EVERY DAY in America approximately …

- 63,000 people miss school or work due to asthma
- 34,000 people have an asthma attack
- 5,000 people visit the emergency room due to asthma
- 1,300 people are admitted to the hospital due to asthma
- 10 people die from asthma

Asthma Remains a Serious Health Risk

What is Asthma?

- Bronchoconstriction
- Inflammation
Shifting Paradigm of Asthma Care

- **Shift from consensus to evidence-based guidelines**
- **Recognition that asthma is a heterogeneous disease with both inflammation and smooth muscle dysfunction**
- **Therapeutic decision-making has shifted from severity based to control based**
- **Importance of formal disease education**

Changing Pattern in Asthma Mortality in the US


Asthma Severity and Control

Severity

- Intrinsic intensity of the disease process
- Most easily and directly measured in patients not receiving long-term therapy
  
  *Guides clinical decisions during the initial evaluation and prior to start of controller therapy*

Control

- Degree to which asthma-related symptoms, functional impairment, and risk of untoward events are minimized and the goals of therapy are met
  
  *Guides clinical decisions to either maintain or adjust therapy once therapy is initiated*

---

Primary Goal of Asthma Therapy

To enable a patient to achieve and maintain control over their asthma

Eliminate impairments:
- Symptoms
- Functional limitations
- Poor quality of life
- Other manifestations of asthma

Reduce risk of:
- Exacerbations
- ED use
- Hospitalizations

Treatment goals are identical for all levels of asthma severity

CJ: 9 yr-old with Persistent Asthma

- Onset of asthma at age 2
- Triggers: viral infections, exercise and inhalant allergens
- Present medications
  - Low-dose inhaled corticosteroid
  - Short-acting beta\textsubscript{2}-agonists 3-4 times a week
- In the past year: 2 bursts of oral corticosteroids and missed 5 days of school for asthma attacks
- Unable to play soccer even with pretreatment with albuterol
- Baseline lung function testing normal
  - FEV\textsubscript{1} of 88% predicted
### Assessing Asthma Control in Patients 5-11 Years of Age

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Well Controlled</th>
<th>Not Well Controlled</th>
<th>Very Poorly Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/wk but not more than once on each day</td>
<td>&gt;2 days/wk or multiple times on ≤2 days/wk</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤1x/month</td>
<td>≥2x/month</td>
<td>≥2x/week</td>
</tr>
<tr>
<td>Interference w/ normal activity</td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>SABA use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Several times per day</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• FEV₁, or PEF</td>
<td>&gt;80% predicted/personal best</td>
<td>60%-80% predicted/personal best</td>
<td>&lt;60% predicted/personal best</td>
</tr>
<tr>
<td>• FEV₁/FVC</td>
<td>≥80%</td>
<td>75%-80%</td>
<td>&lt;75%</td>
</tr>
<tr>
<td>Validated questionnaires</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-ACT</td>
<td>≥20</td>
<td>16-19</td>
<td>≤15</td>
</tr>
</tbody>
</table>

| Risk                  |                 |                     |                        |
| Exacerbations requiring oral systemic corticosteroids | 0-1/year | ≥2/year | Consider severity and interval since last exacerbation |
| Reduction in lung growth | Evaluation requires long-term follow-up | |
| Treatment-related adverse effects | Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk | |

#### Recommended Action for Treatment

- **C-ACT = Childhood Asthma Control Test.**
### Stepwise Approach for Managing Asthma in Children 5-11 Years of Age

<table>
<thead>
<tr>
<th>Intermittent Asthma</th>
<th>Persistent Asthma: Daily Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 1 Preferred:</th>
<th>Step 2 Preferred:</th>
<th>Step 3 Preferred:</th>
<th>Step 4 Preferred:</th>
<th>Step 5 Preferred:</th>
<th>Step 6 Preferred:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose ICS (A)</td>
<td>Low-dose ICS + either LABA (B), LTRA (B), or Theophylline (B)</td>
<td>Either Medium-dose ICS + LABA (B)</td>
<td>Alternative: Medium-dose ICS + either LTRA (B) or Theophylline (B)</td>
<td>High-dose ICS + LABA (B)</td>
<td>High-dose ICS + LABA + Oral Systemic Corticosteroid (D)</td>
</tr>
<tr>
<td>Cromolyn (B), LTRA (B), Nedocromil (B), or Theophylline (B)</td>
<td>Alternative:</td>
<td>High-dose ICS + either LTRA (B) or Theophylline (B)</td>
<td>High-dose ICS + either LTRA (B) or Theophylline (B)</td>
<td>High-dose ICS + either LTRA or Theophylline and Oral Systemic Corticosteroid (D)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medium-dose ICS (B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SABA=short-acting beta-agonist; ICS=inhaled corticosteroid; LTRA=leukotriene receptor antagonist; LABA=long-acting beta-agonist

