

# Overview of Asthma and Guidelines for the Diagnosis and Management of Asthma

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# Asthma Remains a Serious Health Risk

*EVERY DAY in America approximately ...*



**63,000** people miss school or work due to asthma

**34,000** people have an asthma attack

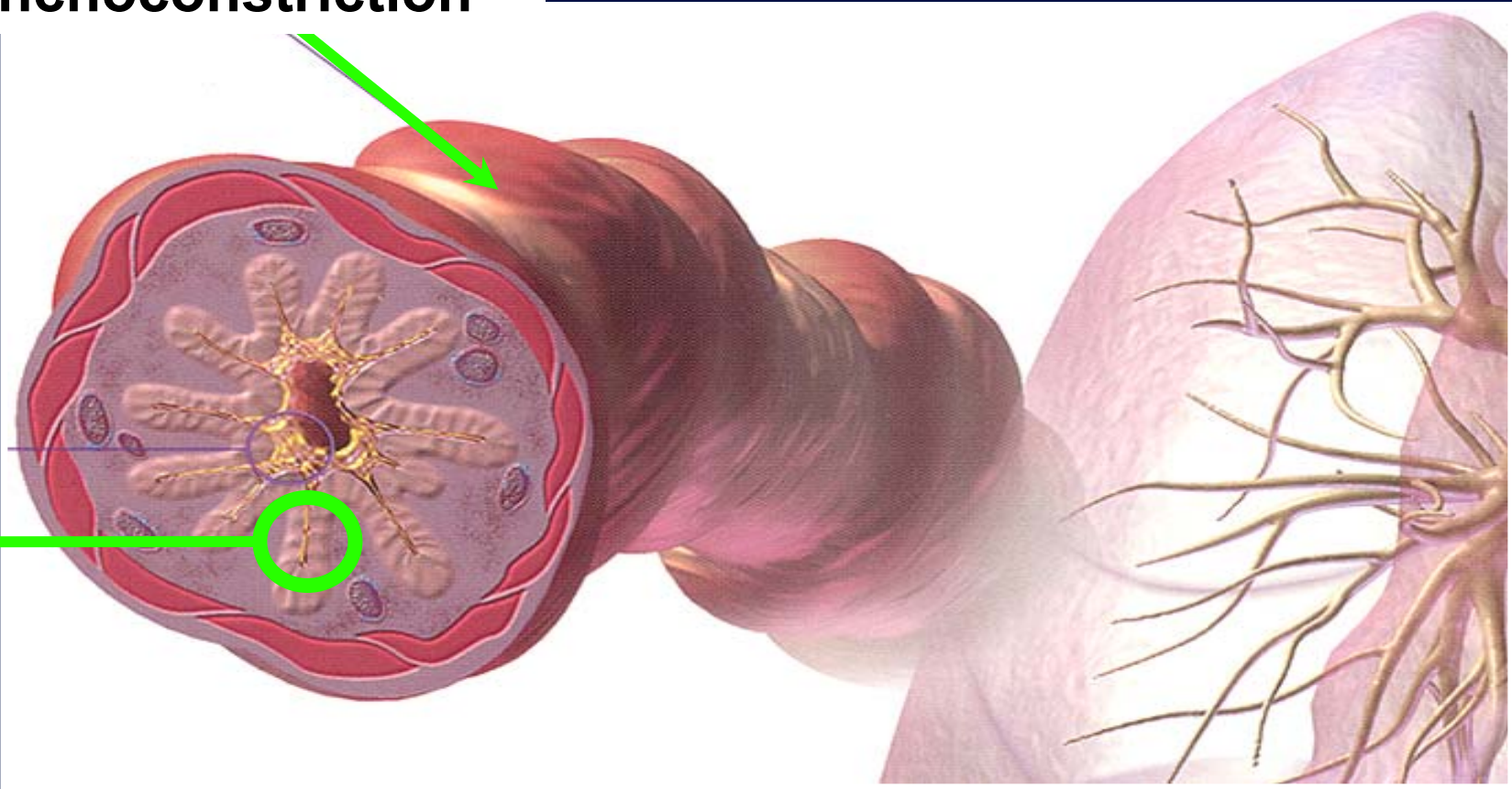
**5,000** people visit the emergency room due to asthma

**1,300** people are admitted to the hospital due to asthma

**10** people **die** from **asthma**

# What is Asthma?

**Bronchoconstriction**

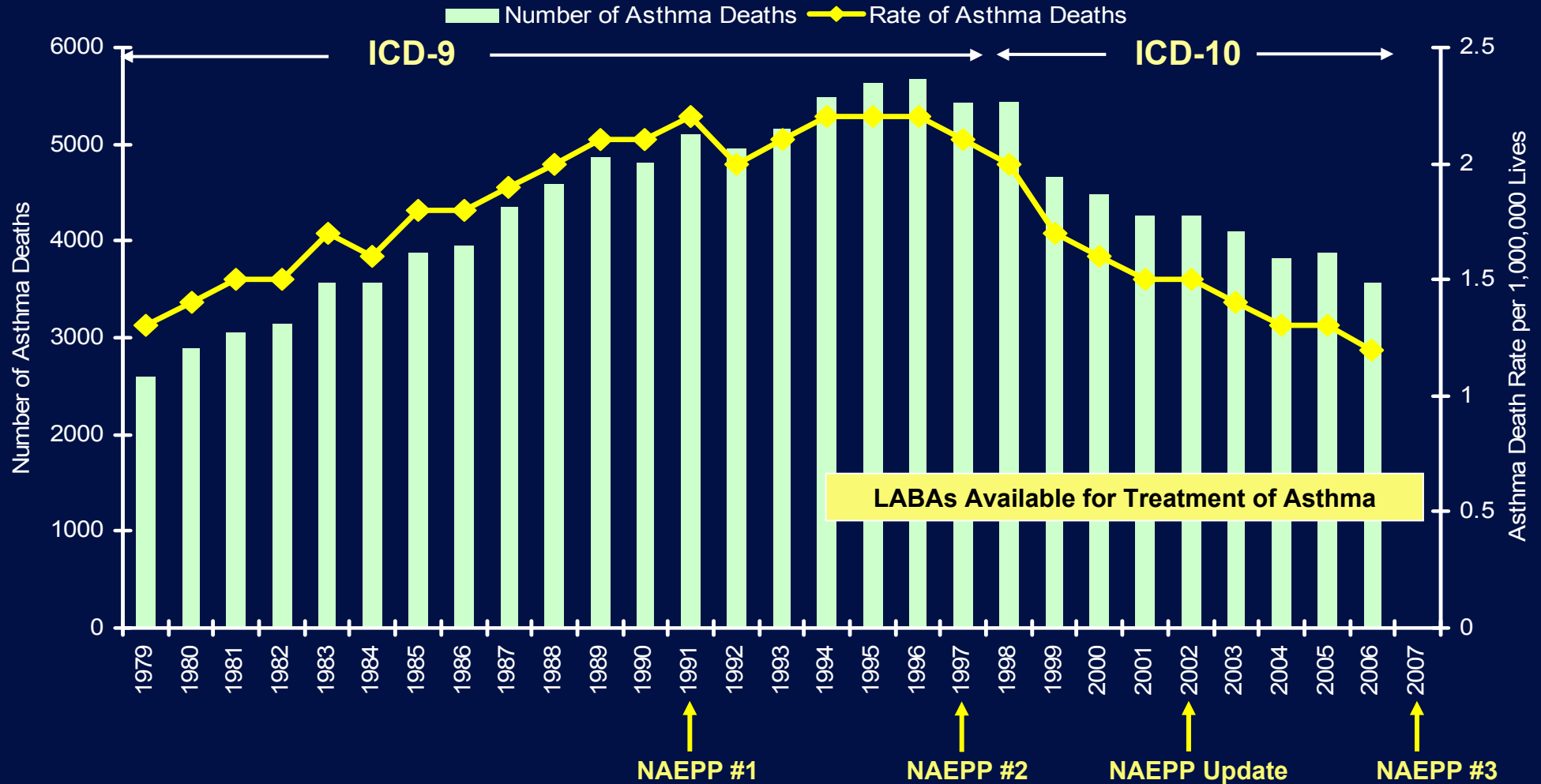


**Inflammation**

# 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



American Lung Association Epidemiology & Statistics Unit Research Program Services. *Trends in Asthma Morbidity and Mortality*. November 2007.

Available at: [www.lungusa.org](http://www.lungusa.org). Accessed October 2, 2008.

Heron MP et al. *Natl Vital Stat Rep*. 2008;56(16):1-52. (preliminary data)

# 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<sub>2</sub>-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<sub>1</sub> of 88% predicted



# Assessing Asthma Control in Patients 5-11 Years of Age

Components of Control		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
	Nighttime awakenings	≤1x/month	≥2x/month	≥2x/week
	Interference w/ normal activity	None	Some limitation	Extremely limited
	SABA use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function <ul style="list-style-type: none"><li>• FEV<sub>1</sub> or PEF</li><li>• FEV<sub>1</sub>/FVC</li></ul>	>80% predicted/ personal best  >80%	60%-80% predicted/ personal best  75%-80%	<60% predicted/ personal best  <75%
	Validated questionnaires C-ACT	≥20	16-19	≤15
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		<ul style="list-style-type: none"><li>• Maintain current step</li><li>• Regular follow-up every 1-6 months</li><li>• Consider step down if well controlled for at least 3 months</li></ul>	<ul style="list-style-type: none"><li>• Step up at least 1 step and</li><li>• Reevaluate in 2 to 6 weeks</li><li>• For side effects, consider alternative treatment options</li></ul>	<ul style="list-style-type: none"><li>• Consider short course of oral systemic corticosteroids</li><li>• Step up 1 or 2 steps, and</li><li>• Reevaluate in 2 weeks</li><li>• For side effects, consider alternative treatment options</li></ul>

C-ACT = Childhood Asthma Control Test.

