAS10016+SAS30031 (see next section).

Salmeterol/FP Population Pharmacokinetic Analysis (RM2005/00368/00)

This population pharmacokinetic analysis was submitted as part of the first salmeterol/FP Article 46 worksharing procedure (SE/W/005/pdWS/001) but is provided again with this Article 45 response.

The population pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials (SAS10006; SAS10007; SAS10016; SAS30031; FAP10006; FAP30007; SAS10013; SFCB3019 and FMS10033) that included 350 patients with asthma aged 4 to 77 years which was modelled using nonlinear mixed-effects analysis. 140 patients were from SAS30031, 20 were from SAS10016 and only 14 were from FAP10006, therefore paediatric results from this analysis primarily reflect salmeterol/FP paediatric data (46% of total). Adult data as well as the FAP studies (FP alone in treatment arms) were included to provide better characterization of the model and decrease variability in estimated PK parameters.

Treatments included different devices (DISKUS, Metered Dose Inhaler [MDI]) and doses (88mcg-500mcg for FP). Half the subjects in this analysis (n=174) ranged between 4-11 years of age. Patient factors explored included race, age, weight, height, body mass index, FEV_1 and co-medications. The objectives of the FP population PK analysis were to characterize the systemic exposure to FP and to identify any influential covariates on FP PK. A one compartment model with zero-order absorption and first-order elimination with a dose/ device/ relative bioavailability scaling term (F1) adequately described the FP PK model. A two-compartment model with first-order distribution and elimination, with a dose/ device relative bioavailability scaling term (F1) adequately described the salmeterol PK model. Results of this analysis showed that age did not affect FP or salmeterol PK parameters.

Comparisons of FP systemic exposure following salmeterol/FP treatments vs FP treatments in all subjects indicated that post-hoc FP systemic exposure following salmeterol/FP and FP were similar for both AUC and Cmax.

Table 1 Dose Normalized Geometric Means and Geometric Mean Ratios [90% CI] for the Comparison of FP Systemic Exposure Following Salmeterol/FP and FP Formulations (All Subjects)

	Salmeterol/FP	**FP**	**Ratio [Salmeterol/FP and FP]**
All Subjects	**Geo. Mean [90%CI]**	**Geo. Mean [90%CI]**	**Ratio [90% CI]**
AUC (pg·hr/mL)	179 [166 – 194]	167 [156 – 178]	1.07 [0.969 – 1.19]
C_{max} (pg/mL)	27.4 [25.1 – 29.9]	24.0 [22.5 – 25.7]	1.14 [1.02 – 1.27]

When the population PK analysis results for FP were divided into subgroups based on FP strength, formulation, and age (adolescents/adults and children), there were some differences in FP exposure. Higher FP exposure from salmeterol/FP DISKUS 50/100mcg compared with FP DISKUS 100mcg was observed in adolescents and adults (ratio 1.52 [90% CI: 1.08, 2.13]) but not in children.

Table 2 Geometric Mean Ratio [90% CI] for the Salmeterol/FP vs. FP DISKUS Comparison in Children and Adolescent/Adult Populations

Treatment (test vs. ref)	**Population**	**AUC**	**C_{max}**
Salmeterol/FP DISKUS 100/50 FP DISKUS 100	Children (4–11yr)	1.20 [1.06 – 1.37]	1.25 [1.11 – 1.41]
Salmeterol/FP DISKUS 100/50 FP DISKUS 100	Adolescent/Adult (≥12yr)	1.52 [1.08 – 2.13]	1.52 [1.08 – 2.16]

However, in clinical studies of up to 12 weeks' duration comparing salmeterol/FP DISKUS 50/100mcg and FP DISKUS 100mcg in adolescents and adults, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed. Similar fluticasone propionate exposure were also observed from salmeterol/FP DISKUS 50/500mcg and FP DISKUS 500mcg (ratio 0.83 [90% CI: 0.65, 1.07]) in adolescents and adults.

Table 3 Geometric Mean Ratio [90% CI] for the Comparison of FP Systemic Exposure following Salmeterol/FP vs. FP

Treatment (test vs. ref)	AUC	C_{max}
Salmeterol/FP DISKUS 100/50 FP DISKUS 100	1.22 [1.07 – 1.39]	1.27 [1.12 – 1.43]
Salmeterol/FP DISKUS 500/50 FP DISKUS 500/50 concurrent with salmeterol	0.760 [0.614 – 0.941]	0.797 [0.662 – 0.959]
Salmeterol/FP DISKUS 500/50 FP DISKUS 500 alone	0.833 [0.649 – 1.07]	0.910 [0.742 – 1.12]
Salmeterol/FP HFA MDI 220/42 FP HFA MDI 220	0.995 [0.659 – 1.50]	1.05 [0.693 – 1.60]

Steady-state systemic exposure to salmeterol when delivered as salmeterol/FP DISKUS 50/100mcg, Salmeterol/FP DISKUS 50/250mcg, or Salmeterol/FP EVOHALER 25/125mcg was evaluated in 127 patients aged 4 to 57 years. The geometric mean AUC was 325 pg•hr/mL (90% CI: 309, 341) in adolescents and adults.