### Stepwise Approach for Managing Asthma in Children ≥12 Years of Age and Adults

<table>
<thead>
<tr>
<th>Step 1 Preferred:</th>
<th>Step 2 Preferred: Low-dose ICS (A) OR Medium-dose ICS (A)</th>
<th>Step 3 Preferred: Low-dose ICS + LABA (A) OR Medium-dose ICS + LABA (B)</th>
<th>Step 4 Preferred: Medium-dose ICS + LABA (B) AND Consider Omalizumab for Patients Who Have Allergies (B)</th>
<th>Step 5 Preferred: High-dose ICS + LABA (B) AND Consider Omalizumab for Patients Who Have Allergies (B)</th>
<th>Step 6 Preferred: High-dose ICS + LABA + Oral Corticosteroid AND Consider Omalizumab for Patients Who Have Allergies (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent Asthma: Daily Medication</td>
<td>Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Step 1** Preferred: SABA PRN

**Step 2** Preferred: Low-dose ICS (A) OR Medium-dose ICS (A)

*Alternative:* Cromolyn (A), LTRA (A), Nedocromil (A), or Theophylline (B)

**Step 3** Preferred: Low-dose ICS + LABA (A) OR Medium-dose ICS + LABA (B)

*Alternative:* Low-dose ICS + either LTRA (A), Theophylline (B), or Zileuton (D)

**Step 4** Preferred: Medium-dose ICS + LABA (B) AND Consider Omalizumab for Patients Who Have Allergies (B)

**Step 5** Preferred: High-dose ICS + LABA (B) AND Consider Omalizumab for Patients Who Have Allergies (B)

**Step 6** Preferred: High-dose ICS + LABA + Oral Corticosteroid AND Consider Omalizumab for Patients Who Have Allergies (B)

---

CJ: Office Visit
November 2008

- Treatment with concurrent ICS and LABA for 10 months
- No exacerbations
- No missed school
- Played fall soccer on a traveling team
Conclusions

- Asthma alters the lives of more than 20 million Americans
- In the past decade, asthma mortality has decreased as the evidence to improve asthma care has advanced
- The concurrent use of ICS with a long-acting bronchodilator is an effective and safe treatment option today for patients uncontrolled on an ICS alone
Overview of Regulatory History of Salmeterol-containing Medications

C. Elaine Jones, PhD  
Vice President  
Respiratory Regulatory Affairs  
GlaxoSmithKline
Previous Surveillance Studies of SEREVENT

- SNS (SEREVENT Nationwide Surveillance Study)
  - 1990 – 1992

- SMART (Salmeterol Multicenter Asthma Research Trial)
  - 1996 – 2003

Results suggested mitigation of risk of severe asthma outcomes with concomitant ICS
Actions Resulting from SMART

- Distribution of a HCP letter
- Revisions to SEREVENT and ADVAIR labeling at termination of SMART study
  - Addition of Boxed Warning
  - Asthma-related death results from SMART
    - African American subgroup analyses suggesting greater risk
Previous Advisory Committee Reviews

LABA Safety

• Pulmonary and Allergy Drugs Advisory Committee – July 2005
  • Unanimous support for benefit to risk profile of salmeterol
  • Labeling Revisions to Boxed Warning and Indications
  • Addition of a Medication Guide

• Pediatric Advisory Committee – November 2007
  • Requirement under the Best Pharmaceuticals for Children Act
  • No new safety signals identified
  • Recommendation for formal benefit to risk profile of LABAs in the treatment of asthma
Today’s Advisory Committee Review

• Efficacy of salmeterol-containing products in persistent asthma

• Safety database of randomized controlled trials
  • 200 studies and over 100,000 patients

• Other databases
Overview of Safety and Efficacy for Salmeterol-containing Medications

Katharine Knobil, M.D.
Vice President
Respiratory Medicines Development Center
GlaxoSmithKline
Presentation Outline

• Efficacy of salmeterol-containing products in persistent asthma

• Safety Review
  • Methods
  • Safety Data with SEREVENT
  • Safety Data with ADVAIR

• Recommendations
ADVAIR Versus ICS Alone

Improvement in Lung Function

Day 1

- **ADVAIR 250/50 (n=81)**
- **SEREVENT 50 mcg (n=84)**
- **FP 250 mcg (n=81)**
- **Placebo (n=90)**

