

# **Pediatric Adverse Event Review: Salmeterol**

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**A 1**

## **Salmeterol**

- **Best Pharmaceuticals for Children Act**
  - Emphasis on salmeterol safety
- **Efficacy demonstrated**
  - Lung function
  - Symptom control
  - Reduction in rescue bronchodilator use

**A 2**

## Burden of Asthma in the US

- **Affects an estimated 21 million Americans**
  - Approximately 6 million children <18 years old
- **Significant morbidity**
  - Approximately 200,000 hospitalizations annually
  - Approximately 13 million missed school days annually

Moorman et al. *MMWR* 2007;56(8):1-54.  
 Kozak et al. *Vital Health Stat* 13(162). 2006.  
 Bener et al. *J Asthma* 2007;44(4):249-52.  
 Akinbami LJ. *The State of Childhood Asthma*, United States, 1980-2005. Advance Data from Vital and Health Statistics: no 381, Revised December 29, 2006. Hyattsville, MD: National Center for Health Statistics, 2006.

**A 3**

## Salmeterol-Containing Products

	SEREVENT® Inhalation Aerosol	SEREVENT® DISKUS®	ADVAIR DISKUS®	ADVAIR® HFA
<b>Asthma ≥12 years</b>	X	X	X	X
<b>Asthma 4-11 years</b>		X	X	
<b>Exercise Induced Bronchospasm</b>	X	X		

- **SEREVENT DISKUS** - approved for use in children if they are symptomatic on another asthma controller medication, such as inhaled corticosteroids
- **ADVAIR DISKUS** - approved for children aged 4-11 years symptomatic on inhaled corticosteroids

**A 4**

## **Salmeterol Pediatric Exclusivity**

- **Written Request for Pediatric Studies issued for SEREVENT Inhalation Aerosol**
- **Pediatric Exclusivity Supplement filed December 2005**
  - **Two Dose Ranging Safety Studies**
  - **Two Safety and Efficacy Studies**
- **Exclusivity granted March 9, 2006**
  - **Results from these studies in children less than 4 years of age have not been incorporated into labeling**

**A 5**

## **Salmeterol for the Treatment of Pediatric Asthma**

- **Significant experience in children**
- **Guidelines support use of salmeterol with ICS in children**
- **Regular review of data ensures that product labels are updated**
- **Approved labeling reflects safety profile of the product in the pediatric population**

National Institutes of Health. The NAEPP Expert Panel Report 3 (EPR-3) Summary Report 2007: October 2007; NIH Publication No. 08-5846.  
Global Initiative for Asthma. Revised 2006; Available at: [www.ginasthma.org](http://www.ginasthma.org)

**A 6**

# **Salmeterol Review**

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**A 7**

# **Review of Spontaneous Adverse Event Reports**

**A 8**

## **Summary of Spontaneously Reported Adverse Events**

- Spontaneous reports increase with increasing exposure, as expected
- Grant of pediatric exclusivity did not result in change in pattern of spontaneously reported adverse events
- Reported cases of fatal events generally included patients with a history of severe or unstable asthma and non-compliance

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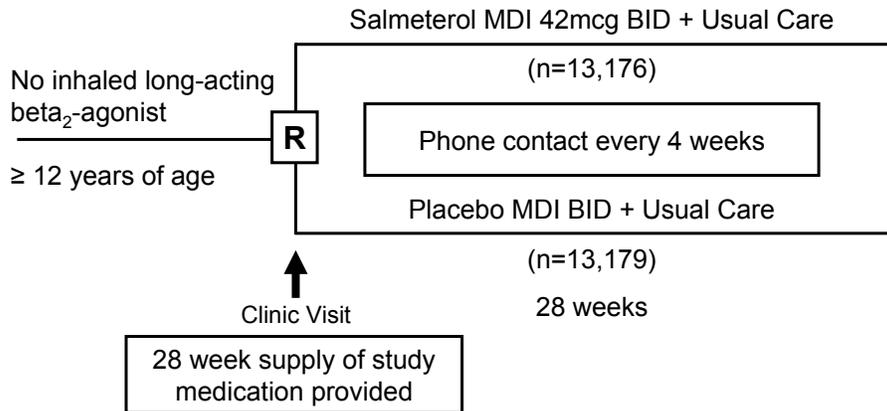
## **SMART**

### **Salmeterol Multicenter Asthma Research Trial**

A 10

# SMART

## Salmeterol Multicenter Asthma Research Trial



Nelson et al. *Chest* 2006;129:15-26.

A 11

## SMART Results in the Total Population

	≥12 Years (N=26,335)		
	Salmeterol (n=13,176)	Placebo (n=13,179)	RR (95% CI)
<b>Primary Endpoint</b>			
Combined respiratory related death or life-threatening experience, n (%)	50 (<1)	36 (<1)	1.40 (0.91, 2.14)
<b>Secondary Endpoint</b>			
Respiratory-related death, n (%)	24 (<1)	11 (<1)	2.16 (1.06, 4.41)
Combined asthma-related death or life-threatening experience, n (%)	37 (<1)	22 (<1)	1.71 (1.01, 2.89)
Asthma-related death, n (%)	13 (<1)	3 (<1)	4.37 (1.25, 15.34)
All-cause hospitalization, n (%)	469 (4)	420 (3)	1.11 (0.98, 1.26)

Nelson et al. *Chest* 2006;129:15-26.

