Supplementary table 1: List of search topics and related search strings used in the literature searches

Search Topic	**Search string**
Age Range	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children))
Asthma severity	(((seretide) OR (fluticasone propionate salmeterol)) AND ((asthma) AND ((moderate) OR (severe) OR (moderate to severe) OR (moderate or severe))) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children))
High dose ICS	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children)) AND ((high dose ICS) OR (high dose inhaled corticosteroids)) OR (high dose ICS monotherapy) OR (high dose inhaled corticosteroid monotherapy)
Low dose ICS	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children)) AND ((low dose ICS) OR (low dose inhaled

	corticosteroids)) OR (low dose ICS monotherapy) OR (low dose inhaled corticosteroid monotherapy)
LTRA	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children)) AND ((LTRA) OR (leukotriene receptor antagonist therapy))
Exacerbation reduction	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children)) AND (exacerbation reduction)
Night-time awakening	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children)) AND ((night-time awakening) OR (nocturnal awakening) OR (nighttime) OR (awakening))
Exacerbation	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children)) AND (exacerbation)
Symptom	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16

control	years) OR (children) OR (preschool) OR (schoolchildren) OR (school children)) AND ((symptom control) OR (asthma control))
Lung function	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children)) AND ((lung function) OR (FEV1))
Asthma symptoms	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children)) and ((shortness of breath) or (wheezing) OR (cough))
Asthma symptoms	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children)) and ((SABA) OR (short-acting beta agonist) OR (rescue medication) OR (short acting bronchodilator))
Safety	(((seretide) OR (fluticasone propionate salmeterol)) AND (asthma)) AND ((pediatric) OR (pediatric) OR (4-11 years) OR (12-16 years) OR (children) OR (preschool) OR (schoolchildren) OR (school children)) AND ((safety) OR (growth) OR (development) OR (caregiver) OR (hospitalisation) OR (hospitalization) OR (emergency intervention) OR (infection) OR (systemic effect) OR (Cushing's syndrome) OR (adrenal suppression))

Supplementary table 2: Details of selected studies and outcomes relevant to FP/SAL

Author(s), year	Title	Study type	Age range (years)	Total participants studied (n)	Comorbidities /phenotypes reported	Device for FP/SAL delivery	Treatment duration/ observation period	Relevant outcomes
Akashi K, et al., 2016	Optimal step-down approach for pediatric asthma controlled by salmeterol/fluticasone: A randomized, controlled trial (OSCAR study)	RCT	5–15	128	NA	pMDI with spacer	12 weeks	For step-down approaches, halving the dose of FP/SAL and switching to FP alone are both optimal approaches.
Bracamonte T, et al., 2005	Efficacy and safety of salmeterol/fluticasone propionate combination delivered by the Diskus or pressurised metered-dose inhaler in children with asthma	RCT	4–11	428	Allergic rhinitis (71% FP/SAL group; 79% FP group)	Randomized to DPI (Diskus^{TM}) or CFC-free pMDI Stratified by spacer use	12 weeks	When administered through either Diskus or pMDI, FP/SAL (100/50 mcg) is very effective and clinically equivalent and improved both lung function and asthma symptoms.

de Blic J, et al., 2009	Salmeterol/fluticasone propionate vs. double dose fluticasone propionate on lung function and asthma control in children	RCT	4–11	321	Allergic rhinitis (71% FP/SAL group; 76% FP group) Eczema (41% FP/SAL group; 38% FP group) Positive SPT/specific IgE (85% FP/SAL group; 91% FP group)	DPI (Diskus^{TM})	12 weeks	FP/SAL had a significant improvement in mean percentage rescue medication-free days (Weeks 1–12) when compared with FPL (difference, 1.4; 95% CI , 0.0–3.4), p=0.025. Switching children, symptomatic on low-dose ICS, to FP/SAL (100/50 mcg bid) is at least as effective as doubling the dose of ICS (FP 200 mcg bid at improving clinical outcomes and achieving asthma control).
Gappa M, et al, 2009	Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind randomized trial (VIAPAED)	RCT	4–16	283	NA	DPI (Diskus^{TM}) A spacer device (Volumatic) was provided for children <7 years) and for those patients who needed it	8 weeks	FP/SAL (100/50 mcg bid) was more effective than a double dose of ICS in children with persistent asthma inadequately controlled on low-dose ICS alone. FP/SAL resulted in significantly more rescue medication-free