National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3 2007). U.S. Department of Health and Human Services. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>. Accessed August 29, 2007.

# Stepwise Approach for Managing Asthma in Children 5-11 Years of Age

<b>Intermittent Asthma</b>	<b>Persistent Asthma: Daily Medication</b> Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.				
<b>Step 1</b> <b>Preferred:</b> SABA PRN	<b>Step 2</b> <b>Preferred:</b> Low-dose ICS (A) <b>Alternative:</b> Cromolyn (B), LTRA (B), Nedocromil (B), or Theophylline (B)	<b>Step 3</b> <b>Preferred:</b> EITHER Low-dose ICS + either LABA (B), LTRA (B), or Theophylline (B) OR Medium-dose ICS (B)	<b>Step 4</b> <b>Preferred:</b> Medium-dose ICS + LABA (B) <b>Alternative:</b> Medium-dose ICS + either LTRA (B) or Theophylline (B)	<b>Step 5</b> <b>Preferred:</b> High-dose ICS + LABA (B) <b>Alternative:</b> High-dose ICS + either LTRA (B) or Theophylline (B)	<b>Step 6</b> <b>Preferred:</b> High-dose ICS + LABA + Oral Systemic Corticosteroid (D) <b>Alternative:</b> High-dose ICS + either LTRA or Theophylline and Oral Systemic Corticosteroid (D)

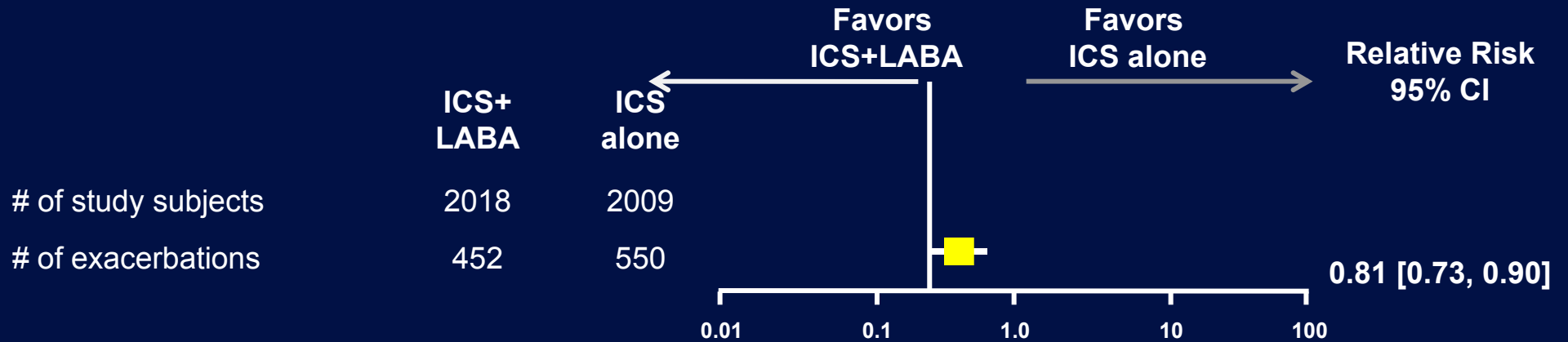
SABA=short-acting beta-agonist; ICS=inhaled corticosteroid; LTRA=leukotriene receptor antagonist; LABA=long-acting beta-agonist

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

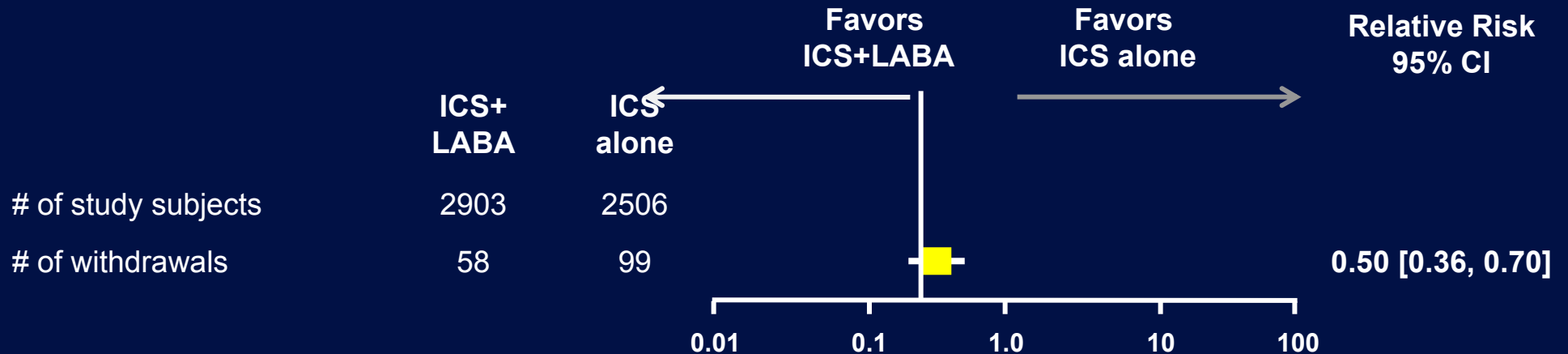
<b>Intermittent Asthma</b>	<b>Persistent Asthma: Daily Medication</b> Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.				
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# ICS + LABA Reduces Exacerbations Requiring Oral Corticosteroids and Study Withdrawals Due to Exacerbations

## Exacerbations requiring systemic steroids



## Study withdrawal due to poor asthma control or exacerbations



# 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**

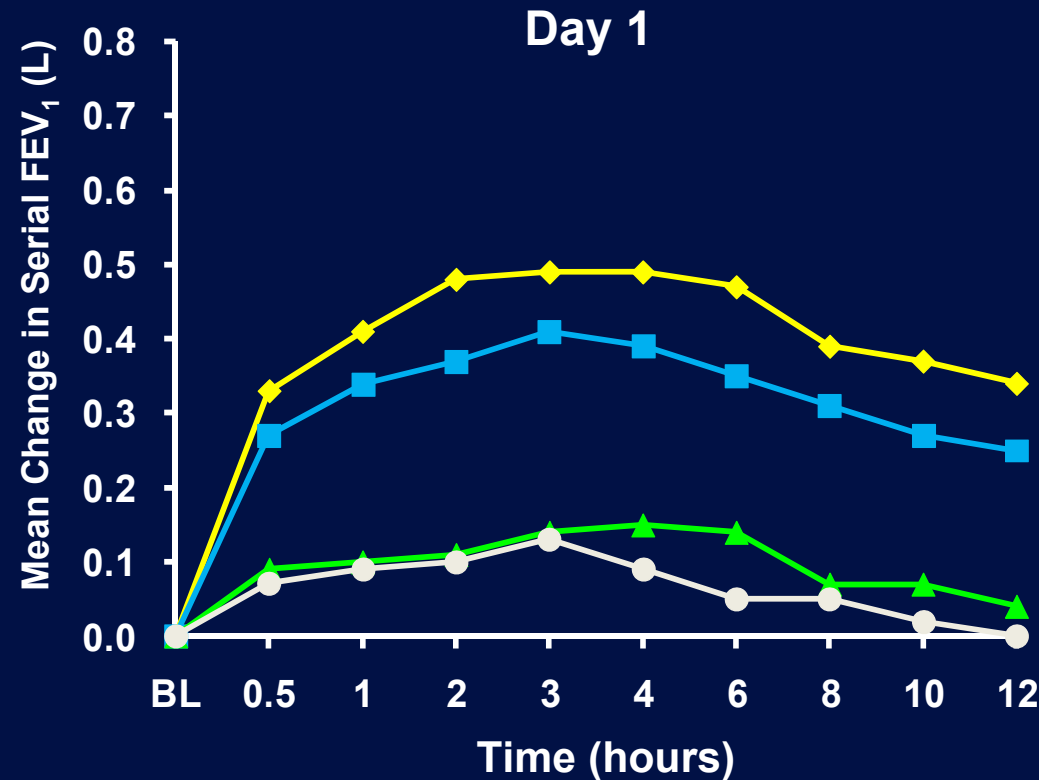
# Presentation Outline

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

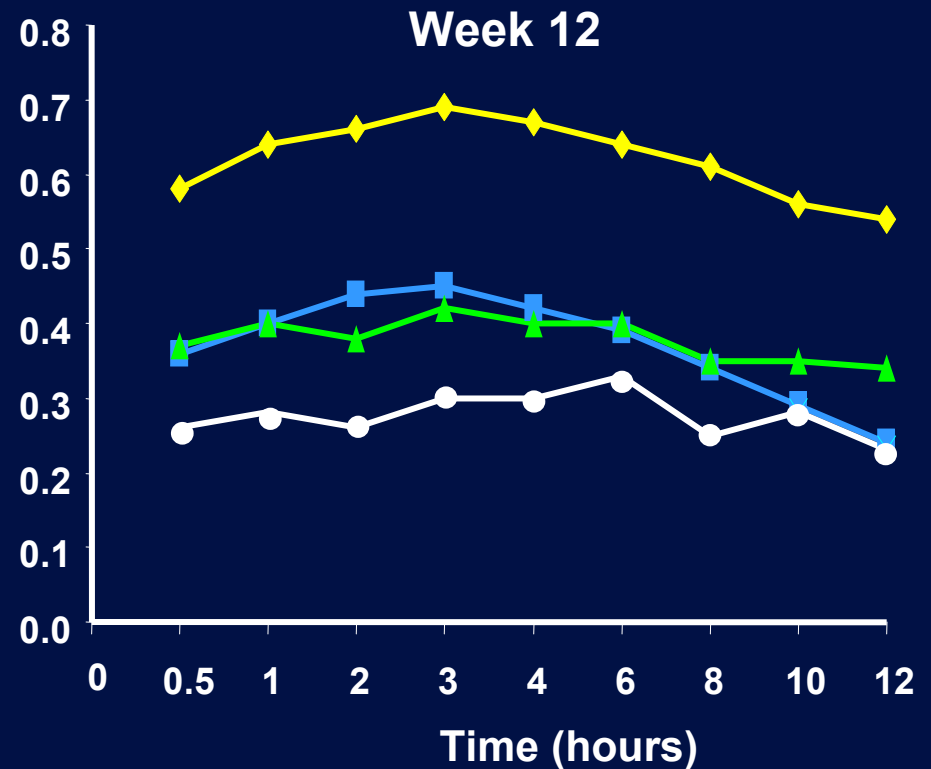
# ADVAIR Versus ICS Alone

## Improvement in Lung Function

◆ ADVAIR 250/50 (n=81)  
 ■ SEREVENT 50 mcg (n=84)  
 ▲ FP 250 mcg (n=81)  
 ● Placebo (n=90)