**Shapiro et al. Am J Respir Crit Care Med. 2000;161:527–534.**

- p<0.001 ADVAIR vs. FP and placebo at all time points
- p<0.05 ADVAIR vs. SEREVENT at 0.5, 1, 2, 4, 6 and 10 hours

Week 12

- p<0.001 ADVAIR vs. FP, SEREVENT and placebo at all time points
Salmeterol plus ICS Versus Alternative Treatments

*Significant Improvement in Lung Function*

Each bar represents an individual treatment comparison within a study

*p<0.05 for all comparisons
Salmeterol plus ICS Versus Alternative Treatments

Significant Improvement in Rescue-free Days*

*p<0.05 for all studies

Each bar represents an individual treatment comparison within a study

- Salmeterol + ICS vs. same dose ICS
- Salmeterol + ICS vs. higher dose ICS
- Salmeterol + ICS vs. FP + theophylline
- Salmeterol + ICS vs. FP + montelukast
## Salmeterol plus ICS Compared with ICS

**Significant Reduction in Risk of Exacerbations Requiring Oral Corticosteroids**

<table>
<thead>
<tr>
<th>Study</th>
<th>Salmeterol + ICS (n)</th>
<th>ICS (n)</th>
<th>Peto Odds Ratio (95% CI)</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearlman</td>
<td>1 46</td>
<td>0 46</td>
<td>0.65 (0.54, 0.79)</td>
<td>-250 per 10,000 patients (-360, -140)</td>
</tr>
<tr>
<td>Baraniuk</td>
<td>7 118</td>
<td>23 232</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baraniuk</td>
<td>4 113</td>
<td>29 217</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLGA5021</td>
<td>20 246</td>
<td>32 243</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condeemi</td>
<td>21 221</td>
<td>31 216</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelsen</td>
<td>26 239</td>
<td>40 244</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray</td>
<td>29 260</td>
<td>35 254</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAS40024</td>
<td>0 99</td>
<td>2 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFA100314</td>
<td>1 124</td>
<td>1 124</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFA100316</td>
<td>2 113</td>
<td>1 118</td>
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<td></td>
</tr>
<tr>
<td>Weiler</td>
<td>1 102</td>
<td>0 90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kavuru</td>
<td>0 92</td>
<td>0 90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray</td>
<td>1 88</td>
<td>0 89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson</td>
<td>2 95</td>
<td>0 97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearlman</td>
<td>0 92</td>
<td>1 89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malone</td>
<td>2 101</td>
<td>3 102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shapiro</td>
<td>1 84</td>
<td>2 84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nathan</td>
<td>1 94</td>
<td>3 91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koenig</td>
<td>2 172</td>
<td>7 159</td>
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</tr>
<tr>
<td>SAS40037</td>
<td>3 161</td>
<td>6 161</td>
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<tr>
<td>Jarjour</td>
<td>5 295</td>
<td>8 279</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busse</td>
<td>6 281</td>
<td>3 277</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAM40065</td>
<td>20 150</td>
<td>49 299</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koenig</td>
<td>20 155</td>
<td>58 307</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td><strong>175 3,541</strong></td>
<td><strong>334 4,008</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Salmeterol plus ICS in Children Aged 4-11 Years

Improvement in Lung Function Compared to Higher Dose ICS*

GSK Study: SAM104926

*p=0.012 over weeks 1-12
### Exacerbations* in Pediatric Studies

**Consistent Benefit with ADVAIR versus Same or Higher Dose ICS**

<table>
<thead>
<tr>
<th>Study Code</th>
<th>Total N</th>
<th>ADVAIR 100/50 BID</th>
<th>FP 100 BID</th>
<th>FP 200 BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFA100314</td>
<td>248</td>
<td>1.6</td>
<td>2.4</td>
<td>-</td>
</tr>
<tr>
<td>SFA100316</td>
<td>231</td>
<td>1.8</td>
<td>0.8</td>
<td>-</td>
</tr>
<tr>
<td>SAS30031</td>
<td>203</td>
<td>3.0</td>
<td>7.8</td>
<td>-</td>
</tr>
<tr>
<td>SFA106484</td>
<td>350</td>
<td>0.6</td>
<td>1.7</td>
<td>-</td>
</tr>
<tr>
<td>SAM40012</td>
<td>531</td>
<td>5.7</td>
<td>12.0</td>
<td>11.7</td>
</tr>
<tr>
<td>SAM102318</td>
<td>281</td>
<td>2.2</td>
<td>-</td>
<td>4.1</td>
</tr>
<tr>
<td>SAM104926</td>
<td>303</td>
<td>1.3</td>
<td>-</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td><strong>2147</strong></td>
<td><strong>2.4</strong></td>
<td><strong>5.2</strong></td>
<td><strong>6.1</strong></td>
</tr>
</tbody>
</table>