Therefore, GlaxoSmithKline believe that the following statement in Section 5.2 of the salmeterol/fluticasone propionate EU SmPCs is accurate and we do not propose any amendments:

"When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately."

The following text was added to Section 5.2 of the salmeterol/fluticasone propionate Evohaler EU SmPCs following the first Article 46 worksharing procedure (SE/W/005/pdWS/001):

Paediatric population

The effect of 21 days of treatment with Seretide Inhaler 25/50mcg (2 inhalations twice daily with or without a spacer) or Seretide Diskus 50/100mcg (1 inhalation twice daily) was evaluated in 31 children aged 4 to 11 years with mild asthma. Systemic exposure to salmeterol was similar for Seretide Inhaler, Seretide Inhaler with spacer, and Seretide Diskus (126 pg hr/mL [95% CI: 70, 225], 103 pg hr/mL [95% CI: 54, 200], and 110 pg hr/mL [95% CI: 55, 219], respectively). Systemic exposure to fluticasone propionate was similar for Seretide Inhaler with spacer (107pg hr/mL [95% CI: 45.7, 252.2]) and Seretide Diskus (138pg hr/mL [95% CI: 69.3, 273.2]), but lower for Seretide Inhaler (24pg hr/mL [95% CI: 9.6, 60.2]).

GlaxoSmithKline does not believe any further PK information is required to either the salmeterol/fluticasone propionate EVOHALER or DISKUS EU SmPCs.

Assessor's comment:
The applicant submitted a Population Pharmacokinetic Analysis (RM2005/00368/00).
In general, the model building strategy is considered adequate, except for the strategy for F1 value allocation.
The parameters used to calculate AUC values were estimated with acceptable precision.

Some specific comments based on the analysis report:
The strategy of combining some F1 values of different preparations is not comprehensible. First, a separate F1 value was assigned to every treatment. Then F1 values for all preparations containing 500 mg FP were combined, independent if it was a mono- or combination preparation. Then F1 values for FP Diskus 400 and FP HFA MDI 440 were combined, which did not have exactly the same dose. Then this F1 value was fixed to 1 meaning that it was supposed to be the same as for the 250/50 preparation (even though the estimated F1 value for the preparation containing 440mcg with a value of 0.825 was not that close to 1). The combination of F1 values was probably driven by instability due to over parameterization of the model and thus by the intention to reduce model parameters. However, this procedure should have been more consistent.

Nevertheless, the population analysis revealed differences between the F1 values (being in this case a surrogate for several differences between preparations: height of dose per inhalation, number of inhalations per application and device differences) between formulations. In combination preparations with low FP doses compared to salmeterol (100/50 µg) F1 values were above 1 and in preparations with FP doses largely exceeding salmeterol doses, F1 values were below 1 (for 500/50 and one monopreparation with 500 mcg FP). F1 values differed between 1.67 (preparation containing FP/salmeterol 100/50) and 0.551 (preparations containing FP/salmeterol 500/50, see table 16 above). This might indicate an interaction between FP and salmeterol (or/and there might be underlying nonlinear pharmacokinetics). This trend is obvious even if it might be more pronounced if F1 values for different preparation had not been combined.

Even if differences in F1 values for the FP mono-preparations were also seen, they were less pronounced (see table 16)).

The described differences in F1 values between preparations resulted in higher exposures of FP (AUC) and higher Cmax values in the combination preparation compared to the mono preparation for the 100/50 formulation in children and in adults/adolescents.
In consequence:
The statement "When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately." does not seem to be correct for Seretide DISKUS 100/50 as the 90% CI for the ratio of the test and the reference product does not lie within the acceptance interval (80.00%-125.00%) laid down in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98/Rev1 Corr.) and the Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents (CPMP/EWP/4151/00 Rev. 1). The problem is not that the interval is too wide due to a low number of participants but that significant differences between the combination and the FP mono-product FP seem to exist. This can be seen in the analysis on the paediatric as well as in the analysis on the adolescent and the adult population (table 2 above).
Regarding the clinical impact, paediatric study SAS30031 is reassuring as it does not show differences in the safety profile of both products. On request, the MAH submitted two additional studies evaluating salmeterol/fluticasone propionate 50/100 DISKUS in the adolescent and adult population. Both studies have already been assessed in previous procedures. They are summarized below focussing on fluticasone propionate safety evaluations:

