

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

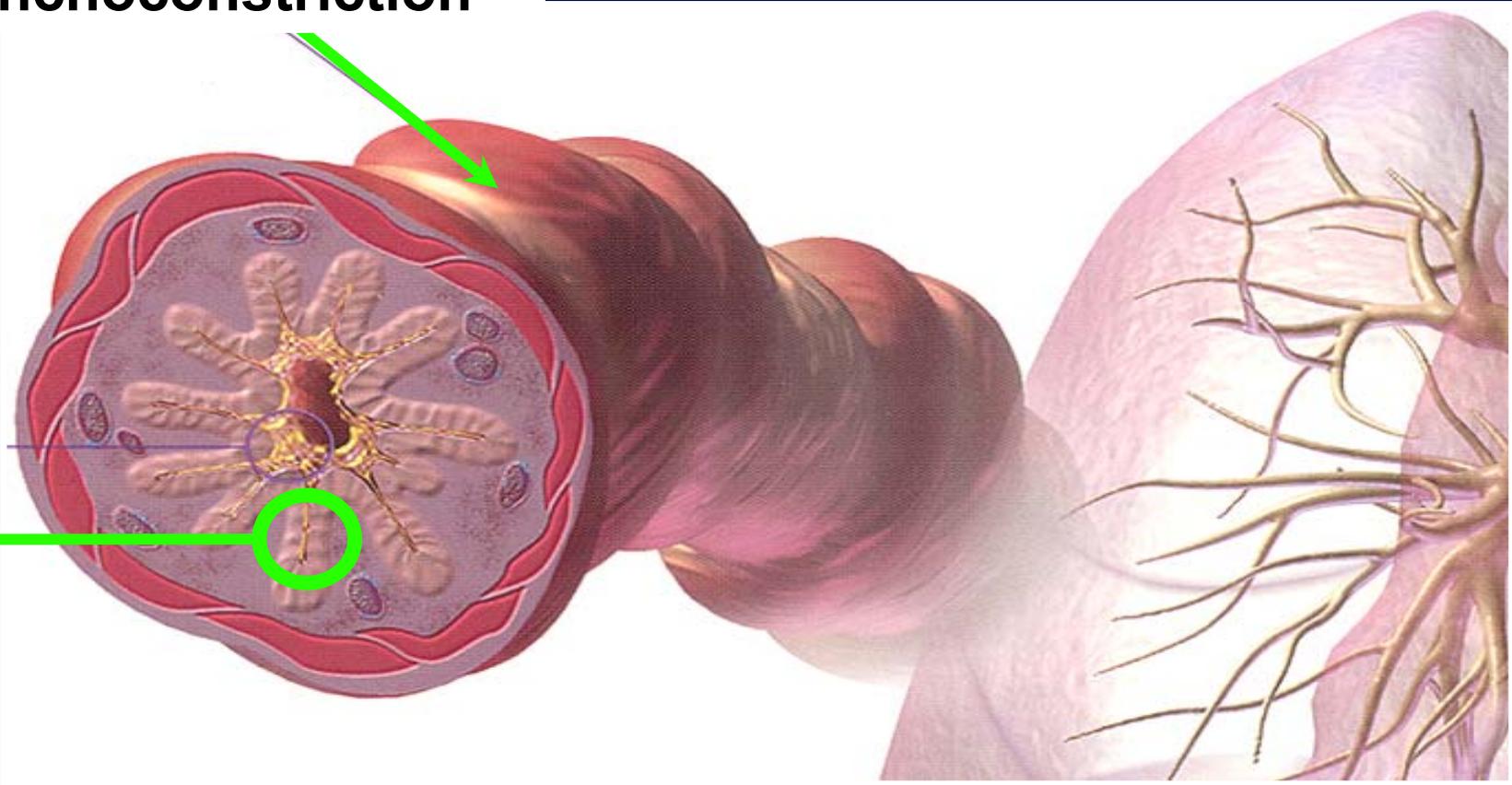
5,000 people visit the emergency room due to asthma

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

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

What is Asthma?

Bronchoconstriction

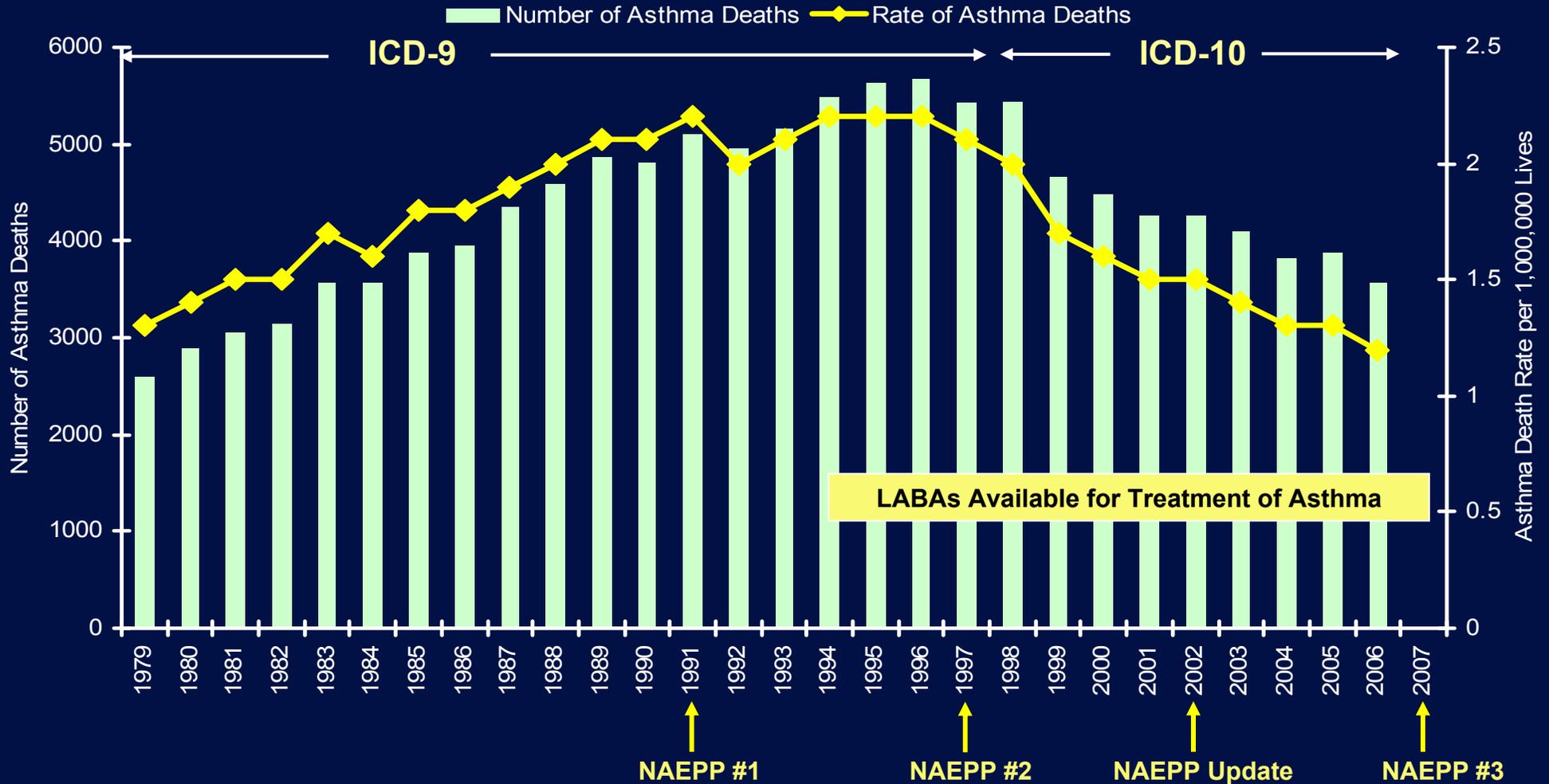


Inflammation

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. 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 beta₂-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
 - FEV₁ 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 • FEV ₁ or PEF • FEV ₁ /FVC	>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"> Maintain current step Regular follow-up every 1-6 months Consider step down if well controlled for at least 3 months 	<ul style="list-style-type: none"> Step up at least 1 step and Reevaluate in 2 to 6 weeks For side effects, consider alternative treatment options 	<ul style="list-style-type: none"> Consider short course of oral systemic corticosteroids Step up 1 or 2 steps, and Reevaluate in 2 weeks For side effects, consider alternative treatment options