*Exacerbation defined as asthma that required medication beyond study drug or albuterol, ER visit, hospitalization, and/or treatment with oral or parenteral corticosteroids.
ADVAIR and SEREVENT plus ICS
Established Efficacy in Adults and Children

- Improved Asthma Control
  - Improvement in lung function
  - Reduction in need for rescue medications to treat asthma symptoms
  - Prevention of serious exacerbations

Preferred treatment option in evidence-based asthma treatment guidelines
Presentation Outline

• Efficacy of salmeterol-containing products in persistent asthma

• Safety Review
  • Methods
  • Safety Data with SEREVENT
  • Safety Data with ADVAIR

• Recommendations
Change in Salmeterol Use for Asthma Over Time

*US Data from a Large Health Insurer*

- ADVAIR 97%
- SEREVENT + ICS 1%
- SEREVENT + Non-ICS 1%
- SEREVENT only 1%
- SEREVENT + ICS only 1%
- SEREVENT + Non-ICS only 33%
- SEREVENT only 31%
- ADVAIR 0%

1994 - 1996

2005 - 2007

GSK Study: WEUSRTP3275
Overview of Safety Data for Salmeterol

Adults and Children

- All GSK-sponsored clinical studies of salmeterol
  - Randomized, controlled, double-blind, chronic dosing

- Outcomes of interest:
  - Asthma-related hospitalization
  - Asthma-related death
  - Asthma-related intubation
  - All-cause death

- Outcomes adjudicated by independent external physicians
Analysis Populations Evaluating Safety

Salmeterol vs. non-LABA
215 studies (N=106,575)

Serevent vs. Placebo (no ICS)
Serevent+ICS(BK) vs. ICS(BK)
Serevent+ICS(SI) vs. ICS(SD)
Advair vs. ICS(SD)

BK=background
SI=separate inhalers
SD=study drug

Increasing Confidence in Adherence to ICS
Presentation Outline

• Efficacy of salmeterol-containing products in persistent asthma

• Safety Review
  • Methods
  • Safety Data with SEREVENT
  • Safety Data with ADVAIR

• Recommendations
# Risk of Asthma-related Death for SEREVENT

## Risk Difference in Overall Population

<table>
<thead>
<tr>
<th>Comparison</th>
<th>n</th>
<th>N</th>
<th>Comparator n</th>
<th>N</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol vs Non-LABA</td>
<td>28</td>
<td>57,607</td>
<td>7</td>
<td>48,968</td>
<td>3.25 per 10,000 pts (-2.83, 9.33)</td>
</tr>
<tr>
<td>SEREVENT vs Placebo (no ICS)</td>
<td>8</td>
<td>9,463</td>
<td>0</td>
<td>8,932</td>
<td>8.79 per 10,000 pts (-8.23, 25.80)</td>
</tr>
<tr>
<td>SEREVENT +ICS&lt;sub&gt;BK&lt;/sub&gt; vs ICS&lt;sub&gt;BK&lt;/sub&gt;</td>
<td>5</td>
<td>10,264</td>
<td>3</td>
<td>10,135</td>
<td>2.03 per 10,000 pts (-12.17, 16.22)</td>
</tr>
<tr>
<td>SEREVENT +ICS&lt;sub&gt;SI&lt;/sub&gt; vs ICS&lt;sub&gt;SD&lt;/sub&gt;</td>
<td>1</td>
<td>2,841</td>
<td>0</td>
<td>3,040</td>
<td>4.64 per 10,000 pts (-28.77, 38.04)</td>
</tr>
<tr>
<td>ADVAIR vs ICS&lt;sub&gt;SD&lt;/sub&gt;</td>
<td>0</td>
<td>11,437</td>
<td>0</td>
<td>11,163</td>
<td>0 per 10,000 pts (Not estimated)</td>
</tr>
</tbody>
</table>