SAM 40027 (2000-2002): this was a multi-centre, stratified, randomised, double-blind, parallel-group, step-up comparison of salmeterol/fluticasone propionate DISKUS to fluticasone propionate DISKUS. The study enrolled 550 patients (70 adolescents) in the fluticasone propionate monotherapy arm, 548 patients (71 adolescents) in the combination therapy arm. Patients had a documented history of asthma of at least 6 months, verified by an airway reversibility of at least 15 %, and were at least 12 to 80 years of age. The study evaluated 3 treatment steps varying in fluticasone propionate dose (100, 250, 500 mcg). Each treatment step was of 12 weeks duration. Patients were to be stepped up, if they did not achieve total control of their asthma. No differences in safety profile regarding AEs, 24-hour free cortisol excretion and urinary cortisol corrected for creatinine (change from baseline to week 12, all patients of 100 mcg bid dose regarding fluticasone propionate) were found. Number of adverse events was similar between groups:

	FP (N=550)		Salmeterol/FP (N=548)	
	n (%)	No. of events	n (%)	No. of events
100mcg b.i.d. dose				
Number of subjects with an AE	174 (32%)	364	195 (36%)	396
Number of subjects with SAEs	2 (<1%)	3	2 (<1%)	2
Number of subjects with drug-related AEs	29 (5%)	44	29 (5%)	53
Number of subjects with an AE leading to withdrawal	7 (1%)	13	6 (1%)	8

Source Table 57 of the CSR

The most common AEs, upper respiratory tract infection, nasopharyngitis, headache and cough occurred with similar frequencies in both groups.
Table 65 of the CSR displays the change from baseline in cortisol/creatinine ratios (Visit 4= after 12 weeks of treatment at a dose of Salmeterol/Fluticasone propionate 50/100 bid or Fluticasone propionate100 bid):

Table 65: Changes From Baseline In Cortisol/Creatinine Ratios (nmol/mmol)

	FP		Salmeterol/FP	
	n	Geometric Ratio[1]	n	Geometric Ratio[1]
Visit 4 [2]	34	0.84	36	0.94
Visit 8 [3]	28	0.66	28	0.86
Visit 9 [4]	10	1.31	6	1.25

Source: Table 15.26

1. Geometric mean ratio is based on the ratio of Visit x/ Visit 2 (baseline) for Visit 4 and Visit 8, and on the ratio of Visit 9/Visit 8 for Visit 9.
2. After 12 weeks of treatment. All subjects taking 100mcg b.i.d. corticosteroid dose. Any subjects who stepped up early at Visit 3 have been excluded.
3. After 52 weeks of treatment. Subjects were using a range of corticosteroid doses.
4. End of open label period after subjects had received prednisolone for 10 days and the salmeterol/FP combination 50/500mcg b.i.d. for 28 days.

SFCA 3002 (1996/7): this was a multicentre, randomised, double-blind, parallel-group, placebo controlled comparison of salmeterol/fluticasone propionate DISKUS 50/100 bid to fluticasone propionate DISKUS 100 bid mono-therapy and salmeterol DISKUS 50 bid mono-therapy. Treatment duration was 12 weeks. The study enrolled 90 patients in the fluticasone propionate monotherapy arm, 92 patients in the combination therapy arm, 92 patients in the salmeterol monotherapy arm and 82 patients in the placebo arm. 9-15% of the patients in the different groups were adolescents. Patients had a documented history of asthma, confirmed by airway reversibility of at least 15%, and were ≥12 years of age. Extent of exposure was the highest in the combination product group (77.3 days (median: 85), fluticasone propionate: 72.4 days (median: 85), salmeterol: 60.5 days (median: 84), placebo 42.5 days (median: 21)). Safety evaluations encompassed: AEs, laboratory values, ECGs and physical examinations. No evaluation of the HPA axis was included. No differences suggestive of a higher systemic exposure to fluticasone propionate with the combination product were seen. 71% of the patients in the combination therapy group and 70% of the patients in the fluticasone propionate group reported an AE. The frequencies of the most common AEs (upper respiratory tract infection, headaches) were similar between groups. However, local reactions were more frequent in the combination therapy group compared to fluticasone propionate monotherapy (throat irritation:12% vs. 7% , hoarseness/dysphonia: 5% vs. 2% and candidiasis: 3% vs. 1%). Two patients in the combination group (appendicitis, herniated disk) and one patient in the fluticasone propionate monotherapy (chest pain) experienced a SAE. Laboratory investigations were not suggestive of higher systemic fluticasone propionate exposure with the combination treatment.