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

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

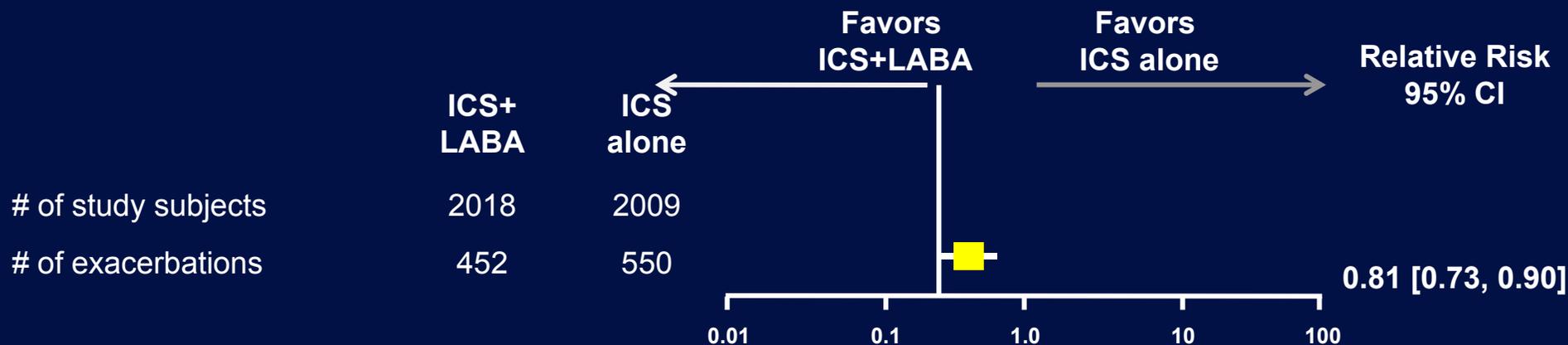
SABA=short-acting beta-agonist; ICS=inhaled corticosteroid; LTRA=leukotriene receptor antagonist; LABA=long-acting beta-agonist

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

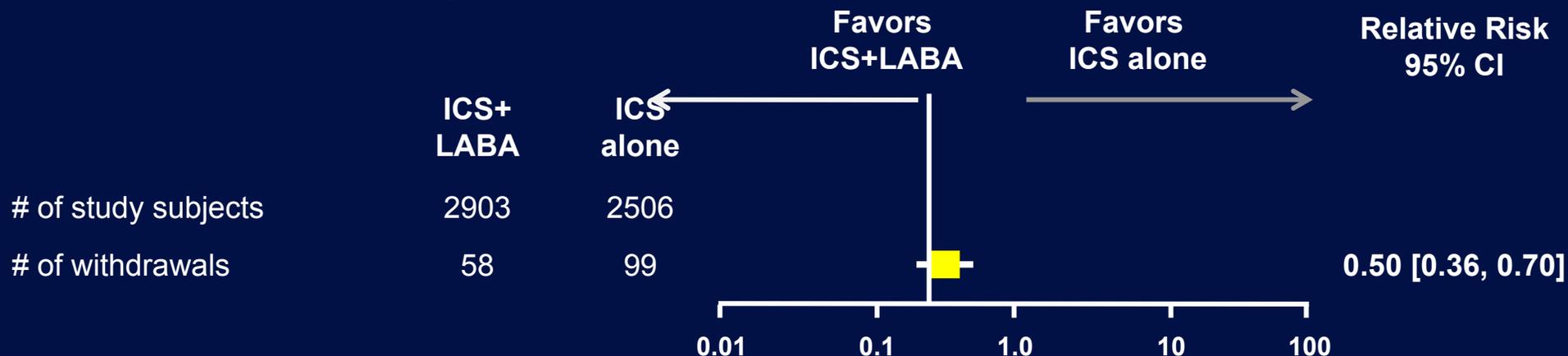
<p>Intermittent Asthma</p>	<p>Persistent Asthma: Daily Medication Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.</p>				
<p>Step 1 Preferred: SABA PRN</p>	<p>Step 2 Preferred: Low-dose ICS (A) Alternative: Cromolyn (A), LTRA (A), Nedocromil (A),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