								days (8.0%; 95% CI, 0.6–15.3) and symptom-free days (8.7%; (95% CI, 1.2–16.3) compared to a double dose of FP alone.
Lemanske Jr. R F, et al., 2010	Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids	RCT	6–17	182	Allergic rhinitis (71% FP/SAL group; 79% FP group)		16 weeks	Step-up with LABA was significantly more likely to provide the best response in children with asthma. A best response to ICS or LTRA step-up also reported in many children which highlights the need for individual monitoring and adjustment of therapy for each child with asthma when considering step-up therapy.

Malone R, et al., 2005	The safety of twice-daily treatment with fluticasone propionate and salmeterol in pediatric patients with persistent asthma	RCT	4–11	203	NA	DPI (Advair Diskus™)	12 weeks	Treatment for 12 weeks with FP/SAL (100/50 mcg bid) is well-tolerated in children with persistent asthma and can provide a treatment option for those not controlled by ICS alone.
Murray CS, et al., 2010	Effect of addition of salmeterol versus doubling the dose of fluticasone propionate on specific airway resistance in children with asthma	RCT	4-11	24	NA	DPI (Accuhaler/Diskus™)	6 weeks	FP/SAL has better improvement in sR_{aw} than a high-dose FP in children with moderate-to-severe persistent asthma.

Murray J, et al., 2011	Evaluation of fluticasone propionate and fluticasone propionate/salmeterol combination on exercise in pediatric and adolescent patients with asthma	RCT	4–17	231	NA	DPI (Diskus™)	4 weeks	FP/SAL and FP both protected against a decrease in FEV_1 following exercise. Therapy with FP/SAL (100/50 mcg bid) can provide additional control if exercise induced asthma is not controlled with FP alone.
Nguyen WT, et al., 2005	Maintenance asthma treatment with fluticasone/salmeterol combination via Diskus: effect on outcomes in inner-city children enrolled in TennCare	RCT	4–17	39	NA	DPI (Diskus™)	52 weeks	FP/SAL is associated with lower risk of exacerbations, ED visits and hospitalizations in inner city children with asthma.

O'Connor R D, et al., 2008	Observational study of the association of Fluticasone propionate/salmeterol via a single device and inhaled corticosteroid use in children on asthma related emergency department and hospitalization visits	Observational	4–11	751,001[d]	NA	NA	4.25 years	FP/SAL was associated with lower asthma-related ED visits and hospitalizations in children aged 4–11 years when compared with ICS alone.
Pearlman D, et al., 2009	Fluticasone propionate/salmeterol and exercise-induced asthma in children with persistent asthma	RCT	4–17	248	NA	DPI (Diskus™)	4 weeks	64% of subjects with <10% decrease in FEV1 following exercise challenge for FP/SAL compared with 47% for FP monotherapy (P=0.026) FP/SAL produced greater protection from exercise induced bronchospasm than FP.

Płoszczuk,et al, 2018	Efficacy and safety of fluticasone propionate/formoterol fumarate in pediatric asthma patients: a randomized controlled trial	RCT	5–12	512	NA	pMDI (Seretide Evohaler)	12 weeks	FP/SAL and FP/FORM were superior to FP monotherapy for the change from pre-dose FEV_1 at baseline to 2-hour post-dose FEV_1 over a 12-week period. Measures of lung function (FEF_{25}, FEF_{50}, FEF_{75} and $FEF_{25–75}$) showed greater predose and 2-hour post dose changes from baseline for FP/SAL and FP/FORM in comparison with FP monotherapy.