In summary, differences in FP exposure after inhalation of the fluticasone propionate 100 mcg mono-substance and the salmeterol/fluticasone propionate 100 DISKUS combination product are indicated by analysis (RM2005/00368/00). At the moment, no safety concern can be deduced from the clinical studies evaluating the safety of the combination product in relation to fluticasone propionate monotherapy
However, the statement "When salmeterol…….administered separately." should be deleted. The wording: "In a population pharmacokinetic analysis utilizing data from 9 controlled clinical trials with different devices (DISKUS, metered dose inhaler) that included 350 patients with asthma aged 4-77 years (174 patients 4-11 years of age) higher FP systemic exposure following treatment with Seretide DISKUS 100/50 compared to FP DISKUS 100 were seen.

Geometric Mean Ratio [90% CI] for the Salmeterol/FP vs. FP DISKUS Comparison in Children and Adolescent/Adult Populations

Treatment (test vs. ref)	***Population***	***AUC***	***C_{max}***
Salmeterol/FP DISKUS 100/50 FP DISKUS 100	*Children (4–11yr)*	*1.20 [1.06 – 1.37]*	*1.25 [1.11 – 1.41]*
Salmeterol/FP DISKUS 100/50 FP DISKUS 100	*Adolescent/Adult (≥12yr)*	*1.52 [1.08 – 2.13]*	*1.52 [1.08 – 2.16]*

"

In addition, special focus should be laid on this issue in future pharmacovigilance procedures.

Besides: The wording agreed for Section 5.2. during the first Article 46 worksharing procedure (SE/W/005/pdWS/001) does not seem to have been implemented in all member states yet.

Question 3 (Rapporteur DE - supported by IE, NL and UK, not supported by SE)

Include a statement indicating that children should administer Seretide under the supervision of an adult in Section 4.2 of the SPC and Section 3 of the PIL.

Response

GlaxoSmithKline agrees to add a statement to Section 4.2 of the EU Summary of Product Characteristics (SmPC) and Section 3 of the package leaflet (PIL) recommending salmeterol/fluticasone propionate is used under the guidance of an adult. The DISKUS wording is given as an example below but the same wording would be added to the EVOHALER SmPC/PIL too:

Section 4.2 of SmPC

Children 4 years and older:

One inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily.

The maximum licensed dose of fluticasone propionate delivered by Seretide Diskus in children is 100 mcg twice daily.

There are no data available for use of Seretide in children aged under 4 years.

The paediatric administration of Seretide Diskus should be conducted under the guidance of an adult.

Section 3 of PIL

Children 4 to 12 years of age

- *Seretide 50/100 Diskus - One inhalation twice a day*
- *Seretide is not recommended for use in children below 4 years of age.*
- ***Children should use Seretide Diskus with an adult's help.***

Assessor's comment: Issue resolved.

Comments on the FAR

Following the circulation of the FAR the following comments were received:

Re Q1.):
The following comment was received from NL:

Section 5.1
We propose an amended wording as clinical equivalence can not be claimed due to deficiencies in the design i.e.:
"*EVOHALER*
Paediatric population
*In a trial which randomized children aged 4-11 years [n=428], ~~clinical equivalence was demonstrated between~~ salmeterol/fluticasone propionate DISKUS (50/100mcg, one inhalation twice daily) ~~and~~ **was compared with** salmeterol/fluticasone propionate MDI (25/50mcg, two inhalations twice daily) over a 12-week treatment period. The adjusted mean change from baseline in mean morning peak expiratory flow over Weeks 1-12 was 37.7L/min in the DISKUS group and 38.6L/min in the MDI group. Improvements were also seen in both treatment groups on rescue and symptom free days and nights*."
Rationale:
As the Rapporteur concluded, the sensitivity of the studies of which the results are proposed to include, are not optimal. The design should have included an additional comparator arm to test for superiority e.g. over ICS monotherapy. Even more methodological deficiencies can be detected, e.g. no difference is made for the separate contribution of the LABA and the ICS. Therefore, clinical equivalence can not be claimed.

Assessor's comment: the new proposal is acceptable.

Re Q2.):
Response by the applicant:

The following statement in Section 5.2 of the salmeterol/fluticasone propionate EU Summaries of Product Characteristics (SmPCs):

When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately

was not based on the Population Pharmacokinetic Analysis (RM2005/00368/00) (submitted as part of our responses to Day 89 preliminary paediatric assessment report - D2012-7282) or on paediatric pharmacokinetic (PK) data but was based on an evaluation of data from SFCB1002, SFCB1004 and SFCB1005 which were cross-over studies in healthy adults with serial PK

sampling designed to assess the relative biopharmaceutical performance of the products by comparing the systemic exposure to fluticasone propionate (FP) for FP and salmeterol/fluticasone propionate (SFC) DISKUS inhalers. These studies were submitted as part of the original salmeterol/fluticasone propionate DISKUS marketing application (SE/H/169/01-03 – initial application). Geometric ratios with 90% confidence intervals are provided below (synopses for these studies are supplied again as reference in Appendix 2):