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

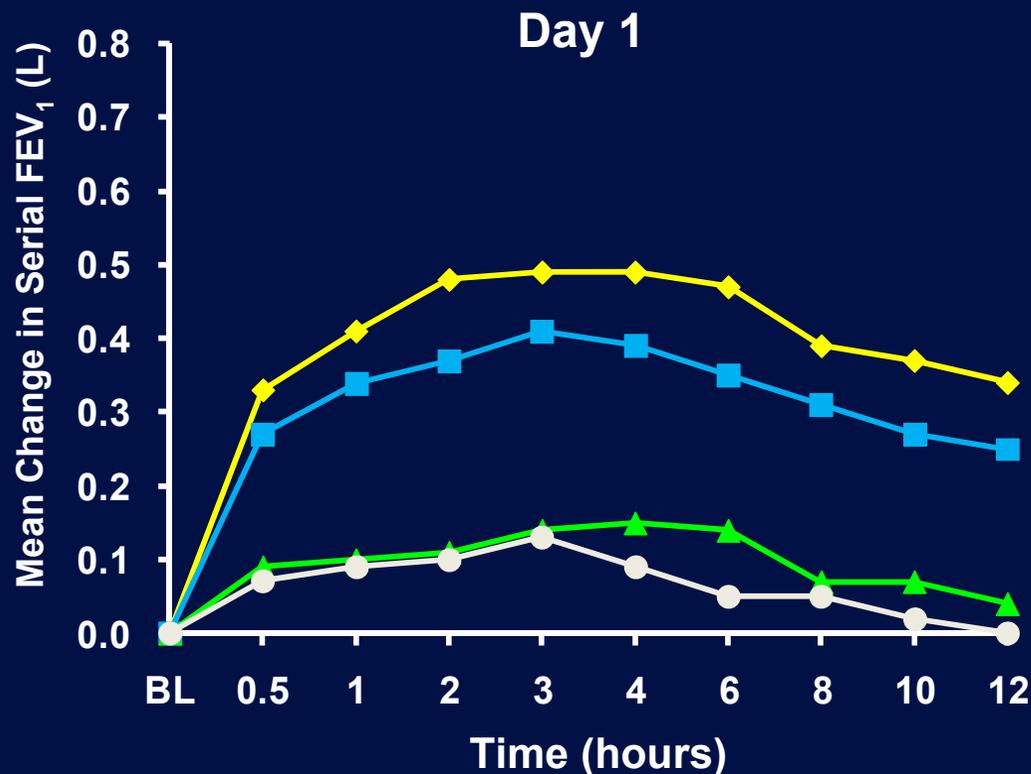
Presentation Outline

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

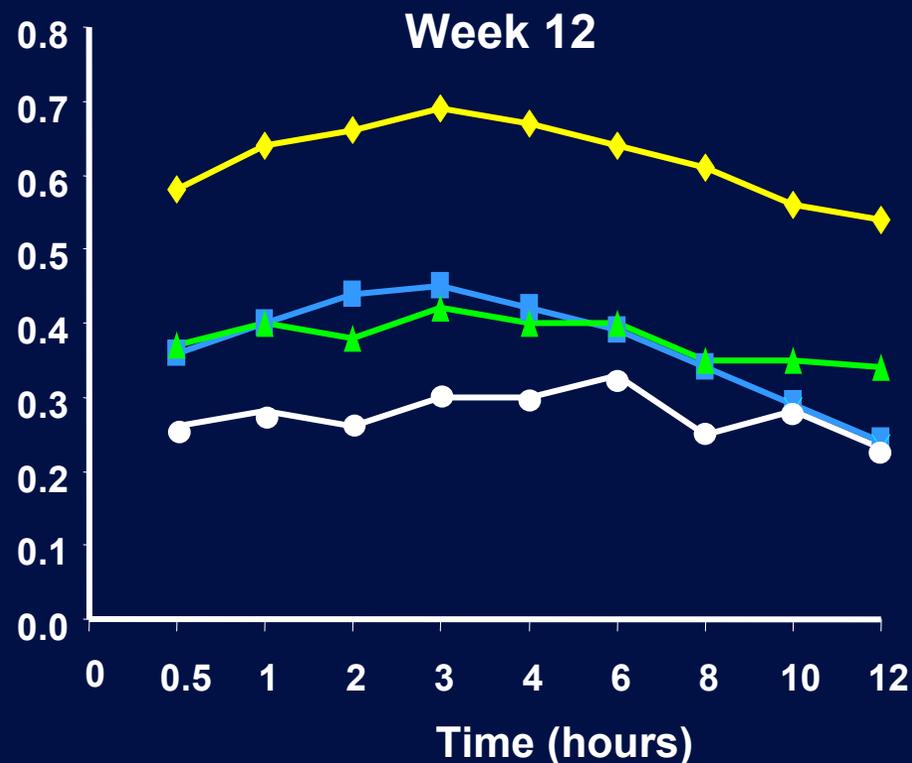
ADVAIR Versus ICS Alone

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

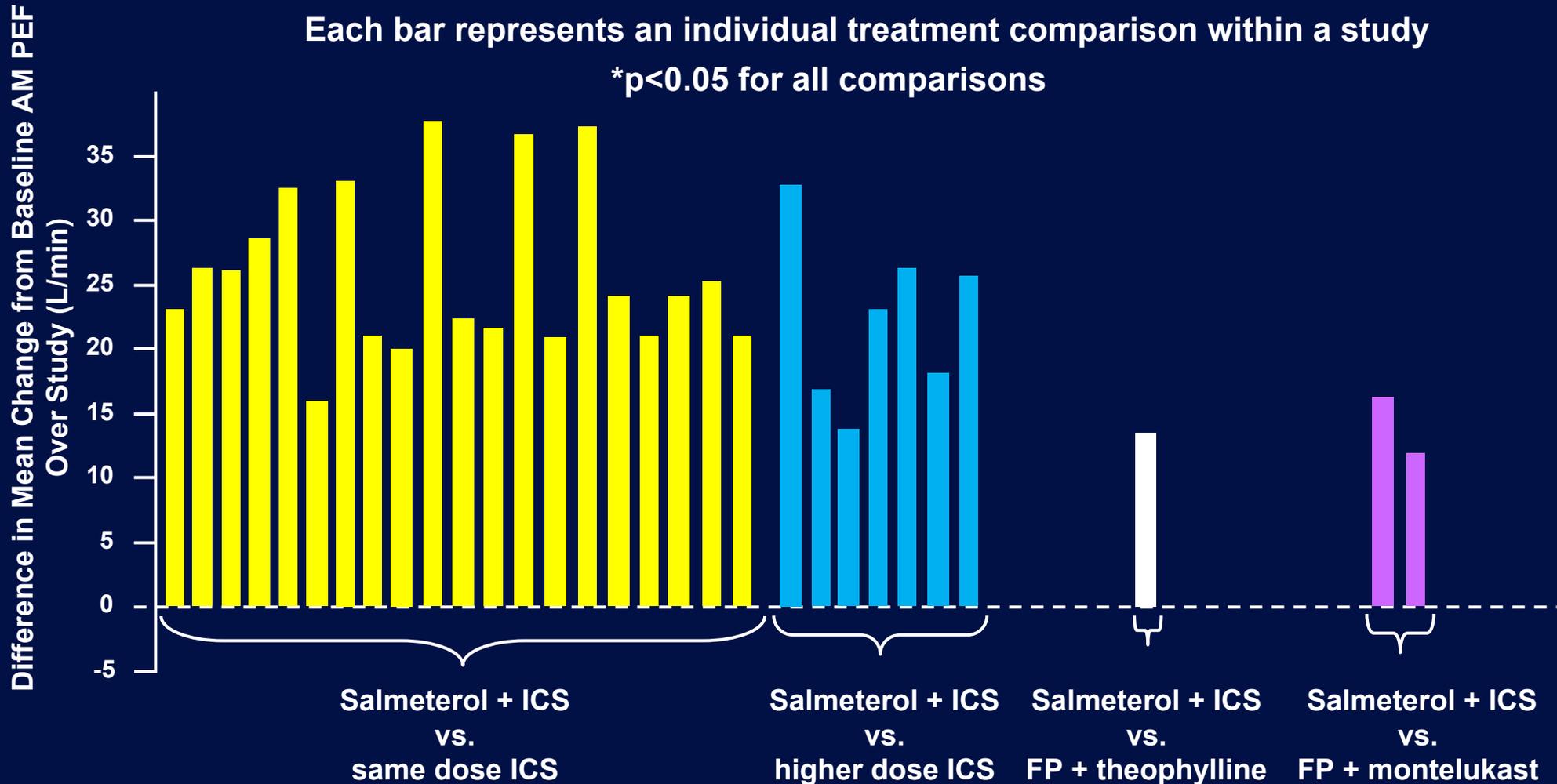


$p < 0.001$ ADVAIR vs. FP, SEREVENT and placebo at all time points

Salmeterol plus ICS Versus Alternative Treatments

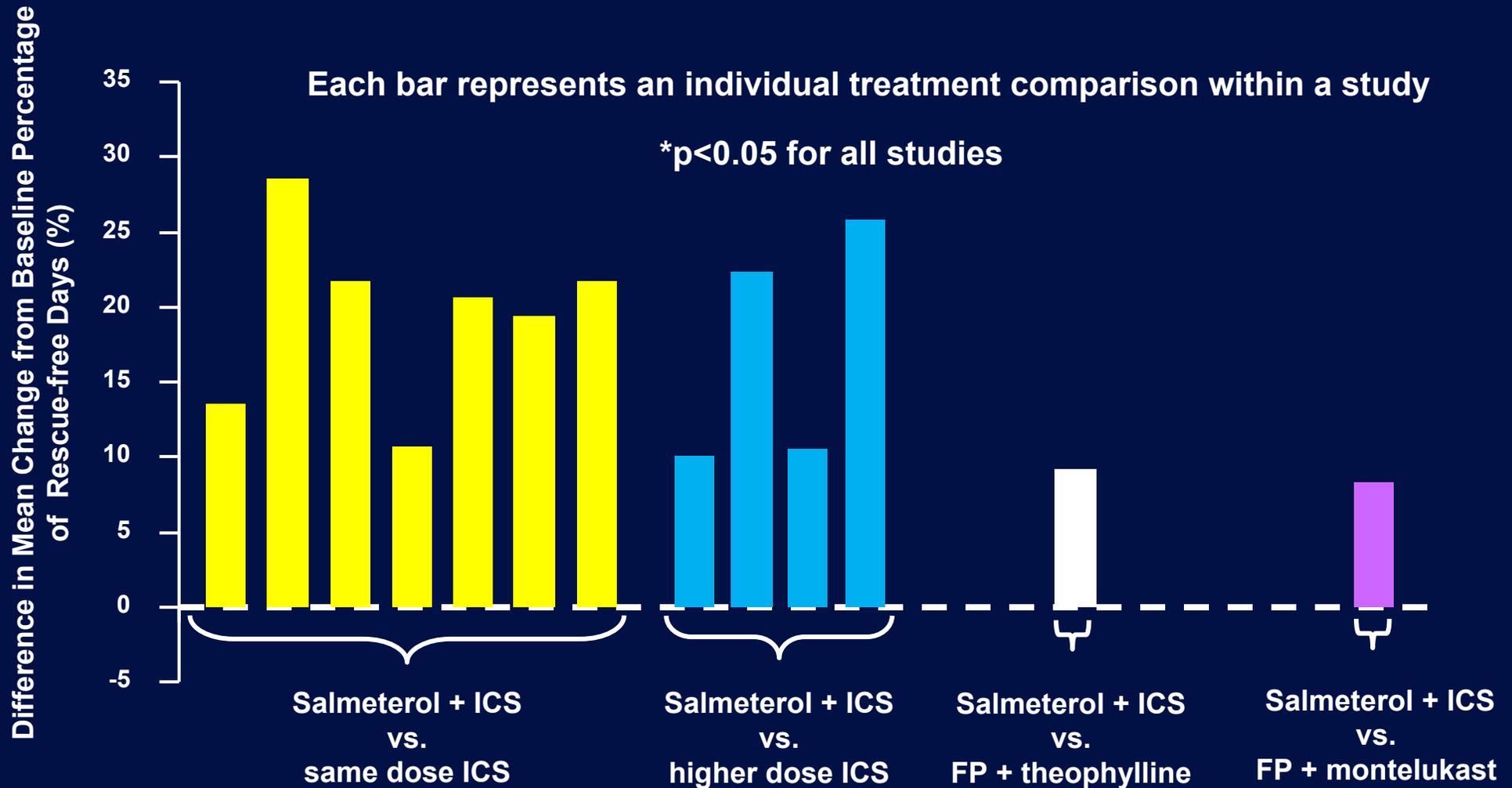
*Significant Improvement in Lung Function**