Prazma CM, et al., 2015	The association between seasonal asthma exacerbations and viral respiratory infections in a pediatric population receiving inhaled corticosteroid therapy with or without long-acting beta-adrenoceptor agonist: a randomized study	RCT	4–11	339	One or more allergies (60%)	DPI (Diskus^{TM})	16 weeks	In the 7 days before and after an exacerbation, FP/SAL was associated with fewer symptoms and reduction in SABA therapy use when compared with FP monotherapy.
Spahn J, et al., 2009	Dispensing of fluticasone propionate/salmeterol combination in the summer and asthma-related outcomes in the fall	Observational	4–11; 12–18	386,116[a]	NA	NA	4 years	Treatment with FP/SAL in the summer associated with lower risk of asthma-related ED visits and hospitalizations in the fall. Risk reduction not noted in patients who collected a prescription for FP/SAL in the fall but not the summer.

Stanford R, et al., 2013	Fluticasone propionate-salmeterol versus inhaled corticosteroids plus montelukast: outcomes study in pediatric patients with asthma	Observational	4–11	3001[b]	Allergic rhinitis (42% FP/SAL group; 47.9% ICS/montelukast group)	NA	8 years	FP/SAL reported to have with reduced utilization of asthma-related healthcare services and costs when compared with ICS+LTRA and should be considered in patients with persistent asthma.
Stauffer J, et al., 2007	Fluticasone propionate/salmeterol administered via Diskus provides protection against activity induced bronchospasm in children and adolescents with persistent asthma	RCT	4–17	479	NA	DPI (Diskus^{TM})	4 weeks	Regular dosing of FP/SAL (100/50 mcg bid) improved asthma control and provided protection against EIB in children with persistent asthma.

Stempel D, et al., 2006	Resource utilization with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies in children with asthma	Observational	4–17	9192[c]	NA	NA	1 year	FP/SAL was associated with reduced necessity for SABA reliever therapy and OCS therapy when compared with various other controller therapies (FP alone, MON, ICS+SAL given separately, and ICS+MON) in controller-naïve children.
Stempel D, et al, 2016	Safety of adding salmeterol to fluticasone propionate in children with asthma	RCT	4–11	6208	NA	DPI (Diskus™)	26 weeks	A higher risk of severe asthma events among children 4–11 years of age was not reported for FP/SAL compared with FP alone.
Vaessen-Verberne A, et al., 2010	Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma	RCT	6–16 years	158	Atopy (77% FP/SAL group; 73% FP group)	DPI (Diskus™)	26 weeks	Efficacy of FP/SAL is equal to a double dose of FP monotherapy in measures of symptom control and lung function in children with moderate asthma symptomatic on ICS monotherapy.

Van den Berg N J, et al., 2000	Salmeterol/fluticasone propionate (50/100 mcg) in combination in a Diskus inhaler (Seretide™) is effective and safe in children with asthma	RCT	4–11	257	Atopy (64% FP/SAL group; 67% SAL + FP group)	DPI (Diskus™)	12 weeks	Significant improvement in lung function and symptoms in children with asthma treated with FP/SAL (100/50 mcg bid). Combination Diskus™ shown to be as safe and effective as concurrent therapy given via two separate Diskus™ inhalers.

[a]Total evaluated observations of healthcare claims identified from a large managed database over a 42-month period. [b]Number of patients identified from a health insurance database with at least one pharmacy claim for FP/SAL, any ICS or MON during the 8-year study period.
[c]Number of patients identified from a healthcare database with a medical claim for asthma and initial pharmacy claim for FP/SAL, FP, other ICS, SAL, or MON.
[d]Number of patient observations identified with asthma and claims for FP/SAL or ICS over a 50-month period.
bid, twice daily; CFC, chlorofluorcarbon; ED, emergency department; FEV_1, forced expiratory volume in one second; FEF, forced expiratory flow; FEF_{25}, forced expiratory flow at 25% vital capacity; FEF_{50}, forced expiratory flow at 50% vital capacity; FEF_{75}, forced expiratory flow at 75% vital capacity; $FEF_{25–75}$, forced expiratory flow at 25–75% vital capacity; FP, fluticasone propionate; FP/FORM, fluticasone propionate/formoterol; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist therapy; MON, montelukast; OCS, oral corticosteroids; PEF, peak expiratory flow; pMDI, pressurized metered dose inhaler; RCT, randomized controlled trial; SABA, short-acting β_2-agonist; SAL, salmeterol; SPT, skin prick test; S_{Raw}, specific airway resistance.