$p < 0.001$  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



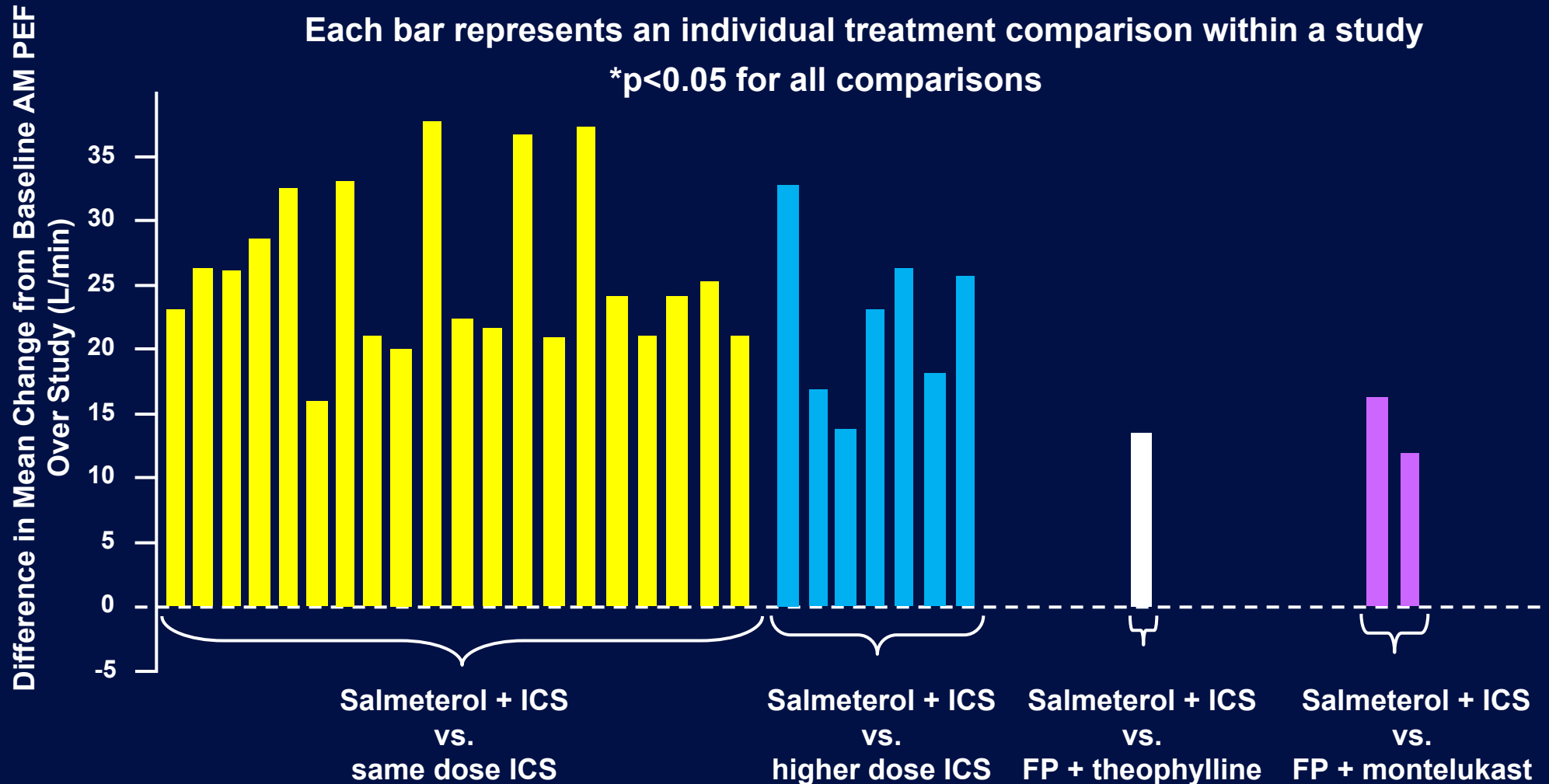
$p < 0.001$  ADVAIR vs. FP, SEREVENT and placebo at all time points

# Salmeterol plus ICS Versus Alternative Treatments

## *Significant Improvement in Lung Function\**

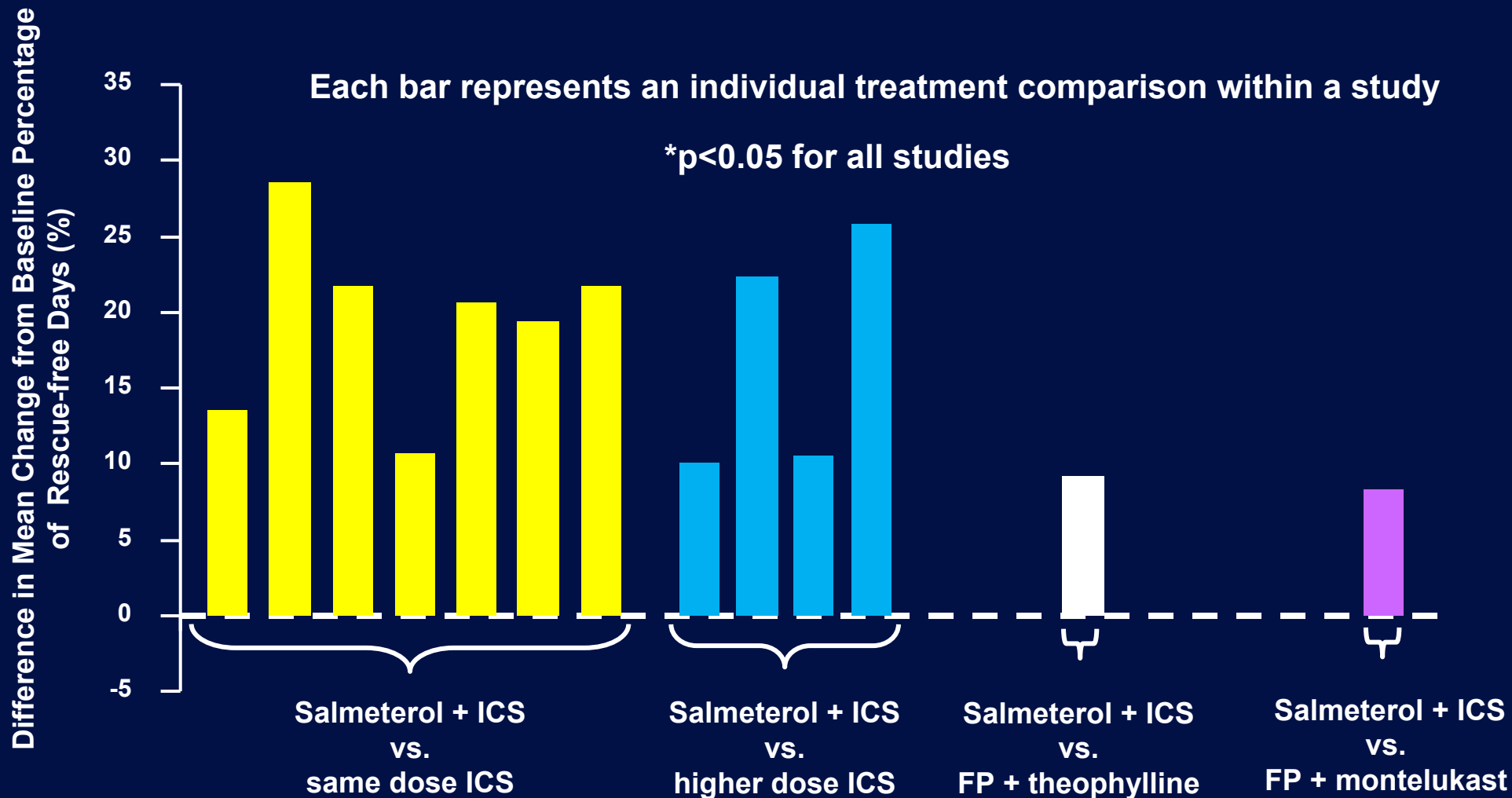
Each bar represents an individual treatment comparison within a study