**Note:**
- BK = background
- SI = separate inhalers
- SD = study drug

---

**Risk Difference per 10,000 patients**

-30 -20 -10 0 10 20 30
Risk of Asthma-related Hospitalization for SEREVENT

Risk Difference in Overall Population

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Salmeterol product n</th>
<th>N</th>
<th>Comparator n</th>
<th>N</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol vs Non-LABA</td>
<td>655 57,607</td>
<td>448 48,968</td>
<td></td>
<td></td>
<td>17.88 per 10,000 pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4.50, 31.26)</td>
</tr>
<tr>
<td>SEREVENT vs Placebo (no ICS)</td>
<td>87 9,463</td>
<td>59 8,932</td>
<td></td>
<td></td>
<td>26.99 per 10,000 pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(-2.43, 56.40)</td>
</tr>
<tr>
<td>SEREVENT +ICS_BK vs ICS_BK</td>
<td>198 10,264</td>
<td>151 10,135</td>
<td></td>
<td></td>
<td>46.02 per 10,000 pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(8.10, 83.93)</td>
</tr>
<tr>
<td>SEREVENT +ICS_Si vs ICS_SD</td>
<td>16 2,841</td>
<td>14 3,040</td>
<td></td>
<td></td>
<td>14.48 per 10,000 pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(-30.83, 59.79)</td>
</tr>
<tr>
<td>ADVAIR vs ICS_SD</td>
<td>31 11,437</td>
<td>29 11,163</td>
<td></td>
<td></td>
<td>0.28 per 10,000 pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(-18.51, 19.06)</td>
</tr>
</tbody>
</table>

BK=background
SI=separate inhalers
SD=study drug
### Risk of Asthma-related Hospitalization for SEREVENT

#### Risk Difference in Overall Population

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Number of Patients</th>
<th>Total Exposure Years</th>
<th>Deaths</th>
<th>Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS (background)</td>
<td>10135</td>
<td>4168</td>
<td>7</td>
<td>362</td>
</tr>
<tr>
<td>ICS (study drug)</td>
<td>14651</td>
<td>6387</td>
<td>0</td>
<td>72</td>
</tr>
</tbody>
</table>

**Adapted from Table 2**

- **Salmeterol**
  - 26.99 per 10,000 pts (4.50, 56.40)
  - 87 patients in 9,463 total

- **SEREVENT vs Placebo (no ICS)**
  - 46.02 per 10,000 pts (8.10, 83.93)
  - 198 patients in 10,264 total

- **SEREVENT + ICS vs ICS (study drug)**
  - 14.48 per 10,000 pts (-30.83, 59.79)
  - 16 patients in 2,841 total

- **ADVAIR vs ICS (study drug)**
  - 0.28 per 10,000 pts (-18.51, 19.06)
  - 31 patients in 11,437 total

- **Salmeterol vs Non-LABA**
  - 17.88 per 10,000 pts (4.50, 31.26)
  - 655 patients in 57,607 total

**BK=background**
**SI=separate inhalers**
**SD=study drug**
Risk of Asthma-related Hospitalization for SEREVENT

Risk Difference in Overall Population

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Salmeterol product</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salmeterol vs Non-LABA</strong></td>
<td>n: 655, N: 57,607</td>
<td>n: 448, N: 48,968</td>
</tr>
<tr>
<td>SEREVENT vs Placebo (no ICS)</td>
<td>n: 87, N: 9,463</td>
<td>n: 59, N: 8,932</td>
</tr>
<tr>
<td>SEREVENT +ICS_{BK} vs ICS_{BK}</td>
<td>n: 198, N: 10,264</td>
<td>n: 151, N: 10,135</td>
</tr>
<tr>
<td>SEREVENT +ICS_{SI} vs ICS_{SD}</td>
<td>n: 16, N: 2,841</td>
<td>n: 14, N: 3,040</td>
</tr>
<tr>
<td>ADVAIR vs ICS_{SD}</td>
<td>n: 31, N: 11,437</td>
<td>n: 29, N: 11,163</td>
</tr>
</tbody>
</table>

- **Risk Difference per 10,000 patients**
  - Salmeterol vs Non-LABA: 17.88 per 10,000 pts (4.50, 31.26)
  - SEREVENT vs Placebo: 26.99 per 10,000 pts (-2.43, 56.40)
  - SEREVENT +ICS_{BK} vs ICS_{BK}: 46.02 per 10,000 pts (8.10, 83.93)
  - SEREVENT +ICS_{SI} vs ICS_{SD}: 14.48 per 10,000 pts (-30.83, 59.79)
  - ADVAIR vs ICS_{SD}: 0.28 per 10,000 pts (-18.51, 19.06)

**Legend**
- BK=background
- SI=separate inhalers
- SD=study drug
Presentation Outline

- Efficacy of salmeterol-containing products in persistent asthma
- Safety Review
  - Methods
  - Safety Data with SEREVENT
    - Pediatrics
  - Safety Data with ADVAIR
- Recommendations
Risk of Serious Outcomes with SEREVENT