A 12

## **Labeling Revisions Resulting from SMART**

- **Incorporated SMART results into labeling**
  - Information regarding use of concurrent ICS and the risk of serious events
- **Pulmonary and Allergy Advisory Committee review**
  - Supported the use of long-acting beta-agonist
  - Addition of Medication Guide
  - Additional labeling revisions

**A 13**

## **Asthma Indication SEREVENT**

Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death (see WARNINGS).

Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS.

It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting beta<sub>2</sub>-agonists or for patients whose asthma can be successfully managed by inhaled corticosteroids or other controller medications along with occasional use of inhaled, short-acting beta<sub>2</sub>-agonists.

**A 14**

## SEREVENT DISKUS – Warning

- Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide in patients receiving SEREVENT
  - In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations)
  - In some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting beta<sub>2</sub>-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function)
  - However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT contributed to these events

A 15

### Results in the Pediatric Population SMART *Post-hoc* Analysis

	Total Population (≥12 Years) (N=26,335)		12-18 Year-Olds (N= 3,275)	
	Salmeterol (n=13,176)	Placebo (n=13,179)	Salmeterol (n=1,653)	Placebo (n=1,622)
<b>Primary Endpoint</b>				
Combined respiratory related death or life-threatening experience, n (%)	50 (<1)	36 (<1)	2 (<1)	2 (<1)
<b>Secondary Endpoint</b>				
Respiratory-related death, n (%)	24 (<1)	11 (<1)	1 (<1)	0
Combined asthma-related death or life-threatening experience, n (%)	37 (<1)	22 (<1)	2 (<1)	2 (<1)
Asthma-related death, n (%)	13 (<1)	3 (<1)	1 (<1)	0
All-cause hospitalization, n (%)	469 (4)	420 (3)	35 (2)	16 (<1)

A 16

## Hospitalizations in Pediatric Population SMART *Post-hoc* Analysis

	Salmeterol (n=1653)	Placebo (n=1622)	RR (95% CI)
All Cause Hospitalization, n (%)	35 (2)	16 (<1)	2.07 (1.15, 3.72)
Respiratory-related Hospitalization, n (%)	18 (1)	9 (<1)	1.90 (0.86, 4.21)
Asthma-related Hospitalization, n (%)	13 (<1)	9 (<1)	1.37 (0.59, 3.19)
Other Respiratory-related* Hospitalization, n (%)	5 (<1)	0	N/A
Non-Respiratory-related Hospitalization, n (%)	17 (1)	7 (<1)	2.29 (0.95, 5.51)

\*Pneumonia, pharyngitis, and viral infection

**A 17**

## Non-respiratory Hospitalizations in Pediatric Patients Treated with Salmeterol

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• Depression               <ul style="list-style-type: none"> <li>– 3 cases</li> </ul> </li> <li>• Vomiting               <ul style="list-style-type: none"> <li>– 2 cases</li> </ul> </li> <li>• Cellulitis</li> <li>• Aspirin overdose</li> <li>• Hydrocephaly</li> <li>• Severe tic and dyslexia</li> <li>• Appendicitis</li> </ul> | <ul style="list-style-type: none"> <li>• Miscarriage</li> <li>• Dehydration</li> <li>• Broken leg</li> <li>• Loss of consciousness</li> <li>• Auto accident</li> <li>• Ovarian cyst</li> <li>• Pyelonephritis</li> <li>• Nasopharyngeal cancer</li> </ul> |
|---|---|

**A 18**

# SMART Summary

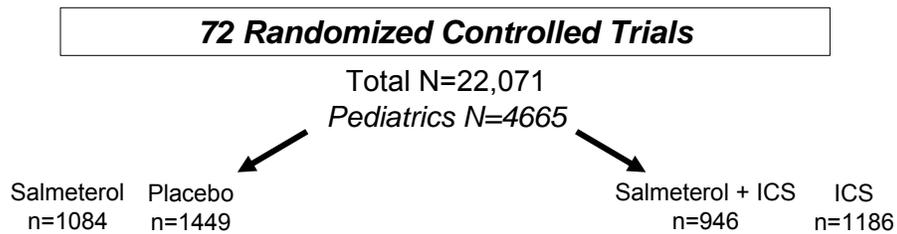
- **Total population**
  - Greater incidence of respiratory- and asthma-related events and all-cause hospitalization for salmeterol versus placebo
- **Pediatric Population**
  - Similar incidence of respiratory- and asthma-related events for salmeterol versus placebo
  - Statistically significantly greater incidence of all-cause hospitalization for salmeterol versus placebo
    - No statistically significant differences in respiratory- and asthma-related hospitalizations or in non-respiratory events leading to hospitalization
- **Warnings and Medication Guide apply to all ages**