Each bar represents an individual treatment comparison within a study
 *p<0.05 for all comparisons



Salmeterol plus ICS Versus Alternative Treatments

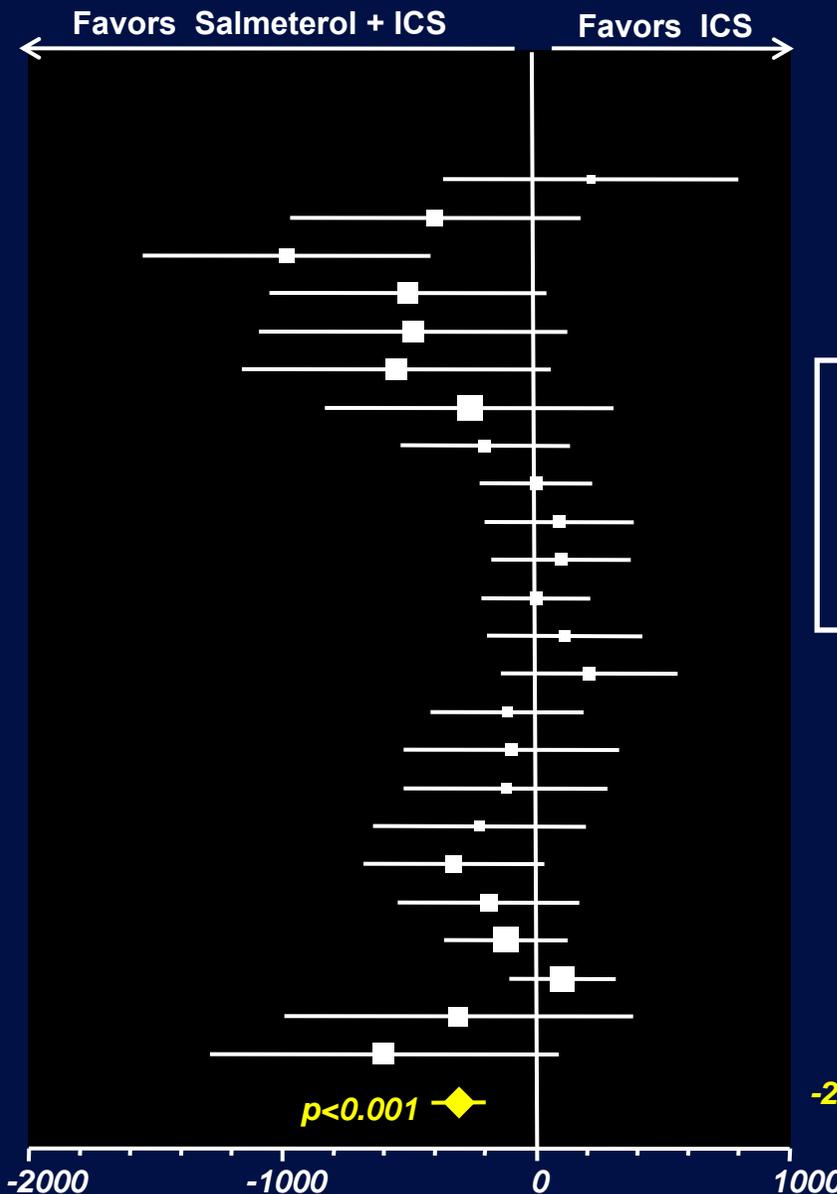
*Significant Improvement in Rescue-free Days**



Salmeterol plus ICS Compared with ICS

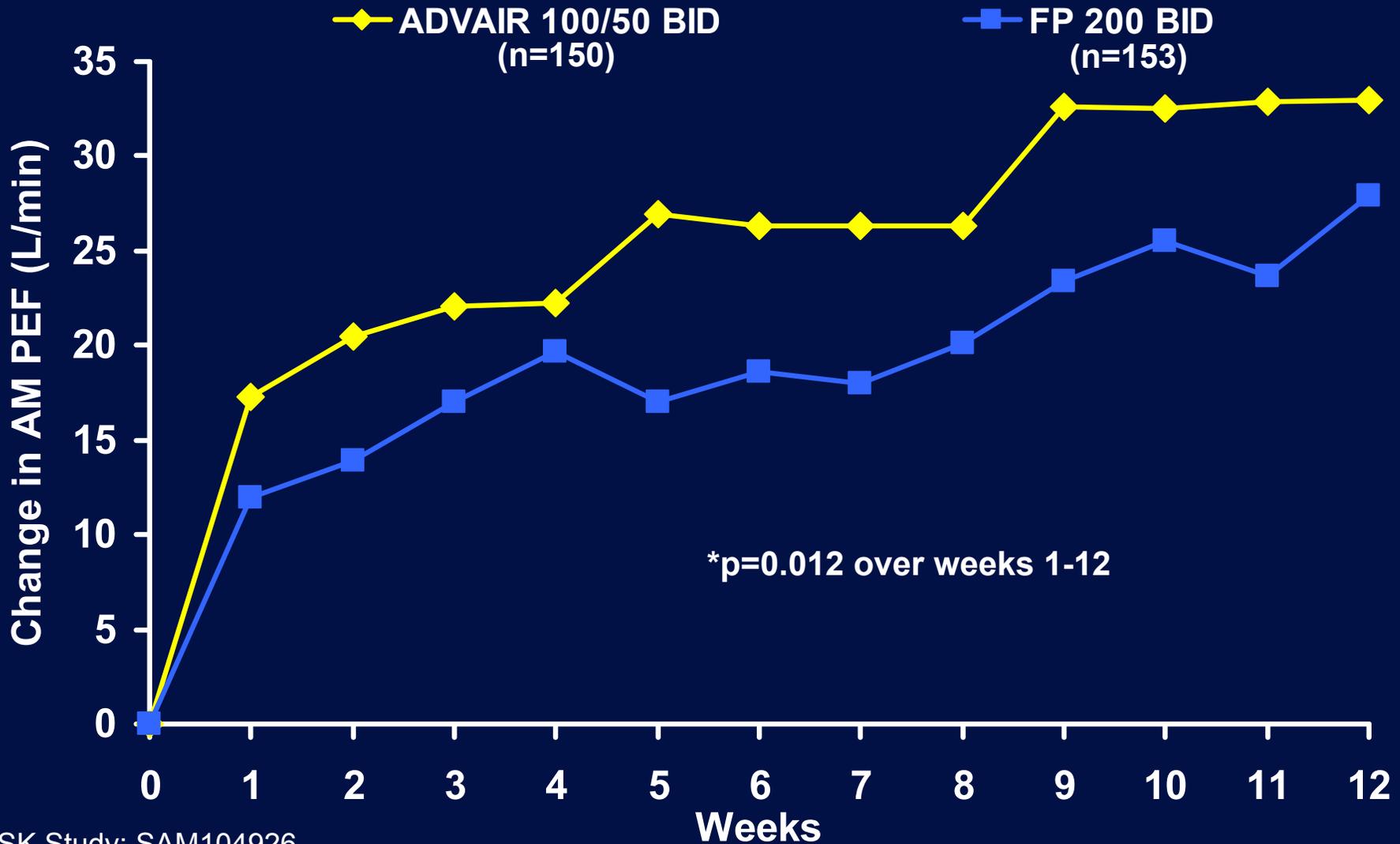
Significant Reduction in Risk of Exacerbations Requiring Oral Corticosteroids

