Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone Stempel DA et al. N Engl J Med 2016; 374:1822-1830	
Background	The safety of using a LABA together with an ICS in asthma therapy is questioned after results of the Serevent Nationwide Surveillance (SNS), Salmeterol Multicenter Asthma Research Trial (SMART), and a meta-analysis conducted by the FDA in 2010 associated LABA use with asthma-related hospitalizations, intubations, and death.
Rationale	Stempel et al. conducted their study in response to the FDA's 2010 request for each manufacturer of a LABA to prospectively evaluate whether the ICS/LABA combination is non-inferior to ICS use alone with respect to the occurrence of serious asthma-related events. Serious asthma-related events are defined as hospitalization, endotracheal intubation, or death.
Objective	• Primary (*Safety*): To assess whether the use of a fixed dose combination of fluticasone/salmeterol is non-inferior to the use of fluticasone alone with respect to the risk of asthma-related adverse events (hospitalization, intubation, and death). • Secondary (*Efficacy*): To assess whether the use of fluticasone/salmeterol is superior to the use of fluticasone alone in asthma therapy as indicated by the incidence of asthma exacerbations and frequency of albuterol/salbutamol use.
Trial Design	• Global (33 countries), multicenter (710 centers), prospective, randomized, stratified, double-blind, non-inferiority trial. • Randomization: interactive voice-response system and stratified into 6 groups based on ACQ-6 score (either < 1.5 or ≥ 1.5) and current asthma medications, then assigned to one of the two interventions on a 1:1 basis according to their stratification group. • Recruitment period: November 2011 to June 2015. • Both interventions were identically packaged; however, the dose of ICS was not double-blinded. All subjects had access to open-label rescue SABA therapy (albuterol, salbutamol MDI). • Total of a 26 week treatment period, which was followed by a 1 week follow-up period.
Patient Population	Men and women ≥ 12 years old with moderate-to-severe asthma present for at least 1 year prior to study enrollment.
Eligibility	**Inclusion Criteria**: • Informed consent • Males and females ≥ 12 years old • Persistent asthma for at least 1 year prior to study recruitment • Require daily asthma therapy • Asthma exacerbation within past year treated with glucocorticoids or hospitalization **Exclusion Criteria:** • Asthma exacerbation treated with glucocorticoids or hospitalization that occurred 30 days prior to randomization • Life-threatening asthma • > 10 pack-years smoker • Unstable asthma • Pregnant or breastfeeding
Intervention	1. Fluticasone/salmeterol: 100/50 mcg, 250/50 mcg, or 500/50 mcg given BID 2. Fluticasone: 100 mcg, 250 mcg, or 500 mcg given BID
Outcomes	**Primary Endpoint:** • *Safety*: First serious asthma-related event (hospitalization, endotracheal intubation, or death) **Secondary Endpoints:** • *Efficacy*: First severe asthma exacerbation requiring glucocorticoid therapy for a minimum x 3/7 with or without hospitalization or ED visit. • *Efficacy*: Albuterol or salbutamol use as rescue therapy.
Statistics	Primary Safety Endpoint: • Stratified Cox proportional-hazards regression model • Intention-to-treat analysis of all patients who received at least one dose of their randomly assigned intervention. • Based on the findings of a 2008 meta-analysis conducted by GSK for the FDA Advisory Committee, it was assumed that the rate of serious asthma-related events in the fluticasone only group would be 0.0075 over the 26 week treatment period. • An upper boundary of < 2.0 on the 95% CI was defined to mean that the fluticasone-salmeterol intervention was non-inferior to fluticasone alone in terms of the primary composite safety endpoint. • A sample size of 11, 664 gives the study a power of 90% to detect non-inferiority of fluticasone/salmeterol compared to

<table>
<tr><td></td><td>fluticasone alone using a one-sided α of 0.025.
<u>Secondary Efficacy Endpoints</u>:
Cox proportional-hazards regression model
The study was not powered for statistical analysis of the secondary endpoints, so descriptive analysis of the data obtained was reported.</td></tr>
<tr><td>Results – Safety</td><td><u>Primary Safety Endpoint</u>:
Fluticasone group:
33 patients had 38 events
Fluticasone/salmeterol group:
34 patients had 36 events
HR 1.03 (95% CI 0.64 to 1.66)
Non-inferiority achieved (p = 0.03)
Table 2. Summary of Safety End Points.*<table><tr><th>Safety End Point</th><th>Fluticasone–Salmeterol (N = 5834)</th><th>Fluticasone Alone (N = 5845)</th></tr><tr><td>Composite safety end point — no. (%)</td><td>34 (<1)</td><td>33 (<1)</td></tr><tr><td>Asthma-related death</td><td>0</td><td>0</td></tr><tr><td>Asthma-related intubation</td><td>0</td><td>2 (<1)</td></tr><tr><td>Asthma-related hospitalization</td><td>34 (<1)</td><td>33 (<1)</td></tr><tr><td>Total no. of asthma-related hospitalizations</td><td>36</td><td>36</td></tr><tr><td>Death from any cause — no. (%)†</td><td>3 (<1)</td><td>6 (<1)</td></tr></table>* The analysis was performed in the intention-to-treat population.
† Details regarding all-cause mortality are provided in Section 4 in the Supplementary Appendix.</td></tr>
<tr><td>Results – Efficacy</td><td><u>Secondary Efficacy Endpoint</u>:
Fluticasone group:
At least 1 asthma exacerbation in 10% of subjects (n: 5845)
Fluticasone/salmeterol group:
At least 1 asthma exacerbation in 8% of subjects (n: 5834)
HR 0.79 (95% CI: 0.70 to 0.89, p = 0.001)</td></tr>
<tr><td>Bottom Line (Conclusion)</td><td>In patients with moderate-to-severe asthma the use of a fixed dose combination of fluticasone/salmeterol over a 26 week period was non-inferior to use of fluticasone alone in terms of occurrence of severe asthma-related events (death, endotracheal intubation, or hospitalization). These adverse events occurred at a similar frequency in both interventions.

The fixed dose combination of fluticasone/salmeterol showed to have a lower risk of asthma exacerbation (21%) compared to fluticasone use alone; however, the study was not powered for this secondary efficacy endpoint.</td></tr>
<tr><td>Limitations</td><td>Short duration (26 weeks)
Infrequent incidence of serious asthma-related events
Studied moderate-to-severe asthmatics (cannot extrapolate to patients with life-threatening or unstable asthma)
High adherence rates seen in study may not be applicable to real world setting (median rate of adherence was 95.1% in both interventions)
Underlying inflammation severity was not assessed</td></tr>
<tr><td>Application to Clinical Practice</td><td>Trial findings help confirm that in patients who are highly adherent to their asthma therapy and do not have either life-threatening or unstable asthma the use of the LABA/ICS combination does not increase the risk of serious asthma related events compared to ICS use alone.
The results cannot be applied to patients who have severe unstable disease, which are patients for whom it is recommended to initiate therapy with a LABA/ICS combination.</td></tr>
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