SFCB1002 - SFC50/100 / FP100 AUC ratio 0.78 90% CI 0.56, 1.08
SFCB1004- SFC50/250 / FP250 AUC ratio 1.08 90% CI 1.03, 1.13
SFCB1005 - SFC50/100 / FP100 AUC ratio 0.96 90% CI 0.75, 1.24

Therefore GlaxoSmithKline believe the following statement should be retained in Section 5.2 of the salmeterol/fluticasone propionate EU SmPCs but suggest that it is modified as indicated below to clarify that it is based on adult data as follows:

"When salmeterol and fluticasone propionate were administered in combination by the inhaled route <u>in healthy adult subjects</u>, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately

On request the applicant provided additional data on the results of studies SFBC 1004 and 1005 (please note that in SFBC 1004 due to a high number of values below the lower limit of quantitation and insufficient data only c_{max} and t_{max} could be calculated as regards salmeterol. In SFBC 1005 for the same reason, the salmeterol plasma profile could not be fully characterized):

SFCB1004: Treatment comparison of FP PK parameters for subjects who received both relevant treatments						
	Treatment (n)	Geometric LS mean[a]	95% CI of LS meanb	Ratio (/) or Difference (-)	Estimate c(%)	90% CI
AUCτ (pg.hr.mL)	SFC (11) FP (11)	722.7 668.4	694.2, 752.4 642.1, 695.9	SFC/FP	108	103, 113
Cmax (pg/mL)	SFC (11) FP (11)	111.9 107.1	105.2, 119.1 100.6, 113.9	SFC/FP	104	97, 112

Treatment comparison for Cmax of salmeterol (Salm) for subjects who received both relevant treatments					
Treatment (n)	Geometric Least Square mean	95% CI of Least Square mean	Ratio	Estimate (%)	90% CI
SFC (22) Salm (22)	0.229 0.220	0.205, 0.256 0.197, 0.245	SFC/Salm	104	92, 118

SFCB1005: Treatment comparison of FP PK parameters for subjects who received both relevant treatments							
	Treatment (n)	Geometric mean	95% CI of mean	Geometric LS mean	Geometric LS mean Ratio	Estimate	90% CI
AUC∞ (pg.hr.mL)	SFC (14) SLG + FP (12)	917 881	(697, 1205)	917 908	SFC/SLG+FP SFC/FP	1.01 0.96	0.78, 1.31 0.75, 1.24

	FP (13)	927	(690, 1125) (642, 1340)	954	SLG+FP/FP	0.95	0.73, 1.24
Cmax (pg/mL)	SFC (14) SLG + FP (12) FP (13)	107 93 121	(86, 133) (75, 116) (97, 152)	107 94 120	SFC/Salm+FP SFC/FP SLG+FP/FP	1.14 0.89 0.78	0.95, 1.36 0.74, 1.06 0.65, 0.94

Treatment comparison for Cmax of salmeterol (Salm) for subjects who received both relevant treatments						
Treatment (n)	Geometric mean	95% CI of mean	Geometric LS mean	Geometric LS mean Ratio	Estimate	90% CI
SFC (13) SLG + FP (12)	0.20 0.15	0.17, 0.24 0.13, 0.17	0.20 0.15	SFC/SLG+FP	1.29	1.07, 1.56

In response to assessor's comments on population PK analysis, we appreciate the thorough review of Population PK analysis. As the reviewer pointed out, analysis was conducted assigning individual dose/device relative bioavailability scaling term (F1) to each treatment and allowing model to estimate that value. F1 parameters were combined only when estimates were closer to each other and this was done only for the purpose of reducing overparameterization and stabilizing model thereby making analysis more robust.

Additionally, we note that post-hoc estimates that we get out of population PK analysis are NOT independent data since all the data are used to define the population model and as such cannot be used for inferential statistics purposes. This is based on a standard assumption that statistical tests and models used for comparison (t-test, Wilcoxon or Kruskal-Wallis test) are independent between subjects and predicted PK parameters are not independent. Therefore it is not appropriate to add paediatric text based on population PK as suggested. Inferences obtained from population PK regarding no difference in systemic exposure seen when data from all 350 subjects (401 individual PK profiles) was utilized and different systemic exposure seen when datasets were sub-divided by device, age etc have been thoroughly discussed in population PK report.

Based on the discussion delineated above and assessor's comment about "no safety concern can be deduced from the clinical studies evaluating the safety of the combination product in relation to fluticasone propionate monotherapy" we suggest retaining the statement in its modified format (detailed below) and request that the summary of the population pharmacokinetic analysis is not added to the salmeterol/fluticasone propionate EU SmPC.