A 19

# Retrospective Pooled Analysis of US Clinical Trials

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## Studies and Subjects Contributing to Pooled Analysis



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## Fatal Outcomes

- There were no deaths in patients 0-18 years of age
- Five deaths occurred in subjects  $\geq 19$  years
  - Two asthma-related deaths

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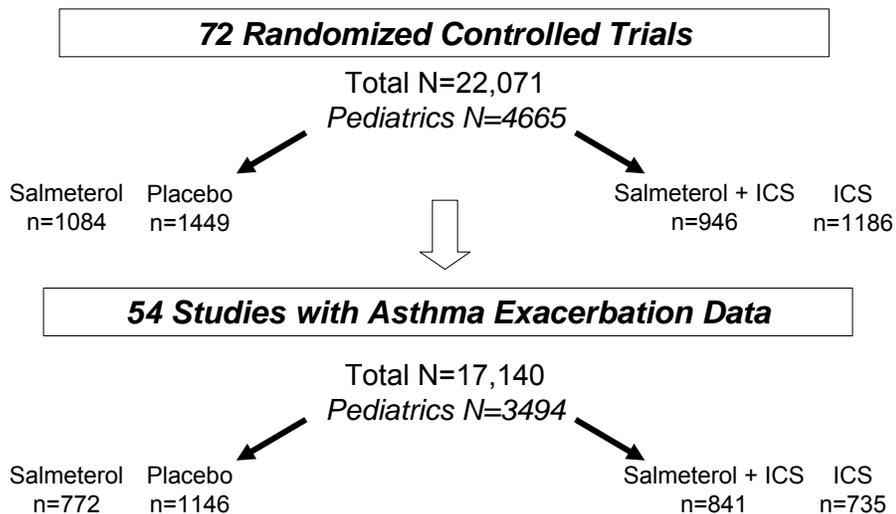
## Serious Adverse Events: Cardiovascular and Respiratory

0 – 18 Years	Salmeterol (n=1084)	Placebo (n=1449)	Salmeterol + ICS (n=946)	ICS (n=1186)
Cardiovascular n (%)	0	0	0	0
Respiratory n (%)	19 (2)	11 (<1)	1 (<1)	4 (<1)

≥19 Years	Salmeterol (n=4486)	Placebo (n=3162)	Salmeterol + ICS (n=5320)	ICS (n=4434)
Cardiovascular n (%)	9 (<1)	7 (<1)	19 (<1)	16 (<1)
Respiratory n (%)	54 (1)	17 (<1)	13 (<1)	22 (<1)

**A 23**

## Studies and Subjects Contributing to Pooled Analysis



**A 24**

## Asthma-related Exacerbations and Hospitalizations

<b>0 – 18 Years</b>	<b>Salmeterol (n=772)</b>	<b>Placebo (n=1146)</b>	<b>Salmeterol + ICS (n=841)</b>	<b>ICS (n=735)</b>
Subjects with an Exacerbation n (%)	165 (21)	264 (23)	42 (5)	72 (10)
No. of Exacerbations	234	384	53	87
Asthma-related Hospitalizations n (%)*	8 (3)	5 (1)	1 (2)	2 (2)

<b>≥19 Years</b>	<b>Salmeterol (n=3444)</b>	<b>Placebo (n=2475)</b>	<b>Salmeterol + ICS (n=4342)</b>	<b>ICS (n=3386)</b>
Subjects with an Exacerbation n (%)	498 (15)	611 (25)	248 (6)	416 (12)
No. of Exacerbations	643	964	306	516
Asthma-related Hospitalizations n (%)*	31 (5)	13 (1)	6 (2)	10 (2)

\*Hospitalizations / # exacerbations

**A 25**

## Summary of Retrospective Pooled Analysis

### In children:

- **Safety profile similar for children and adults**
  - No fatalities
  - No cardiovascular serious adverse events
  - Low incidence of respiratory serious adverse events
  - Asthma exacerbations or hospitalizations were lowest when salmeterol was used with an inhaled corticosteroid

**A 26**

## **Other Sources Evaluating Asthma-related Hospitalizations**

- **No increased risk of asthma-related hospitalizations comparing salmeterol + ICS vs. ICS alone**
  - Large observational studies in over 300,000 children do not suggest increased risk in clinical practice
  - Meta-analysis of GSK trials in over 20,000 patients does not suggest increased risk
    - Including 1,254 children

A 27

## **Overall Summary**

- **SEREVENT and ADVAIR exhibit a favorable safety profile**
- **Review of pediatric safety, conducted to meet regulatory requirements, further confirms this favorable safety profile**
- **Current product labels for SEREVENT and ADVAIR define the population who may benefit from use**
- **Current product labels appropriately inform on the safe and effective use of SEREVENT and ADVAIR in children**

A 28