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
Condemi	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
Combined	175	3,541	334	4,008



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
Combined	2147	2.4	5.2	6.1

*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**

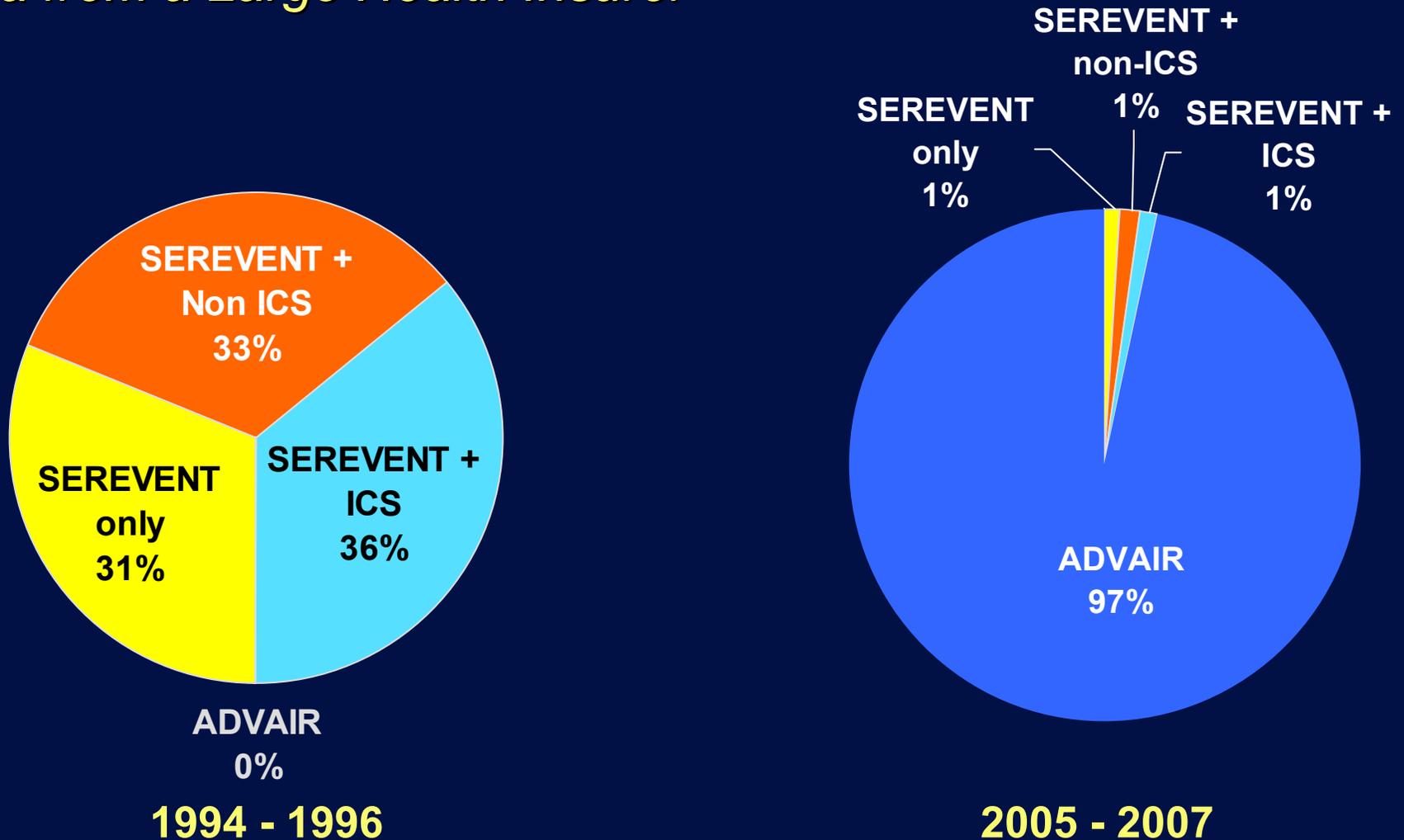
Preferred treatment option in evidence-based asthma treatment guidelines

Presentation Outline

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Change in Salmeterol Use for Asthma Over Time