Re Rapporteur's comment: "The wording agreed for Section 5.2 during the first Article 46 worksharing procedure (SE/W/005/pdWS/001) does not seem to have been implemented in all member states yet." GlaxoSmithKline confirm that the wording agreed for Section 5.2 of the salmeterol/fluticasone propionate metered-dose inhaler Summary of Product Characteristics during the first Article 46 worksharing procedure (SE/W/005/pdWS/001) has been implemented in all EU member states as indicated below except in Cyprus where the national review is still ongoing as they could not submit the variation until GSK had received approval in the Reference Member State (UK). The product is not registered in Romania.

Assessor's comment:
The applicant's clarification is acknowledged. The statement "When salmeterol and fluticasone propionate were administered in combination by the inhaled route in healthy adult subjects, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately." is based on three cross-over studies in healthy volunteers (SFCB 1002, 1004, 1005).
*In order to clarify the comment given below, we'd like to point out that "similar PK data" in our understanding means that the PK parameters (AUC, c_{max}) for both components do at least not show significant **and** clinically relevant differences (indicated by a 90% CI outside the bioequivalence acceptance range of 0.8-1.25 and completely below or above 1.0)*

50/100 strength:
Regarding the 50/100 strength only study SFCB 1002 is relevant (although indicated otherwise in the applicant's response, SFBC 1005 was conducted using the 50/500 strength and can not be taken into account in this discussion on Seretide Diskus 50/100). The relevant study SFCB 1002 enrolled 12 healthy adult male subjects and compared Seretide DISKUS 50/100 to the Fluticasone propionate mono-preparation also administered by DISKUS at single doses. The results were as follows: Ratio SFC/FP: Cmax: point estimate: 1.39 (90% CI: 1.29, 1.51); Ratio SFC/FP AUC last: point estimate: 0.78 (90% CI: 0.56, 1.08). Based on these results it has to be concluded that Cmax was significantly higher after combined administration with the 90% CI outside the acceptance range. This result is in accordance with the popPK analysis. Unlike in the popPK analysis, the AUC values did not show significant differences. The 90% CI is rather wide, while the sample size is low. The CI does not lie within the acceptance interval (80.00%-125.00%) laid down in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98/Rev1 Corr.) and the Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents (CPMP/EWP/4151/00 Rev. 1). It can only be speculated how it would evolve if the sample size was increased.
These data do not give evidence to a clear statement on the similarity of the pharmacokinetics between mono-or combi-preparation of fluticasone propionate at this dose level. In summary, with regard to the 50/100 strength the statement in question seems to be misleading and is not based on sufficiently reliable data and should therefore be deleted without replacement.

50/250 strength:
The statement in question is based on results of study SFCB 1004. This cross-over study investigates the pharmacokinetics of salmeterol and fluticasone propionate in 28 healthy subjects after multiple dosing. Again, the inhaler is the DISKUS device. Comparisons are made between the combination product and the single components. Significant differences in fluticasone propionate exposure were found as regards the comparison of AUCs between the combination treatment and fluticasone propionate at steady state (point estimate: 1.08, 90% CI: 1.03-1.13). However the 90% CI is contained within the bioequivalence acceptance criteria and the differences seen here could be regarded as not clinically relevant. The remaining comparisons for cmax of salmeterol and fluticasone propionate are not significantly different and within the bioequivalence range. Therefore as regards the 50/250 strength the amended statement is correct and could be kept.

50/500 strength:
This strength was investigated in single dose study SFCB 1005. 14 healthy volunteers were treated with the combination product, the mono-substances as a free combination or fluticasone

propionate monotherapy. All products were administered by DISKUS inhaler. Results for fluticasone propionate parameters AUC and c_{max} were not significantly different between treatments although they were not contained within the bioequivalence acceptance range, which might be due to the low number of patients.
Regarding salmeterol c_{max}, results were significantly different with the 90% CI outside the acceptance range indicating a higher maximal exposure after treatment with the combination product. Therefore the statement that "pharmacokinetics were similar" is not correct for this strength and should consequently be deleted.

In summary the statement ***"When salmeterol and fluticasone propionate were administered in combination by the inhaled route <u>in healthy adult subjects</u>, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately"*** *is misleading as regards the 50/100 and 50/500 strength and should be deleted for these preparations.*

So far there is no paediatric data on the 100/50 formulation in Section 5.2 comparing the single compound fluticasone propionate to the combination. The ***PopPK analysis*** *provides this kind of data and it also reveals differences between mono- and combi-preparation for the 50/100 strength which might be important to know. The provided visual predictive check plots of the PopPK analyses show that with the developed model, clearance is underestimated and inter-individual variability is overestimated. Thus, the PopPK-model is not adequately validated for predictions. Nevertheless the goodness of fit plots of the final model were acceptable so the model seems to describe the data of the patients enrolled in these studies rather well and the results of the population PK analyses should not be disregarded.*
The wording suggested by the Rapporteur merely describes the results of this popPK analysis without speculating on any conclusions. Therefore, we do not see any reason why it should not be added to the SPC.
The reason for the differences seen between the results of the AUC in study SFCB 1002 and in the popPk analysis is not known. One major issue might be that the popPK analysis utilized data from 176 asthma patients ≥ 12 years of age while study SFCB 1002 enrolled healthy adult volunteers. It is well known that lung deposition might differ between healthy volunteers and asthma patients. Differences in lung deposition can translate into differences in PK parameters. Seretide is licensed for asthma patients and differences seen in this population should be made available to the prescriber.
For the reasons given above, the present statement should be deleted for the 50/100 and the 50/500 strength and the wording suggested by the Rapporteur enclosed.