\* $p < 0.05$  for all comparisons



# Salmeterol plus ICS Versus Alternative Treatments

## *Significant Improvement in Rescue-free Days\**

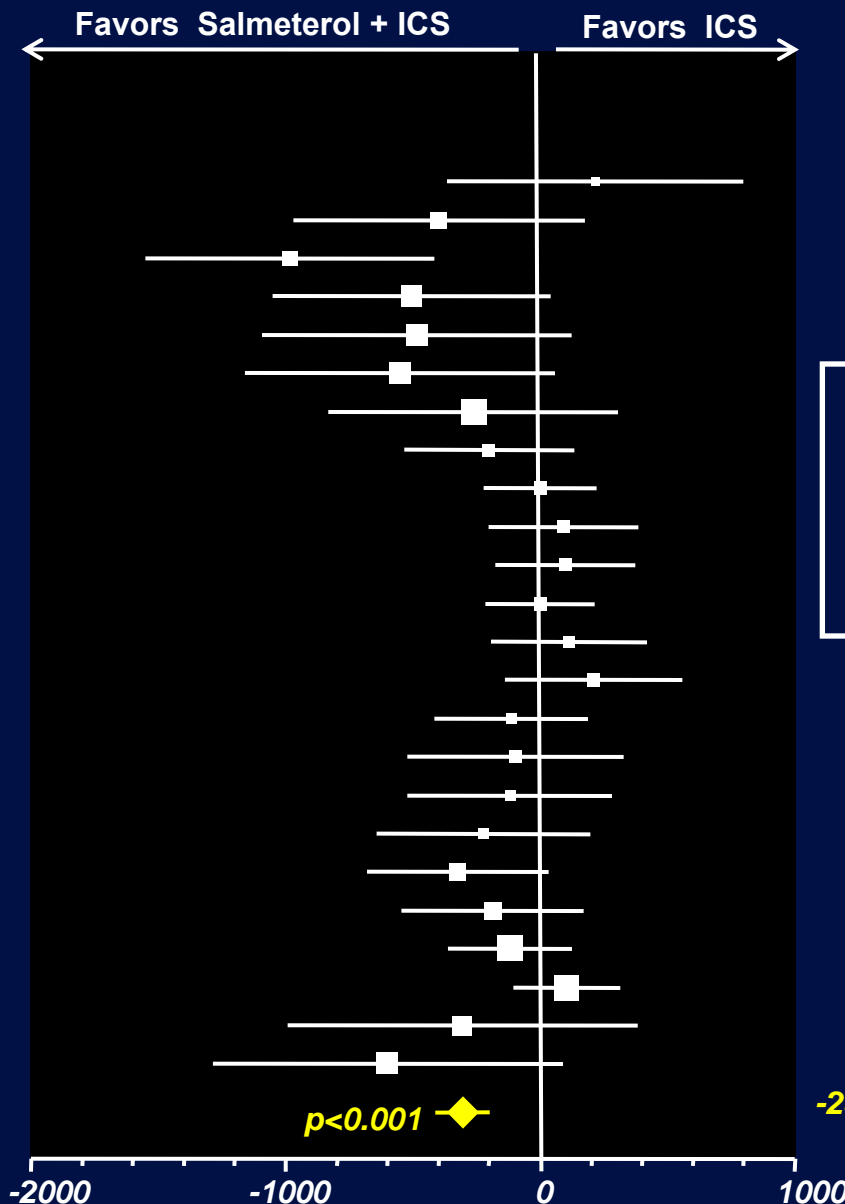




# Salmeterol plus ICS Compared with ICS

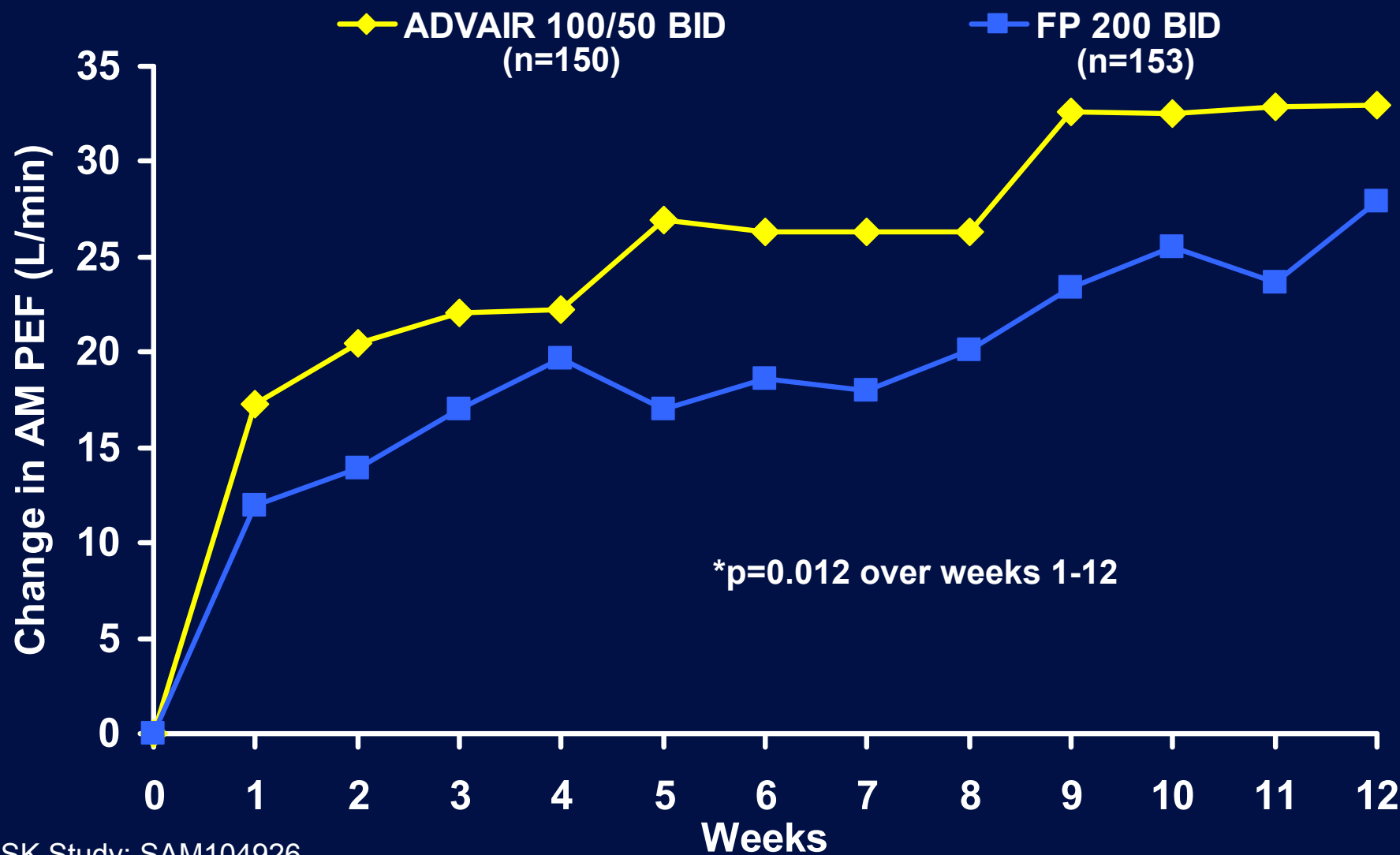
*Significant Reduction in Risk of Exacerbations Requiring Oral Corticosteroids*

Study	Salmeterol + ICS		ICS	
	(n)	(N)	(n)	(N)
Pearlman	1	46	0	46
Baraniuk	7	118	23	232
Baraniuk	4	113	29	217
SLGA5021	20	246	32	243
Condemni	21	221	31	216
Kelsen	26	239	40	244
Murray	29	260	35	254
SAS40024	0	99	2	100
SFA100314	1	124	1	124
SFA100316	2	113	1	118
Weiler	1	102	0	90
Kavuru	0	92	0	90
Murray	1	88	0	89
Nelson	2	95	0	97
Pearlman	0	92	1	89
Malone	2	101	3	102
Shapiro	1	84	2	84
Nathan	1	94	3	91
Koenig	2	172	7	159
SAS40037	3	161	6	161
Jarjour	5	295	8	279
Busse	6	281	3	277
SAM40065	20	150	49	299
Koenig	20	155	58	307
<b>Combined</b>	<b>175</b>	<b>3,541</b>	<b>334</b>	<b>4,008</b>



# Salmeterol plus ICS in Children Aged 4-11 Years

## *Improvement in Lung Function Compared to Higher Dose ICS\**



# Exacerbations\* in Pediatric Studies

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

% Patients with Exacerbation				
	Total N	ADVAIR 100/50 BID	FP 100 BID	FP 200 BID
SFA100314	248	1.6	2.4	-
SFA100316	231	1.8	0.8	-
SAS30031	203	3.0	7.8	-
SFA106484	350	0.6	1.7	-
SAM40012	531	5.7	12.0	11.7
SAM102318	281	2.2	-	4.1
SAM104926	303	1.3	-	1.3
<b>Combined</b>	<b>2147</b>	<b>2.4</b>	<b>5.2</b>	<b>6.1</b>

\*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

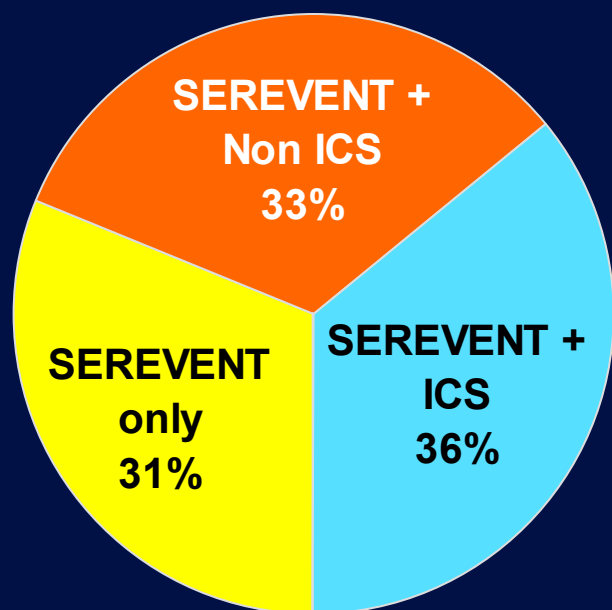
**Preferred treatment option in evidence-based asthma treatment guidelines**

# Presentation Outline

- Efficacy of salmeterol-containing products in persistent asthma
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  - Safety Data with ADVAIR
- Recommendations