Pediatric Population

• 37 pediatric studies in 7448 patients
• Asthma-related deaths
  • 1 death in a child receiving QID albuterol
• Asthma-related intubations
  • 1 intubation in a child receiving QID albuterol
  • 1 intubation in a child receiving SEREVENT
• All outcomes occurred in children not receiving ICS
## Risk of Asthma-related Hospitalization with SEREVENT

### Pediatric Population

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Salmeterol</th>
<th>Comparator</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEREVENT vs Non-LABA</td>
<td>103 3,703</td>
<td>68 3,745</td>
<td>50.23 per 10,000 pts (-24.24, 124.71)</td>
</tr>
<tr>
<td>SEREVENT vs Placebo (no ICS)</td>
<td>9 623</td>
<td>2 415</td>
<td>146.10 per 10,000 pts (-36.97, 329.16)</td>
</tr>
<tr>
<td>SEREVENT +ICS_BK vs ICS_BK</td>
<td>37 602</td>
<td>22 463</td>
<td>266.69 per 10,000 pts (-39.68, 573.06)</td>
</tr>
<tr>
<td>SEREVENT +ICS_SI vs ICS_SD</td>
<td>1 60</td>
<td>2 116</td>
<td>-5.75 per 10,000 pts (-407.05, 395.55)</td>
</tr>
<tr>
<td>ADVAIR vs ICS_SD</td>
<td>1 1,138</td>
<td>2 1,340</td>
<td>-5.39 per 10,000 pts (-60.34, 49.57)</td>
</tr>
</tbody>
</table>

**Legend:**
- **BK** = background
- **SI** = separate inhalers
- **SD** = study drug

**Note:** Risk Difference per 10,000 patients.
Positive Benefit to Risk Profile
SEREVENT plus ICS

**Benefit**
- SEREVENT + ICS is highly effective
  - Improvement in lung function
  - Decreased symptoms
  - Decrease in exacerbations
- Fixed dose combination may not meet patient needs
  - Different ICS
  - Different dose of ICS
  - Frequent titration

**Risk**
- Increased risk seen when ICS use was not controlled
- No safety signal when used concurrently with ICS

Proposed labeling now requires that SEREVENT should only be used concurrently with ICS
Presentation Outline

• Efficacy of salmeterol-containing products in persistent asthma

• Safety Review
  • Methods
  • Safety Data with SEREVENT
  • Safety Data with ADVAIR

• Recommendations
### Asthma-related Death and Hospitalization with ADVAIR

**Overall Population**

<table>
<thead>
<tr>
<th></th>
<th>ADVAIR</th>
<th>ICS</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>11,437</td>
<td>11,163</td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0 per 10,000 pts (Not estimated)</td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td>31</td>
<td>29</td>
<td>0.28 per 10,000 pts (-18.51, 19.06)</td>
</tr>
<tr>
<td></td>
<td>11,437</td>
<td>11,163</td>
<td></td>
</tr>
</tbody>
</table>

**Risk Difference per 10,000 patients**

- Favors ADVAIR
- Favors ICS

A-43
## Asthma-related Death and Hospitalization with ADVAIR
### Pediatric Population

### Risk Difference

<table>
<thead>
<tr>
<th>Event</th>
<th>ADVAIR</th>
<th>ICS</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0 1,138</td>
<td>0 1,340</td>
<td>0 per 10,000 pts (Not estimated)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1 1,138</td>
<td>2 1,340</td>
<td>-5.39 per 10,000 pts (-60.34, 49.57)</td>
</tr>
</tbody>
</table>
Presentation Outline

• Efficacy of salmeterol-containing products in persistent asthma

• Safety Review
  • Methods
  • Safety Data with SEREVENT
  • Safety Data with ADVAIR
    • Outcomes in African Americans

• Recommendations
# Asthma-related Exacerbation and Hospitalization with ADVAIR

## African American Population

<table>
<thead>
<tr>
<th></th>
<th>SFA103153*</th>
<th>ADVAIR 100/50 BID (n=239)</th>
<th>FP 100 BID (n=236)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbation rate per year</td>
<td>0.45</td>
<td>0.53</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th>GSK Database</th>
<th>ADVAIR (n=724)</th>
<th>ICS (n=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma-related Hospitalizations †</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

†All studies in African Americans receiving ADVAIR and ICS
Efficacy of salmeterol-containing products in persistent asthma

Safety Review
  - Methods
  - Safety Data with SEREVENT
  - Safety Data with ADVAIR
    - Observational studies

Recommendations
# Reduction in Risk of ED and Hospitalizations with ADVAIR in Adults