After circulation of the FAR comments requesting that changes to Section 5.2 should be implemented for all strengths of Seretide DISKUS were received from NL and the UK.

The following comment was received from NL:
Section 5.2.

1. We do not agree with the Rapporteur to delete the first paragraph but propose an amended wording to indicate that this paragraph concerns the absence of a PK interaction. i.e.:"*When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately,* ***indicating that there is no pharmacokinetic interaction between salmeterol and fluticasone propionate.****"*
   <u>Rationale:</u>
   Deletion of the alinea is not agreed upon as this alinea refers to the absence of a PK interaction between salmeterol and fluticasone propionate, while the PK results of the popPK analysis refer to comparable bioavailability of fluticasone propionate between fixed dose

combination or fluticasone propionate alone using the DISKUS inhaler. In order to prevent confusion, it is proposed to add to the first paragraph that this concerns a PK interaction.

2. The proposal of the RMS to include the results of the popPK analysis is endorsed if added under the subheading fluticasone.
3. Finally, it is proposed to include the pharmacokinetic data in paediatric patients as included in the SPC of Seretide Inhalator EU SmPCs following the first Article 46 worksharing procedure (SE/W/005/pdWS/001); i.e.:

"*Paediatric population*

The effect of 21 days of treatment with Seretide Inhaler 25/50mcg (2 inhalations twice daily with or without a spacer) or Seretide Diskus 50/100mcg (1 inhalation twice daily) was evaluated in 31 children aged 4 to 11 years with mild asthma. Systemic exposure to salmeterol was similar for Seretide Inhaler, Seretide Inhaler with spacer, and Seretide Diskus (126 pg hr/mL [95% CI: 70, 225], 103 pg hr/mL [95% CI: 54, 200], and 110 pg hr/mL [95% CI: 55, 219], respectively). Systemic exposure to fluticasone propionate was similar for Seretide Inhaler with spacer (107pg hr/mL [95% CI: 45.7, 252.2]) and Seretide Diskus (138pg hr/mL [95% CI: 69.3, 273.2]), but lower for Seretide Inhaler (24pg hr/mL [95% CI: 9.6, 60.2])."

Assessor's comment:
Re 1.: The Dutch comment is acknowledged. However for the reasons given above, we do not think that this wording should be retained for the 50/100 and the 50/500 strengths. In addition, from our point of view interactions can not be ruled out.
It is not clear what the reason for the differences in exposure to fluticasone propionate observed here really is. Study SFCB 1002 compared the combination product to fluticasone propionate monotherapy. Both treatments were administered by DISKUS. It resulted in "similar" AUCs (SFCB1002 - SFC50/100 / FP100 AUC ratio 0.78 90% CI 0.56, 1.08) according to the applicant. In contrast, the popPk analysis compared the same products but resulted in a higher exposure to fluticasone propionate with the combination product. This significant difference in cmax and AUC was seen in paediatric as well as in adolescent and adult patients. One major difference is that SFBC 1002 enrolled healthy adult volunteers while in the popPK analysis patients are studied. It is not clear if data is transferable between groups here.
The popPK analysis utilized data from more patients and samples which resulted in tighter CIs compared to study SFBC 1002. We do not know, what the results of this study might have been if the sample size had been higher. However, in accordance with the popPK analysis, even with the low sample size c_{max} results are significantly different, questioning the conclusion drawn by the applicant.
Differences seen with the low strength have not been observed when the higher strengths were studied in the popPk analysis. These strengths have a different salmeterol/fluticasone propionate ratio and interactions can not be ruled out.
Data published by Taki et al. (Eur J Pharm Sci 2011, 43 (4), 225-35) indicate that in vitro deposition characteristics differ between the administration of single-active versus combination formulations, which might translate in differences in PK parameters. This should also have been detectable in healthy volunteers, but in this case the sample size might just have been too low.
Re 2.: The heading "fluticasone" will be added..
Re 3.: The proposal is supported as this paragraph also provides information on paediatric salmeterol PK data. This wording has already been agreed in the first Article 46 worksharing procedure.