US Data from a Large Health Insurer

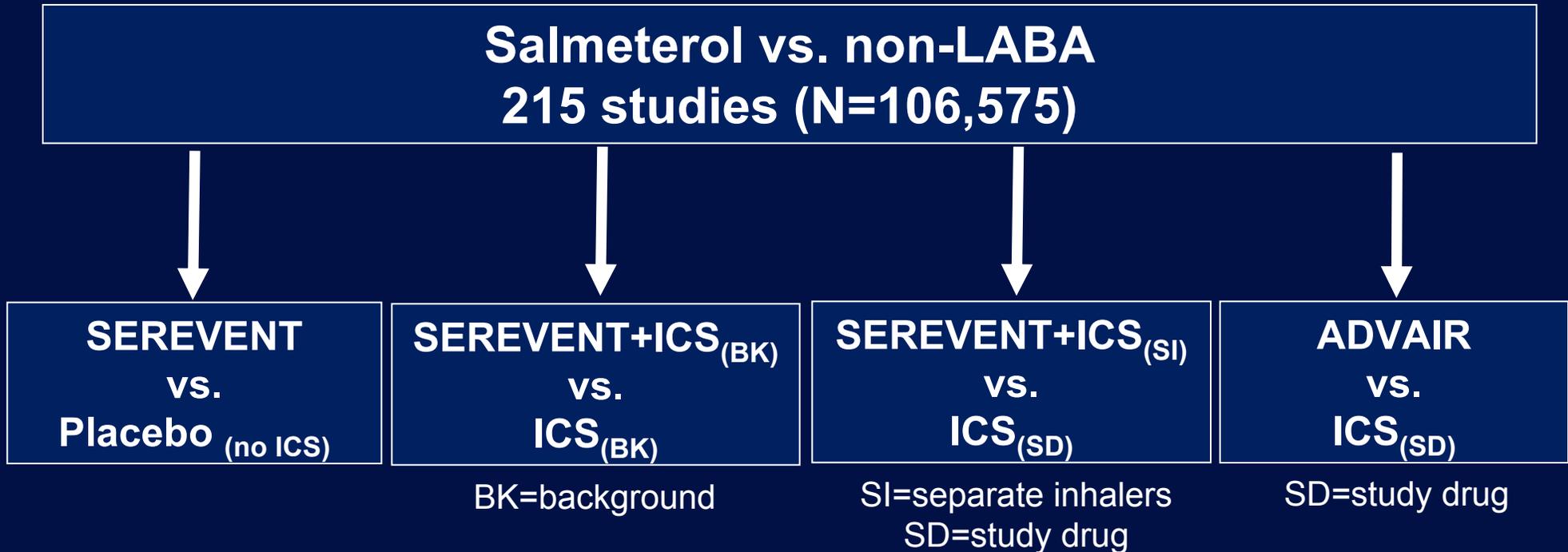


Overview of Safety Data for Salmeterol

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



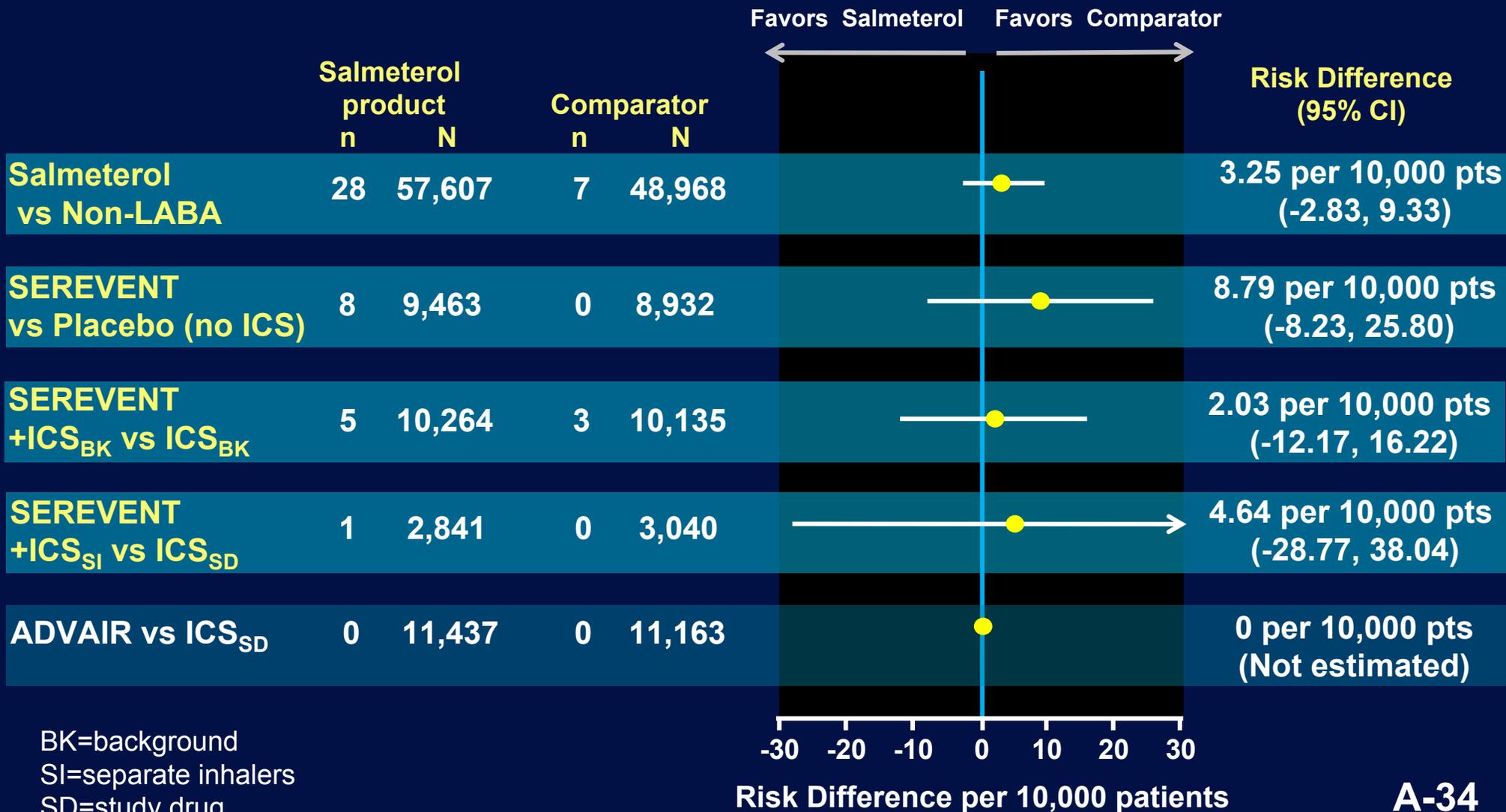
Increasing Confidence in Adherence to ICS

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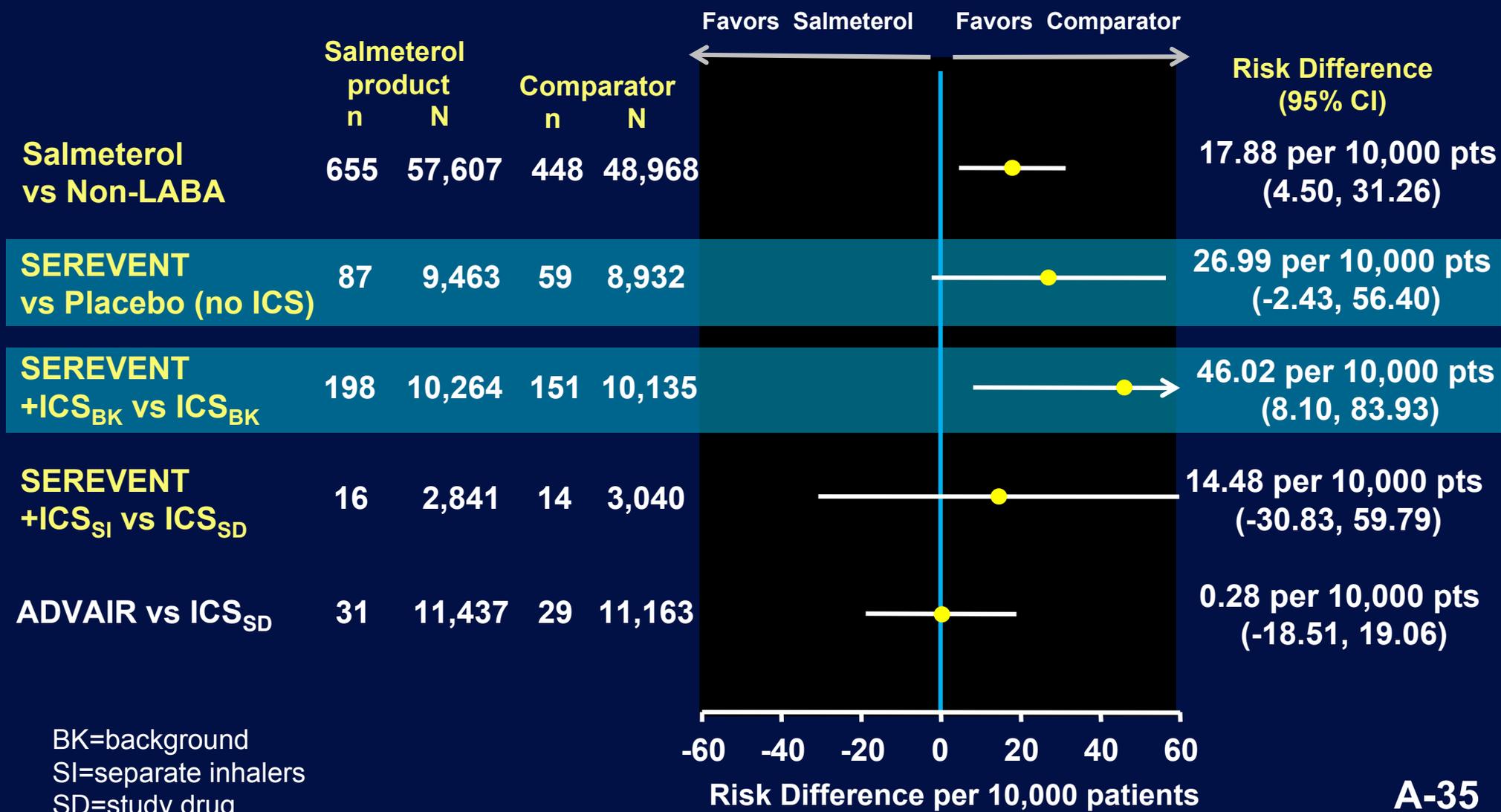
Risk of Asthma-related Death for SEREVENT