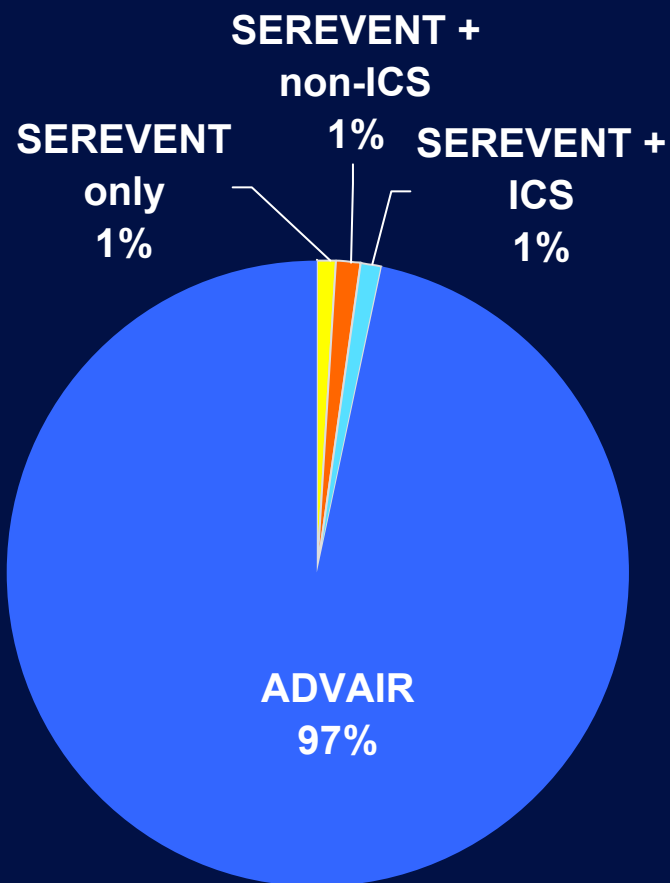
# Change in Salmeterol Use for Asthma Over Time

*US Data from a Large Health Insurer*



ADVAIR  
0%

**1994 - 1996**



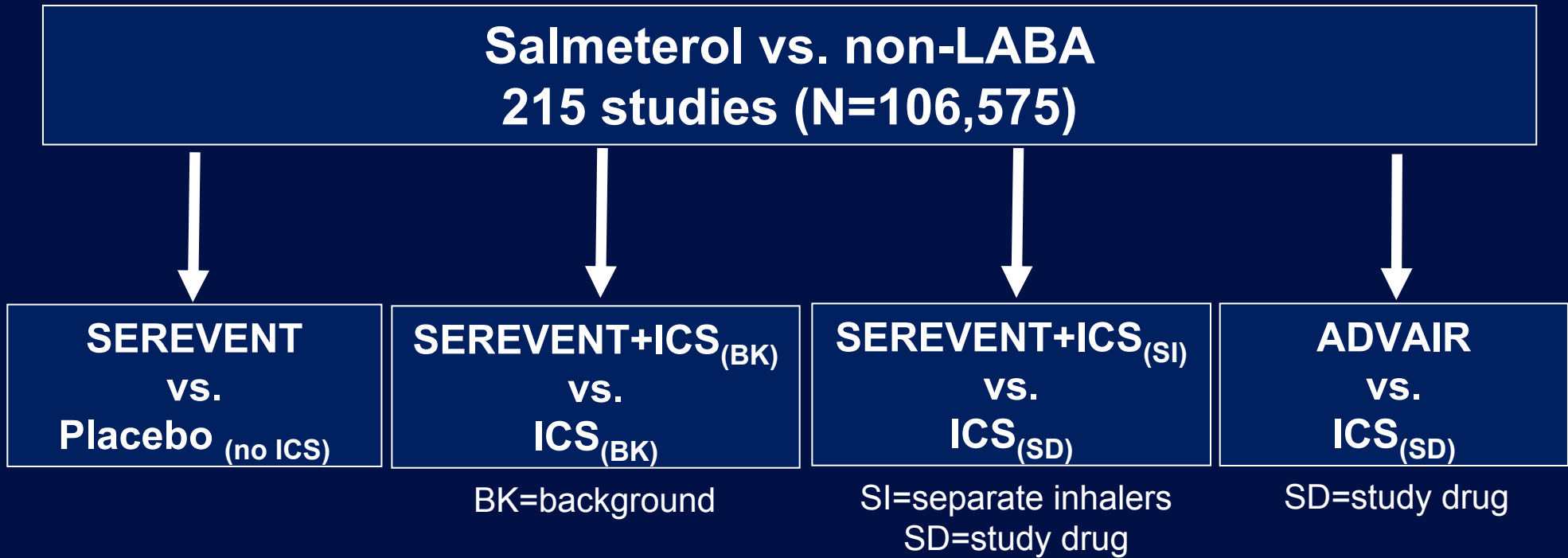
**2005 - 2007**

# 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



Increasing Confidence in Adherence to ICS

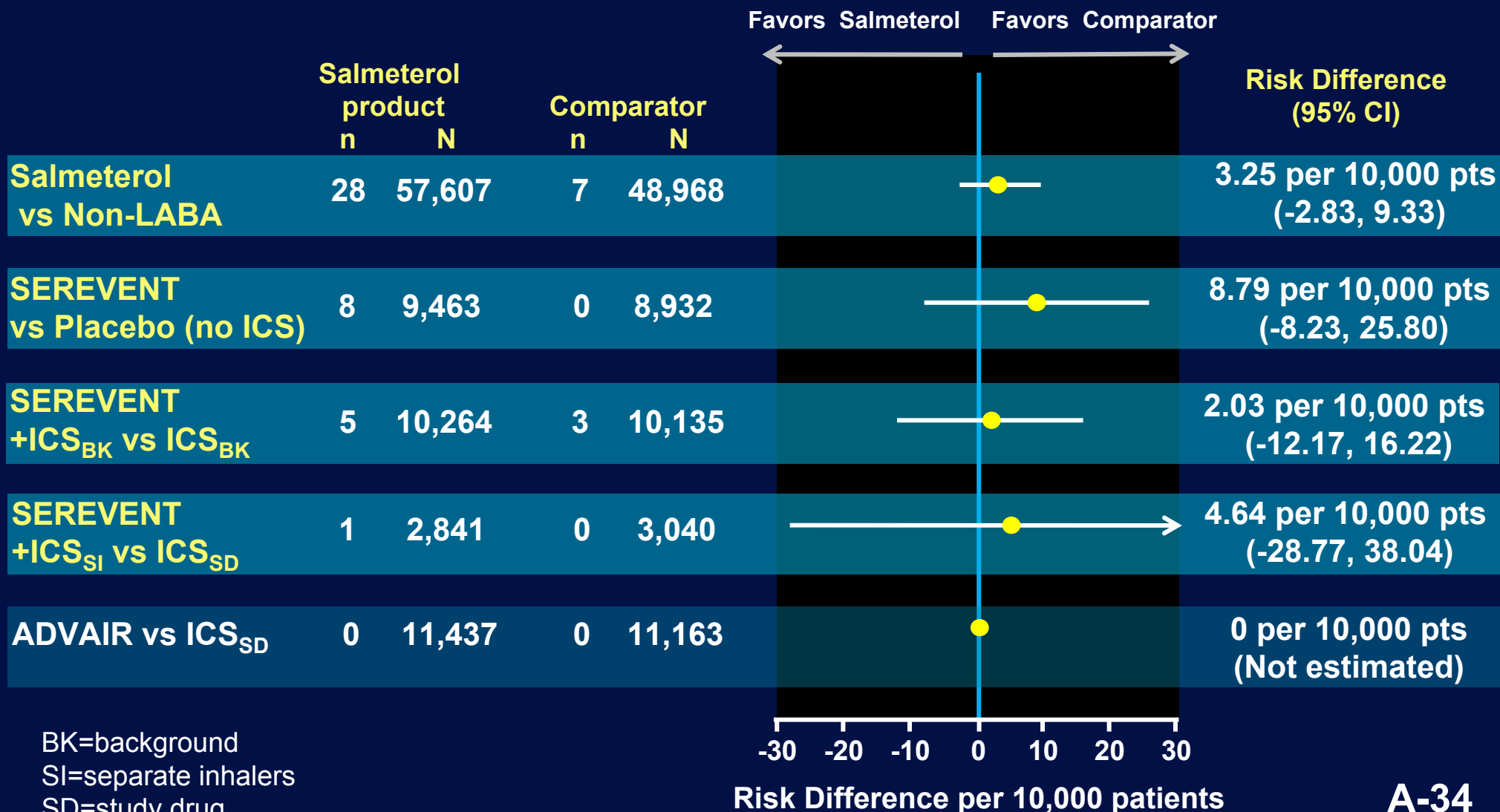


# Presentation Outline

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  - Safety Data with SEREVENT
  - Safety Data with ADVAIR
- Recommendations