**Observational Studies**

<table>
<thead>
<tr>
<th></th>
<th>ADVAIR</th>
<th>ICS alone</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ED Visits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colice et al</td>
<td>25</td>
<td>26</td>
<td>0.84 (0.76, 0.94)</td>
</tr>
<tr>
<td>Friedman &amp; Yawn</td>
<td>18</td>
<td>24</td>
<td>0.85 (0.74, 0.97)</td>
</tr>
<tr>
<td>ADA108941</td>
<td>2,786</td>
<td>1,375</td>
<td>0.85 (0.74, 0.97)</td>
</tr>
<tr>
<td>Stanford et al</td>
<td>1,354</td>
<td>643</td>
<td>0.85 (0.74, 0.97)</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td>4,183</td>
<td>2,068</td>
<td>0.84 (0.76, 0.94)</td>
</tr>
</tbody>
</table>

|                |        |           |                     |
| **Hospitalizations** | |           |                     |
| Colice et al   | 5      | 5         | 0.84 (0.76, 0.94)   |
| Friedman & Yawn| 20     | 18        | 0.85 (0.74, 0.97)   |
| ADA108941      | 389    | 183       | 0.85 (0.74, 0.97)   |
| Stanford et al | 205    | 102       | 0.85 (0.74, 0.97)   |
| **Combined**   | 619    | 308       | 0.85 (0.74, 0.97)   |
Reduction in Risk of ED/Hospitalizations with ADVAIR in Pediatrics

Observational Studies

<table>
<thead>
<tr>
<th>ED Visits &amp; Hospitalizations</th>
<th>ADVAIR n</th>
<th>N</th>
<th>ICS alone n</th>
<th>N</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA108941</td>
<td>1,638</td>
<td>13,950</td>
<td>2,947</td>
<td>19,799</td>
<td>0.91 (0.86, 0.97)</td>
</tr>
<tr>
<td>GHO101587</td>
<td>15</td>
<td>226</td>
<td>359</td>
<td>2,976</td>
<td>0.46 (0.27, 0.76)</td>
</tr>
<tr>
<td>RES41189</td>
<td>81</td>
<td>1,168</td>
<td>183</td>
<td>2,473</td>
<td></td>
</tr>
<tr>
<td>GHO101577</td>
<td>14</td>
<td>599</td>
<td>97</td>
<td>2,455</td>
<td></td>
</tr>
<tr>
<td>ADA104601</td>
<td>11</td>
<td>239</td>
<td>50</td>
<td>831</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>1,759</td>
<td>16,182</td>
<td>3,636</td>
<td>28,534</td>
<td></td>
</tr>
</tbody>
</table>

Reduction in Risk of ED/Hospitalizations with ADVAIR in Pediatrics

Odds Ratio

ADVAIR ICS + MON

Combined

Odds Ratio

0.91 (0.86, 0.97)

0.46 (0.27, 0.76)
Positive Benefit to Risk Profile for ADVAIR
Adults and Children

**Benefit**
- ADVAIR is highly effective for the treatment of asthma
  - Improvement in lung function
  - Decreased symptoms
  - Decrease in exacerbations
- Decreased risk for ED visits and hospitalizations in observational studies
- Ensures concurrent ICS use

**Risk**
- No asthma-related deaths reported
- No increased risk in asthma-related hospitalizations
- No asthma-related intubations reported
- No increased risk in all-cause death
Overall Assessment
ADVAIR and SEREVENT plus ICS

• ADVAIR
  • Positive benefit to risk

• SEREVENT
  • Inappropriate to use alone
  • Positive benefit to risk when used concurrently with ICS

SEREVENT when used with an ICS remains an important treatment option for some patients
Recommendations

C. Elaine Jones, PhD
Vice President
Respiratory Regulatory Affairs
GlaxoSmithKline
SEREVENT DISKUS
Proposed Labeling Supplement: September 2008

- Revised indication for asthma in patients 4 years of age and older
  - Only as concomitant therapy with an ICS

- Boxed Warning
  - Addition of asthma-related hospitalizations

- Medication Guide
  - Must be used with an inhaled corticosteroid
  - Instructions not to stop or reduce the dose of ICS even if they feel better
Further Risk Management Actions

• Healthcare Practitioner Initiatives
  • Labeling Change
  • Targeted Education
    • Dear HCP Letter
    • Educational Programs for Healthcare Practitioners

• Managed Care / Pharmacy Initiatives
  • Update formulary algorithms
  • Update pharmacy computer systems
  • Inform physicians

• Patient Focused Initiatives
  • Medication Guide Change
  • Packaging Change
ADVAIR and SEREVENT plus ICS in Asthma Management