Risk Difference in Overall Population



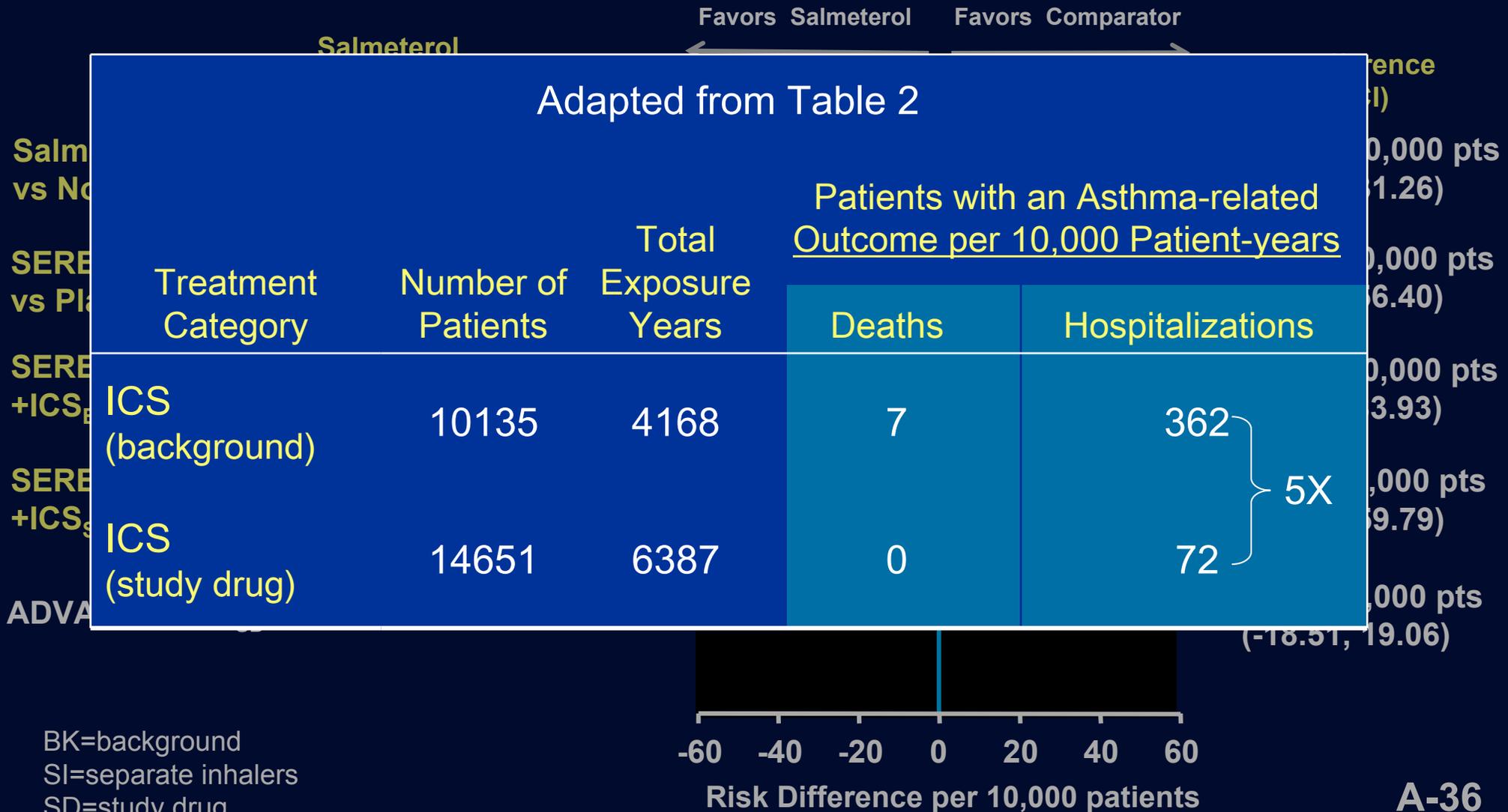
Risk of Asthma-related Hospitalization for SEREVENT

Risk Difference in Overall Population



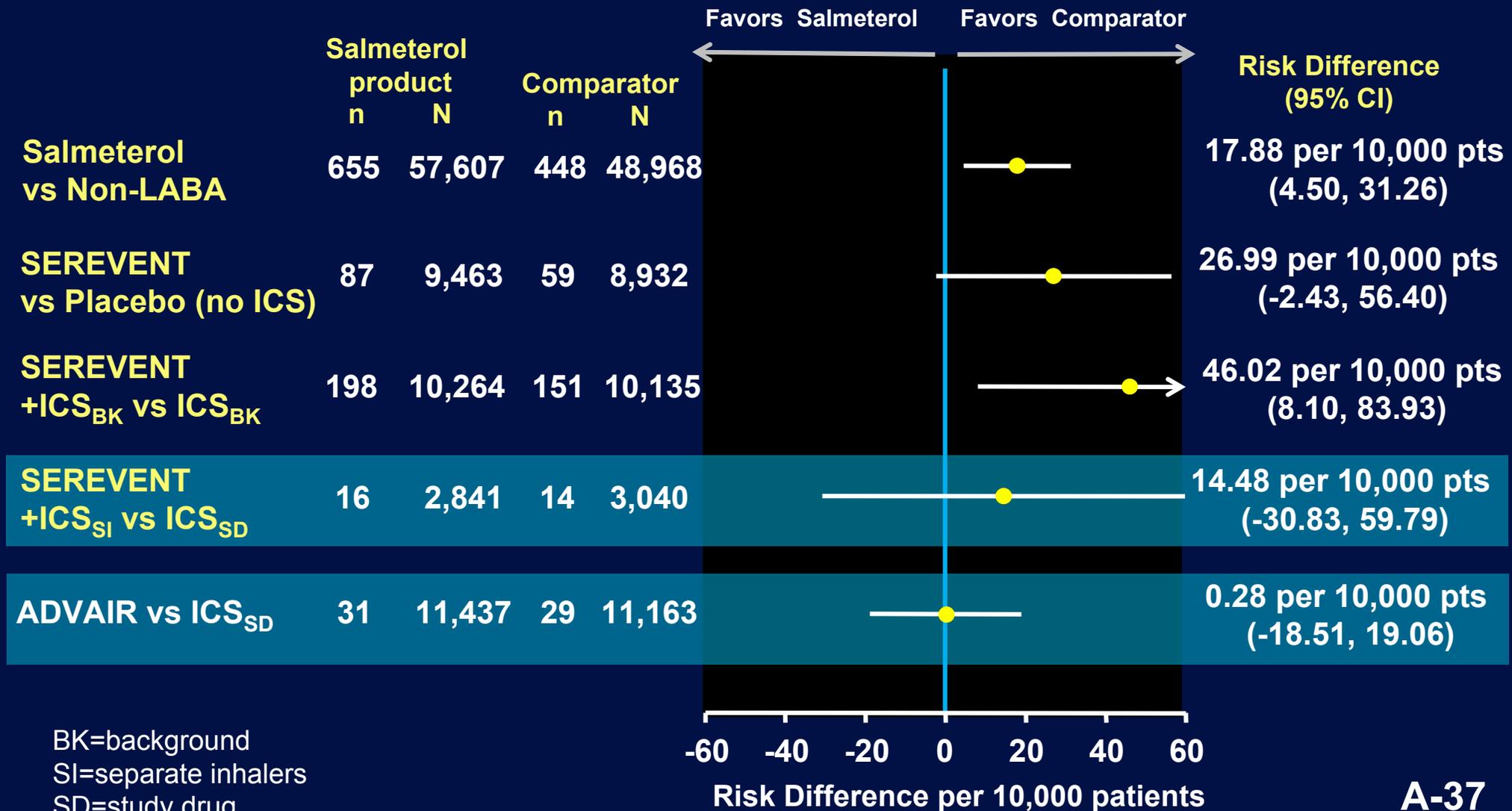
Risk of Asthma-related Hospitalization for SEREVENT