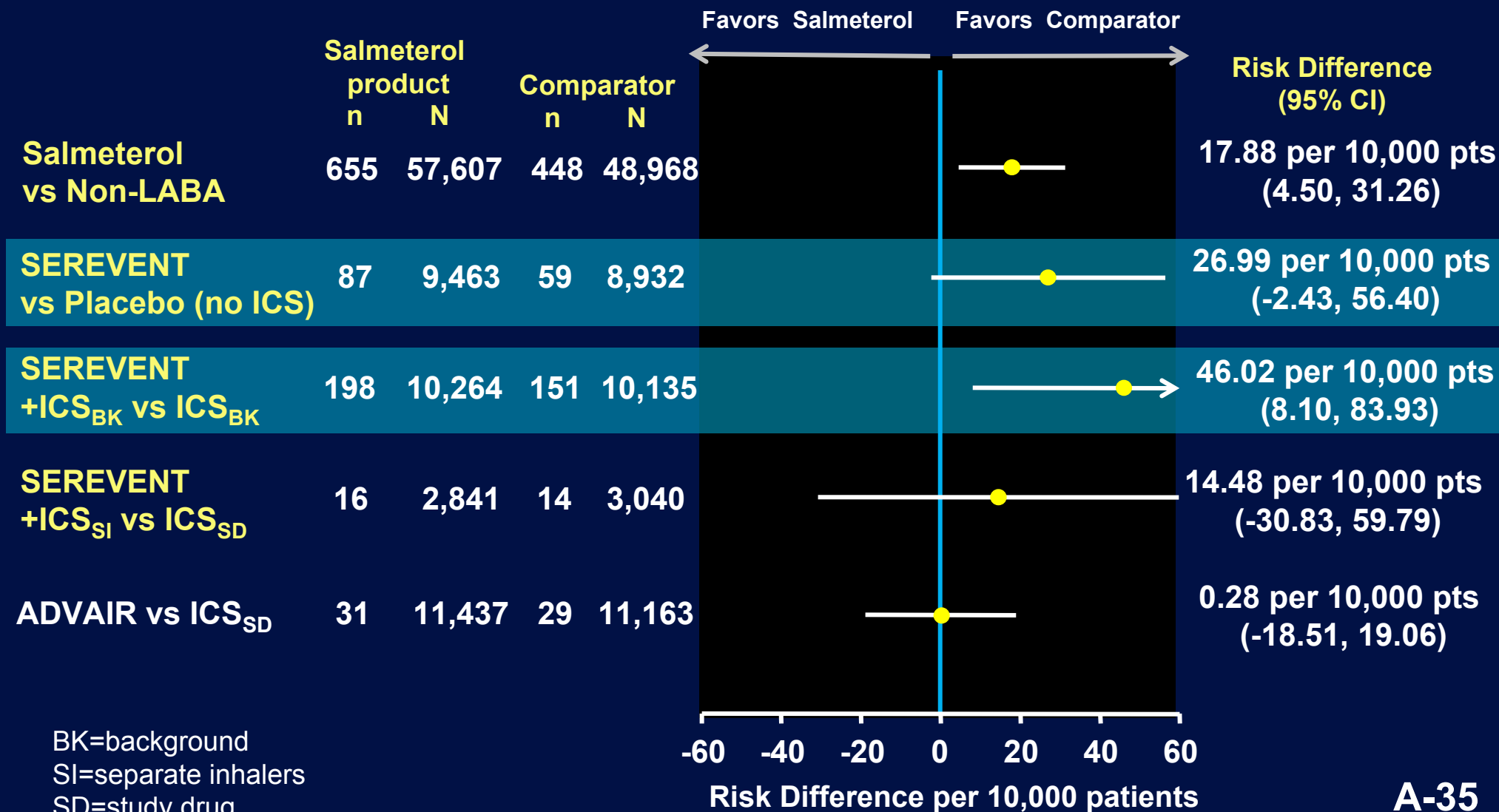
# Risk of Asthma-related Death for SEREVENT

## Risk Difference in Overall Population



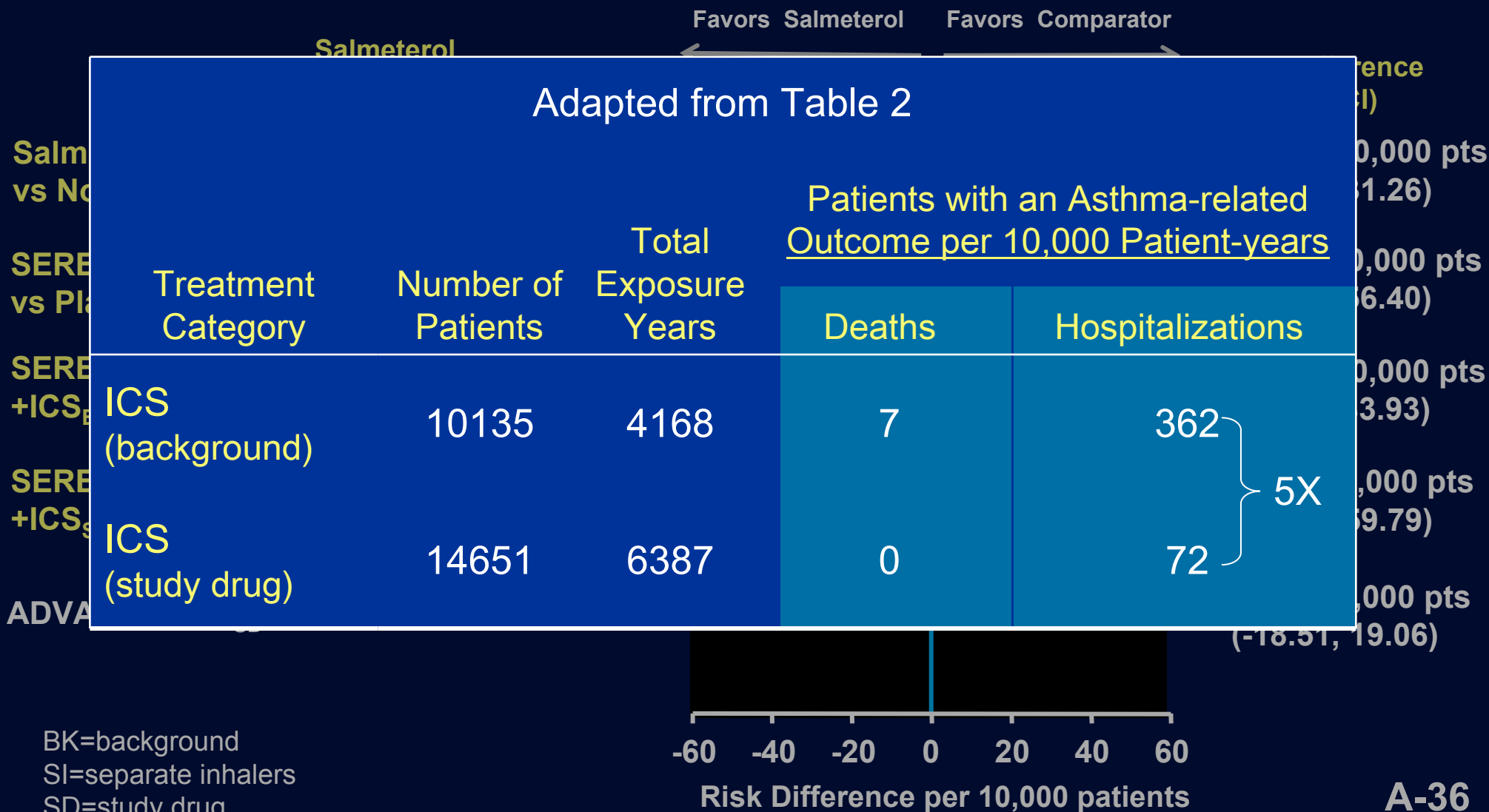
# Risk of Asthma-related Hospitalization for SEREVENT

*Risk Difference in Overall Population*



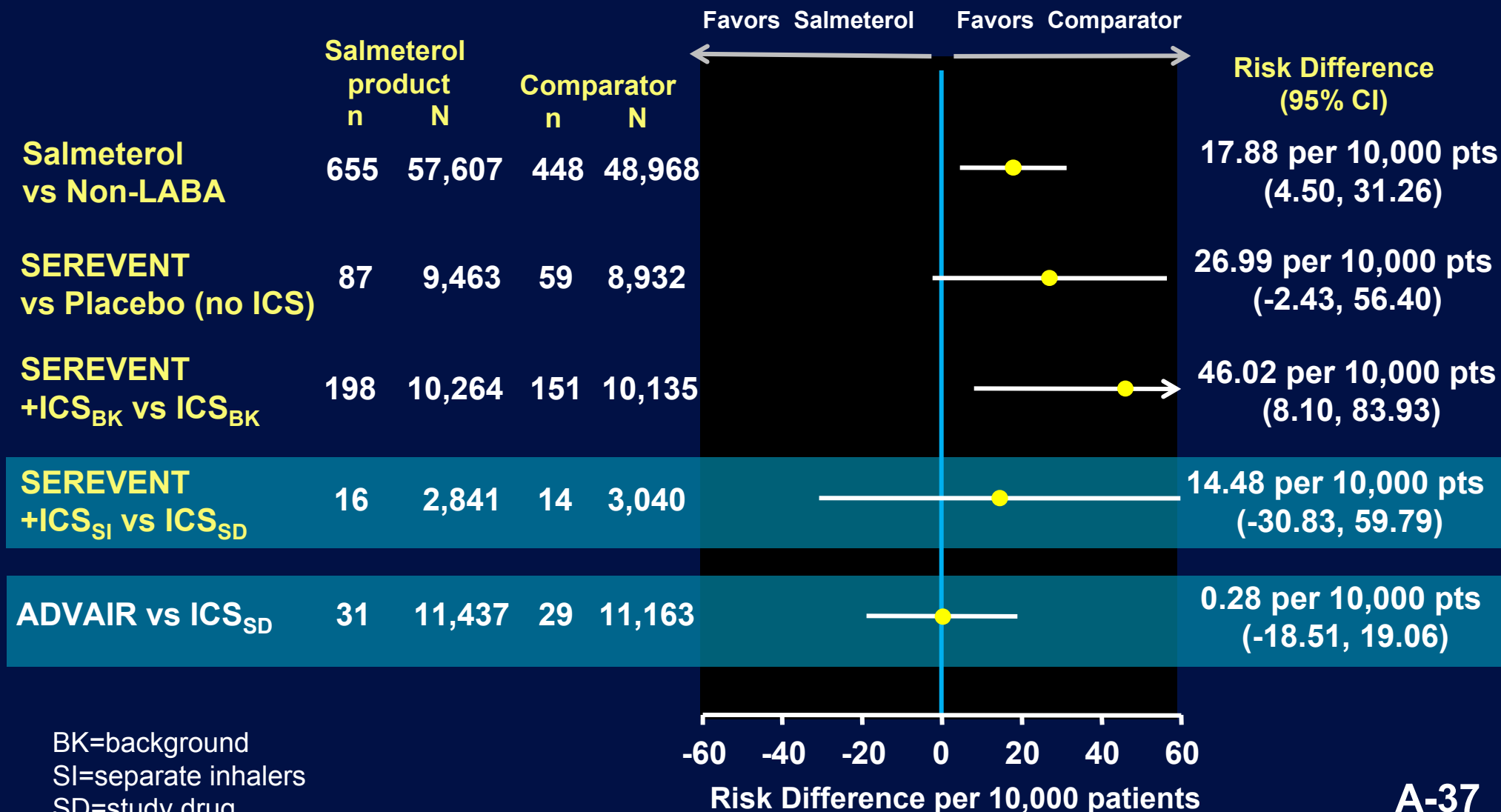
# Risk of Asthma-related Hospitalization for SEREVENT