Re Q3.):

A comment from Sweden on the FAR was received suggesting to amend the wording to be included in Section 4.2/SPC and Section 3/PIL in line with what was adopted for Symbicort

(DE/W/046/pdWS/001). The MPA suggested that the following information was added to the PIL only: *"As with all inhalers, caregivers should ensure that children prescribed Seretide Discus/Evohaler use correct inhalation technique, as described above."*
This comment was supported by France, the Netherlands and the UK.

Assessor's comment: *The amendment to the wording is acceptable.*

VII. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion:
The applicant provided additional information on the issues on the list of questions. Comments received from the MSs were taken into account. As detailed above the following changes to the SPC/PIL are deemed necessary:

1.) Section 3 of PIL

Children 4 to 12 years of age

Inclusion of:

- ***"As with all inhalers, caregivers should ensure that children prescribed Seretide Discus/Evohaler use correct inhalation technique, as described above."***

2.) Section 5.1 of the SmPC under the heading "Paediatric population".

Inclusion of:

DISKUS

Paediatric population

In a 12 week trial of children aged 4-11 years [n=257] treated with either salmeterol/fluticasone propionate 50/100 or salmeterol 50 mcg + fluticasone propionate (FP) 100mcg both twice daily, both treatment arms experienced a 14% increase in peak expiratory flow rate as well as improvements in symptom score and rescue salbutamol use. There were no differences between the 2 treatment arms. There were no differences in safety parameters between the 2 treatment arms.

In a 12 week trial of children 4-11 years of age [n=203] randomized in a parallel-group study with persistent asthma and who were symptomatic on inhaled corticosteroid, safety was the primary objective. Children received either salmeterol/FP (50/100 mcg) or FP (100 mcg) alone twice daily. Two children on salmeterol/FP and 5 children on FP withdrew because of worsening asthma. After 12 weeks no children in either treatment arm had abnormally low 24-hour urinary cortisol excretion. There were no other differences in safety profile between the treatment arms.

EVOHALER

Paediatric population

In a trial which randomized children aged 4-11 years [n=428], salmeterol/fluticasone propionate DISKUS (50/100mcg, one inhalation twice daily) **was compared with** ***salmeterol/fluticasone propionate MDI (25/50mcg, two inhalations twice daily) over a 12-week treatment period. The adjusted mean change from baseline in mean morning peak expiratory flow over Weeks 1-12 was 37.7L/min in the DISKUS group and 38.6L/min in the MDI group. Improvements were also seen in both treatment groups on rescue and symptom free days and nights*****."**

3.) Section 5.2. of the SPC:
Seretide Diskus

Deletion of :
"When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately."

Inclusion of:

"Fluticasone propionate (FP):
In a population pharmacokinetic analysis utilizing data from 9 controlled clinical trials with different devices (DISKUS, metered dose inhaler) that included 350 patients with asthma aged 4-77 years (174 patients 4-11 years of age) higher FP systemic exposure following treatment with Seretide DISKUS 100/50 compared to FP DISKUS 100 were seen.

Geometric Mean Ratio [90% CI] for the Salmeterol/FP vs. FP DISKUS Comparison in Children and Adolescent/Adult Populations

Treatment (test vs. ref)	***Population***	***AUC***	***C_{max}***
Salmeterol/FP DISKUS 100/50 FP DISKUS 100	***Children (4–11yr)***	***1.20 [1.06 – 1.37]***	***1.25 [1.11 – 1.41]***
Salmeterol/FP DISKUS 100/50 FP DISKUS 100	***Adolescent/Adult (≥12yr)***	***1.52 [1.08 – 2.13]***	***1.52 [1.08 – 2.16]***

Paediatric population
The effect of 21 days of treatment with Seretide Inhaler 25/50mcg (2 inhalations twice daily with or without a spacer) or Seretide Diskus 50/100mcg (1 inhalation twice daily) was evaluated in 31 children aged 4 to 11 years with mild asthma. Systemic exposure to salmeterol was similar for Seretide Inhaler, Seretide Inhaler with spacer, and Seretide Diskus (126 pg hr/mL [95% CI: 70, 225], 103 pg hr/mL [95% CI: 54, 200], and 110 pg hr/mL [95% CI: 55, 219], respectively). Systemic exposure to fluticasone propionate was similar for Seretide Inhaler with spacer (107pg hr/mL [95% CI: 45.7, 252.2]) and Seretide Diskus (138pg hr/mL [95% CI: 69.3, 273.2]), but lower for Seretide Inhaler (24pg hr/mL [95% CI: 9.6, 60.2])."

4.) In addition, future pharmacovigilance procedures for Seretide 100/50 should focus on the effect on the HPA axis.

VIII. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Name of the active substance(s): Salmeterol / Fluticasone propionate
Name of the medicinal product: Seretide
Formulation: Inhalation powder/metered dose inhaler