Overall Summary

• ADVAIR and SEREVENT + ICS have significantly advanced the care of patients with asthma

• Preferred treatment options in evidence based asthma guidelines

It is critical that these medications remain available to maintain the high standard of asthma care
Table 2: Patient-Years of Exposure and Asthma-Related Death and Hospitalization in all GSK Studies (US and Non-US)

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Number of Studies</th>
<th>Number of Subjects</th>
<th>Total Exposure Years</th>
<th>Asthma-Related Deaths per 10,000 Pt-Yrs</th>
<th>Subjects with an Asthma-Related Hospitalization per 10,000 Pt-Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol-containing product</td>
<td>263</td>
<td>67219</td>
<td>23486</td>
<td>14</td>
<td>321</td>
</tr>
<tr>
<td>Non-LABA</td>
<td>231</td>
<td>48968</td>
<td>18433</td>
<td>4</td>
<td>246</td>
</tr>
<tr>
<td>Sal (without ICS)</td>
<td>80</td>
<td>11342</td>
<td>4352</td>
<td>25</td>
<td>239</td>
</tr>
<tr>
<td>Pla (without ICS)</td>
<td>62</td>
<td>9935</td>
<td>4104</td>
<td>2</td>
<td>175</td>
</tr>
<tr>
<td>ICS&lt;sub&gt;BK&lt;/sub&gt;</td>
<td>44</td>
<td>10135</td>
<td>4168</td>
<td>7</td>
<td>362</td>
</tr>
<tr>
<td>ICS&lt;sub&gt;SD&lt;/sub&gt;</td>
<td>96</td>
<td>14651</td>
<td>6387</td>
<td>0</td>
<td>72</td>
</tr>
<tr>
<td>Sal + ICS&lt;sub&gt;BK&lt;/sub&gt;</td>
<td>51</td>
<td>12881</td>
<td>5059</td>
<td>12</td>
<td>484</td>
</tr>
<tr>
<td>Sal + ICS&lt;sub&gt;SD&lt;/sub&gt;</td>
<td>109</td>
<td>21695</td>
<td>8056</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td>Sal + ICS&lt;sub&gt;Si&lt;/sub&gt;</td>
<td>27</td>
<td>3804</td>
<td>1486</td>
<td>7</td>
<td>155</td>
</tr>
<tr>
<td>ADVAIR</td>
<td>86</td>
<td>17891</td>
<td>6571</td>
<td>0</td>
<td>65</td>
</tr>
</tbody>
</table>

SMART Sub-Groups (numbers included in categories above)

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Number of Studies</th>
<th>Number of Subjects</th>
<th>Total Exposure Years</th>
<th>Asthma-Related Deaths per 10,000 Pt-Yrs</th>
<th>Subjects with an Asthma-Related Hospitalization per 10,000 Pt-Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sal (without ICS)</td>
<td>1</td>
<td>6513</td>
<td>2993</td>
<td>27</td>
<td>184</td>
</tr>
<tr>
<td>Pla (without ICS)</td>
<td>1</td>
<td>6463</td>
<td>2930</td>
<td>0</td>
<td>140</td>
</tr>
<tr>
<td>Pla + ICS&lt;sub&gt;BK&lt;/sub&gt;</td>
<td>1</td>
<td>6716</td>
<td>3156</td>
<td>10</td>
<td>355</td>
</tr>
<tr>
<td>Sal + ICS&lt;sub&gt;BK&lt;/sub&gt;</td>
<td>1</td>
<td>6663</td>
<td>3194</td>
<td>16</td>
<td>379</td>
</tr>
</tbody>
</table>

Note: Some studies contain more than one treatment comparison
## Background Use of ICS in Clinical Studies

**Patient-Years of Exposure and Asthma-Related Deaths and Hospitalizations in all GSK Studies**

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Number of Studies</th>
<th>Number of Patients</th>
<th>Total Exposure Years</th>
<th>Asthma-Related Deaths per 10,000 Pt-Yrs</th>
<th>Pts with an Asthma-Related Hosp per 10,000 Pt-Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (without ICS)</td>
<td>62</td>
<td>9935</td>
<td>4104</td>
<td>2</td>
<td>175</td>
</tr>
<tr>
<td>ICS (background)</td>
<td>44</td>
<td>10135</td>
<td>4168</td>
<td>7</td>
<td>362</td>
</tr>
<tr>
<td>ICS (study drug)</td>
<td>96</td>
<td>14651</td>
<td>6387</td>
<td>0</td>
<td>72</td>
</tr>
</tbody>
</table>