*Risk Difference in Overall Population*



# Risk of Asthma-related Hospitalization for SEREVENT

*Risk Difference in Overall Population*



# Presentation Outline

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

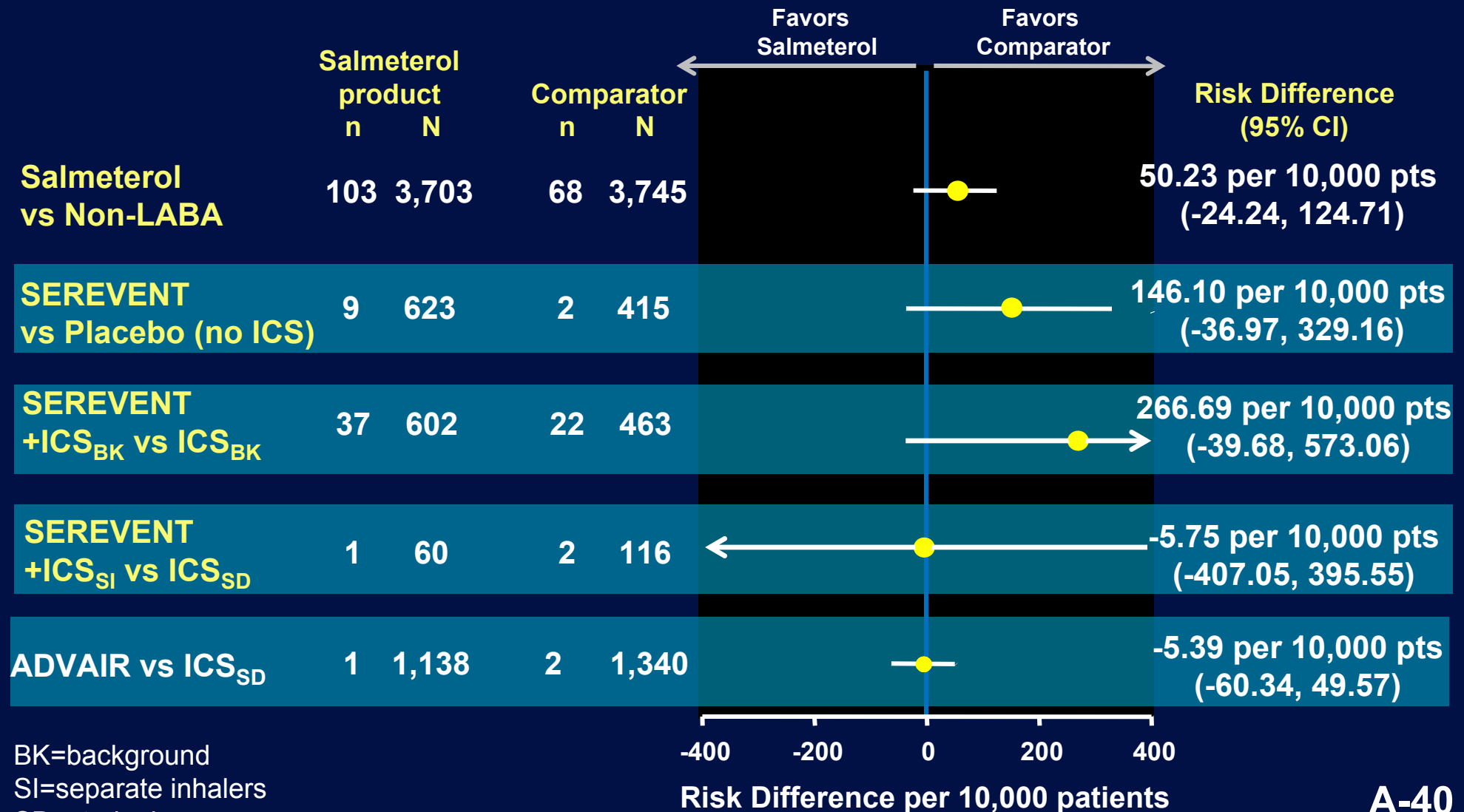
# Risk of Serious Outcomes with SEREVENT

## *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





# 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**

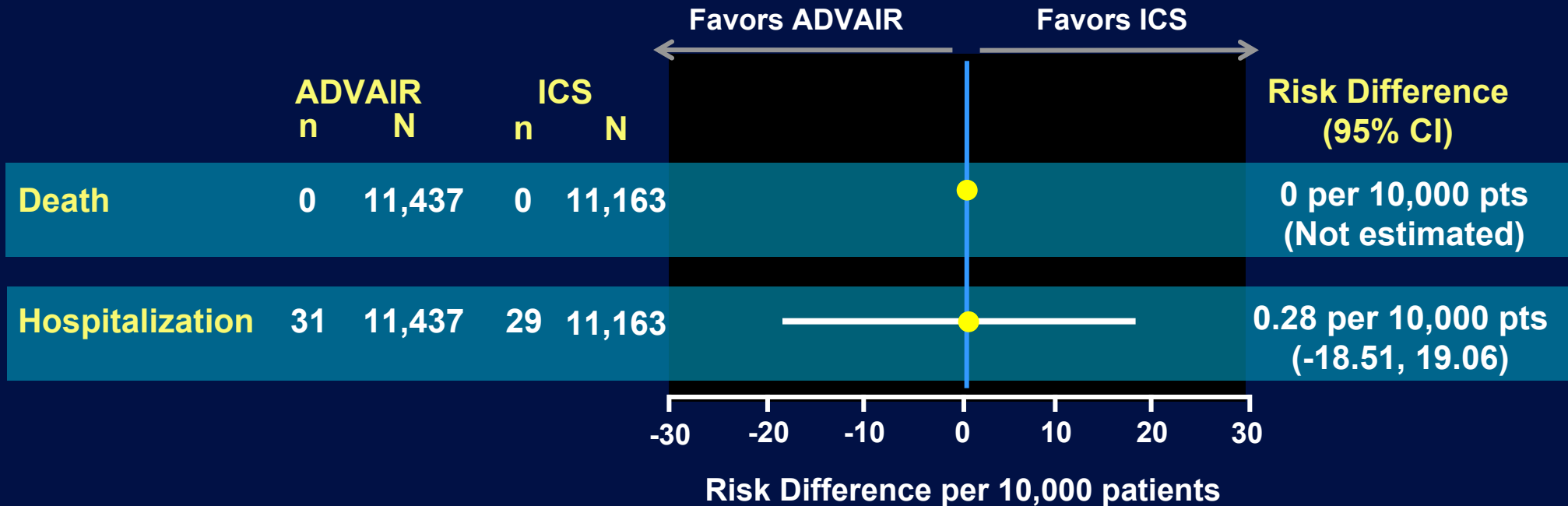
**Proposed labeling now requires that SEREVENT should only be used concurrently with ICS**

# Presentation Outline

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  - Safety Data with ADVAIR
- Recommendations

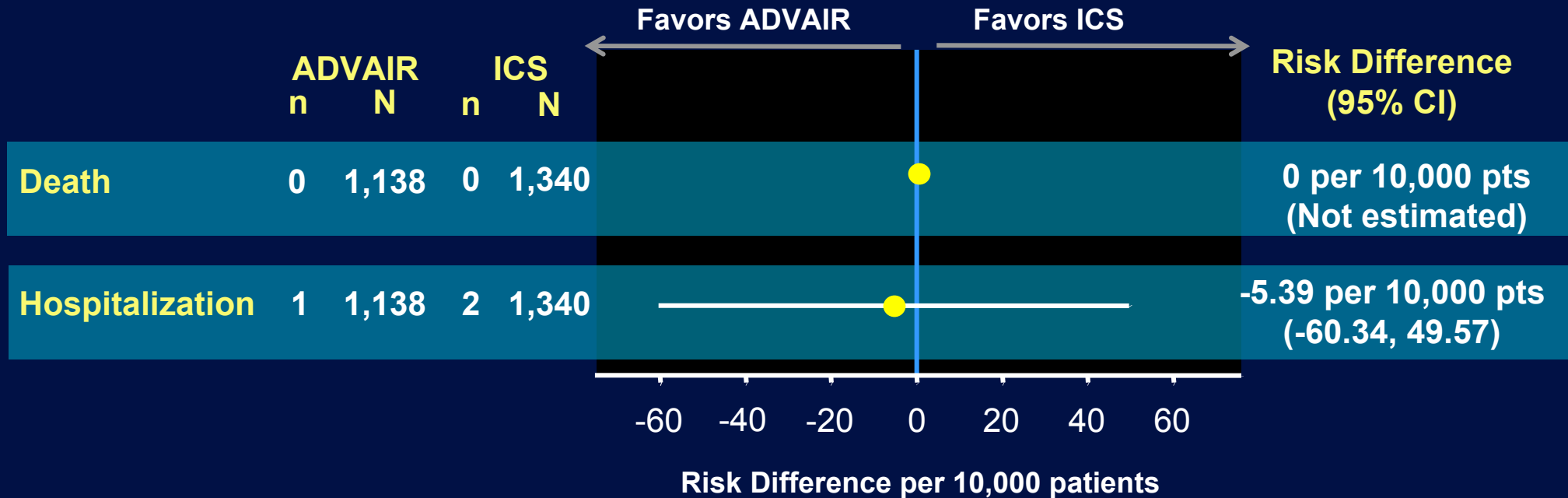
# Asthma-related Death and Hospitalization with ADVAIR

## Overall Population



# Asthma-related Death and Hospitalization with ADVAIR

## *Pediatric Population*



# 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*

**SFA103153\***

**ADVAIR 100/50 BID**

**FP 100 BID**

**(n=239)**

**(n=236)**

**Exacerbation rate per  
year**

**0.45**

**0.53**

\*Bailey, et al. *Curr Med Res Opin* 2008;24:1669-82.

**GSK Database**

**ADVAIR**

**ICS**

**(n=724)**

**(n=706)**

**Asthma-related  
Hospitalizations†**

**4**

**4**

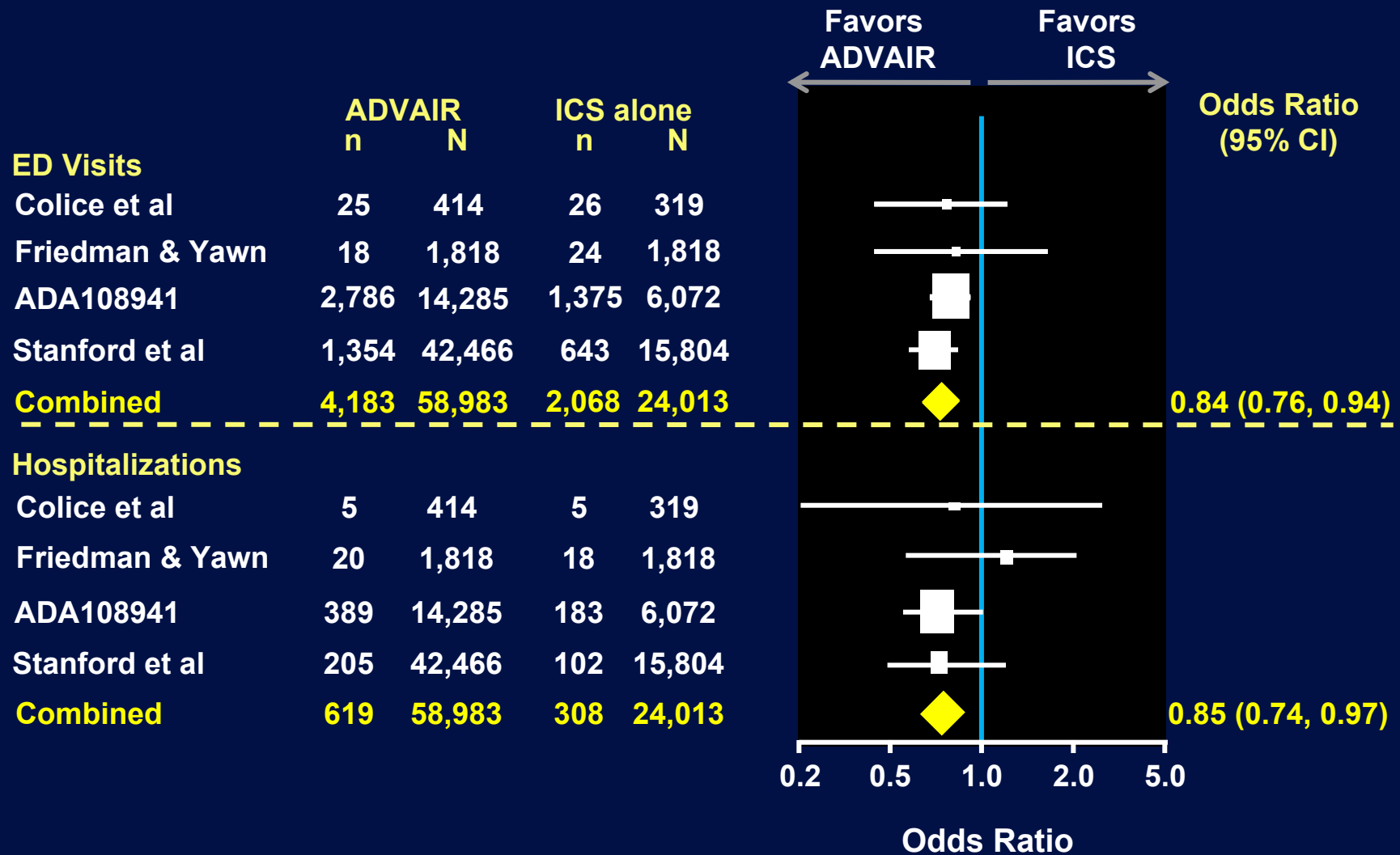
†All studies in African Americans receiving ADVAIR and ICS

# Presentation Outline

- 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

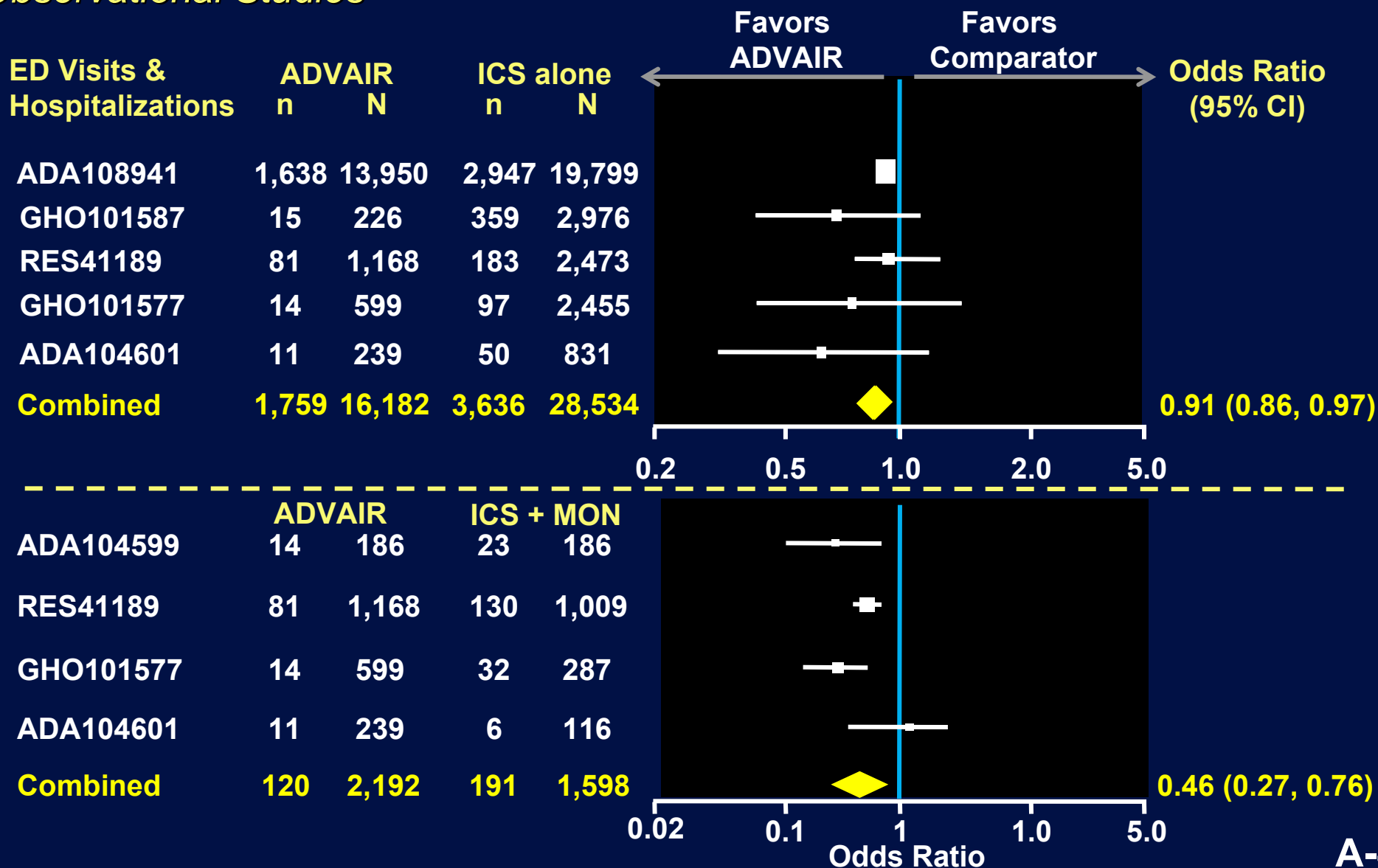
## Observational Studies





# Reduction in Risk of ED/Hospitalizations with ADVAIR in Pediatrics

## Observational Studies



# 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**

# SEREVENT DISKUS

## *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)**

Treatment Category	Number of Studies	Number of Subjects	Total Exposure Years	Asthma-Related Deaths per 10,000 Pt-Yrs	Subjects with an Asthma-Related Hospitalization per 10,000 Pt-Yrs
Salmeterol-containing product	263	67219	23486	14	321
Non-LABA	231	48968	18433	4	246
Sal (without ICS)	80	11342	4352	25	239
Pla (without ICS)	62	9935	4104	2	175
ICS <sub>BK</sub>	44	10135	4168	7	362
ICS <sub>SD</sub>	96	14651	6387	0	72
Sal + ICS <sub>BK</sub>	51	12881	5059	12	484
Sal + ICS <sub>SD</sub>	109	21695	8056	1	82
Sal + ICS <sub>SI</sub>	27	3804	1486	7	155
ADVAIR	86	17891	6571	0	65
<b>SMART Sub-Groups (numbers included in categories above)</b>					
Sal (without ICS)	1	6513	2993	27	184
Pla (without ICS)	1	6463	2930	0	140
Pla + ICS <sub>BK</sub>	1	6716	3156	10	355
Sal + ICS <sub>BK</sub>	1	6663	3194	16	379
• 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*

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