Risk Difference in Overall Population



Risk of Asthma-related Hospitalization for SEREVENT

Risk Difference in Overall Population



Presentation Outline

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

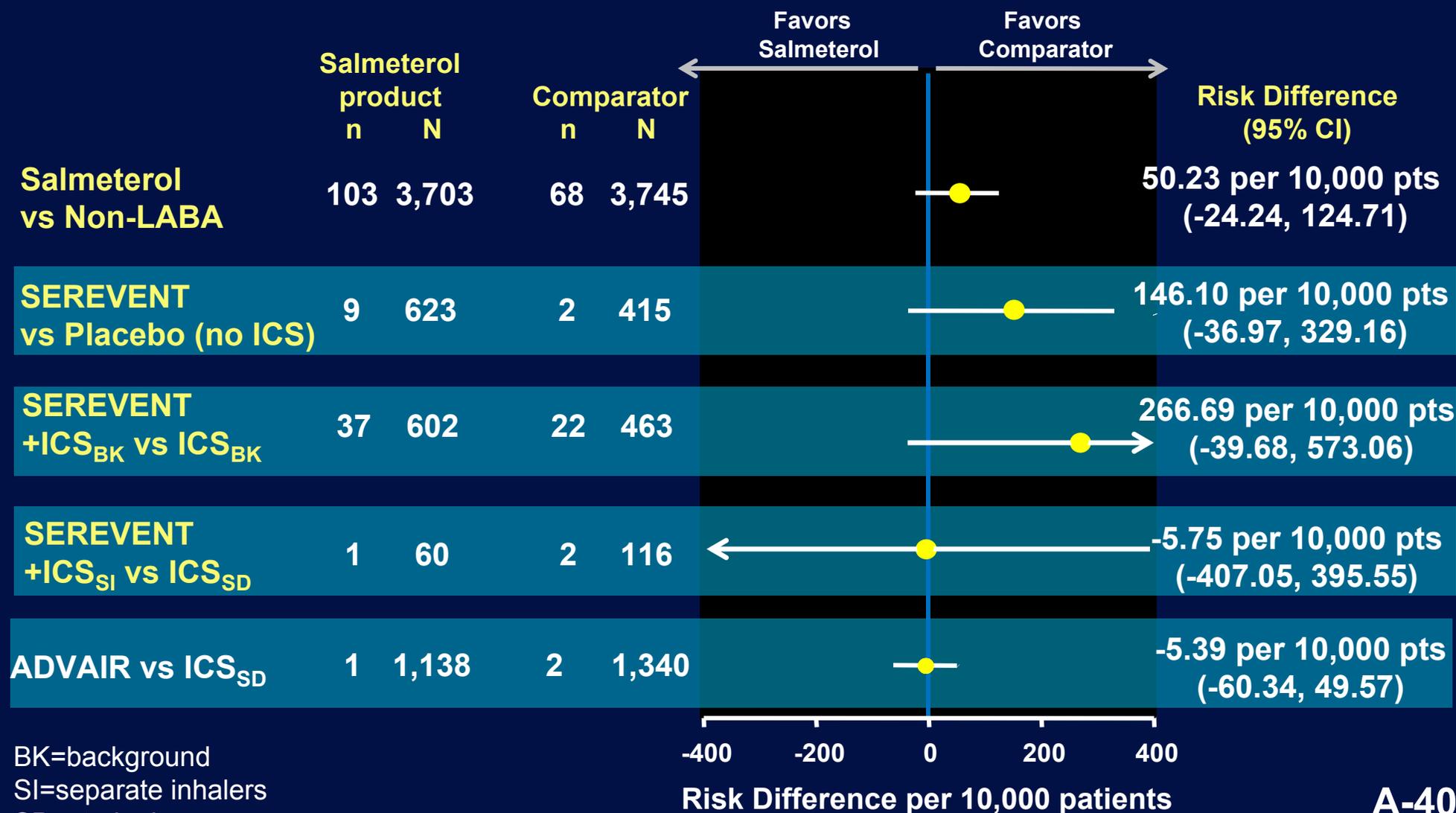
Risk of Serious Outcomes with SEREVENT

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**

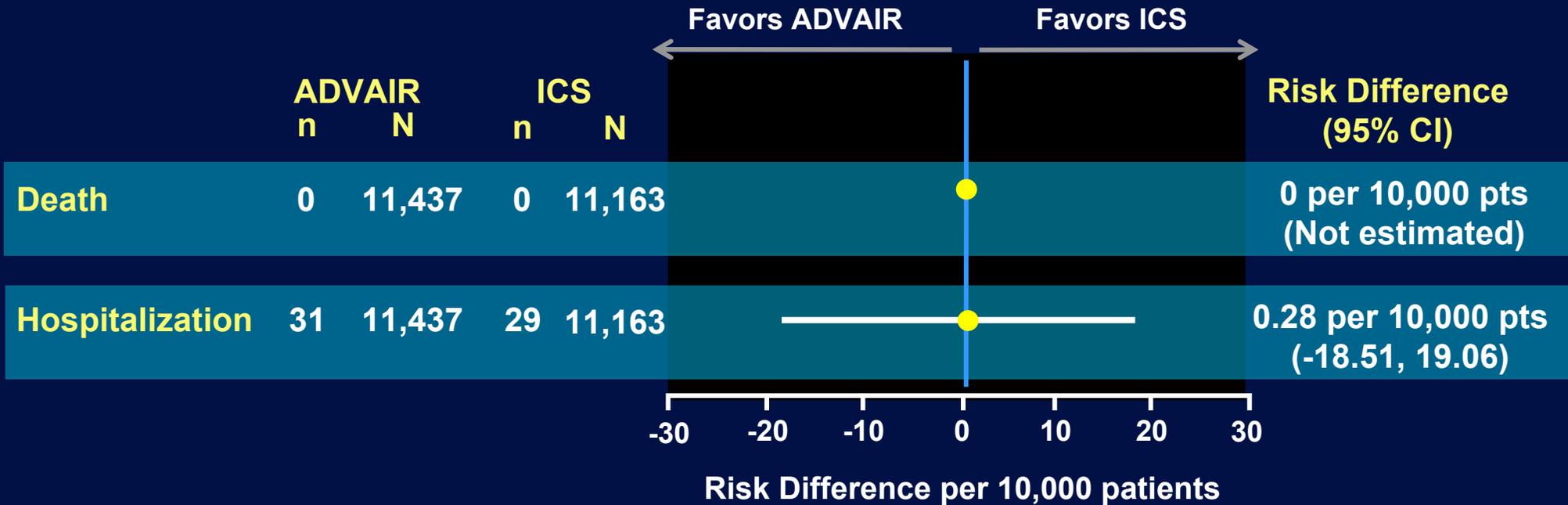
Proposed labeling now requires that SEREVENT should only be used concurrently with ICS

Presentation Outline

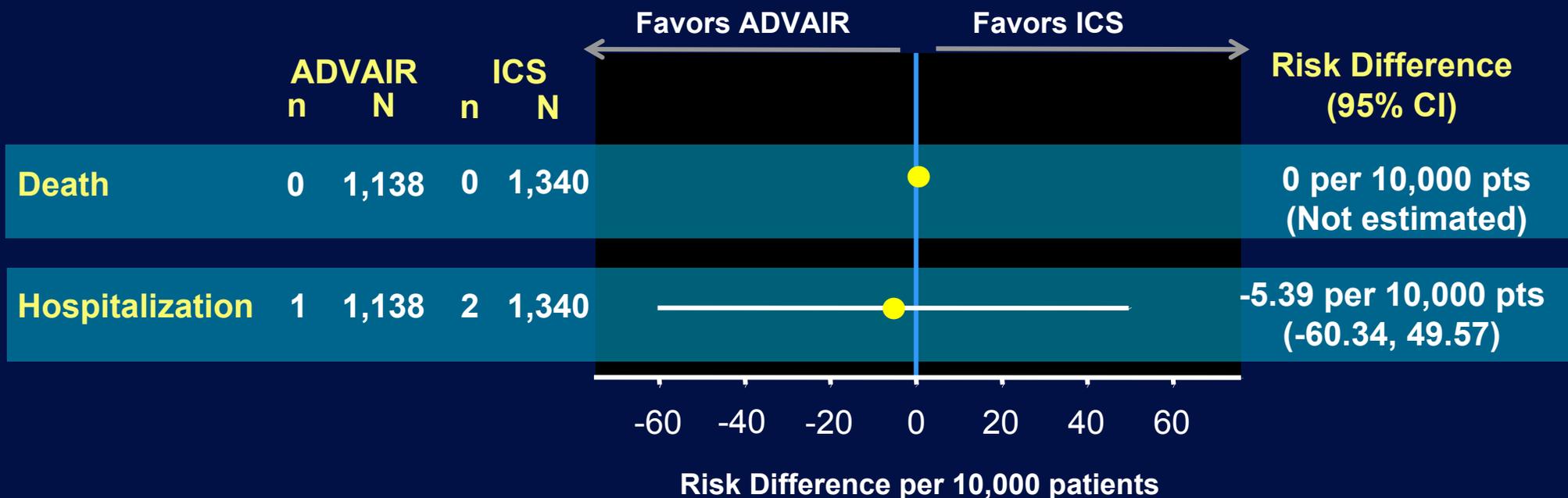
- Efficacy of salmeterol-containing products in persistent asthma
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 - Safety Data with ADVAIR
- Recommendations

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

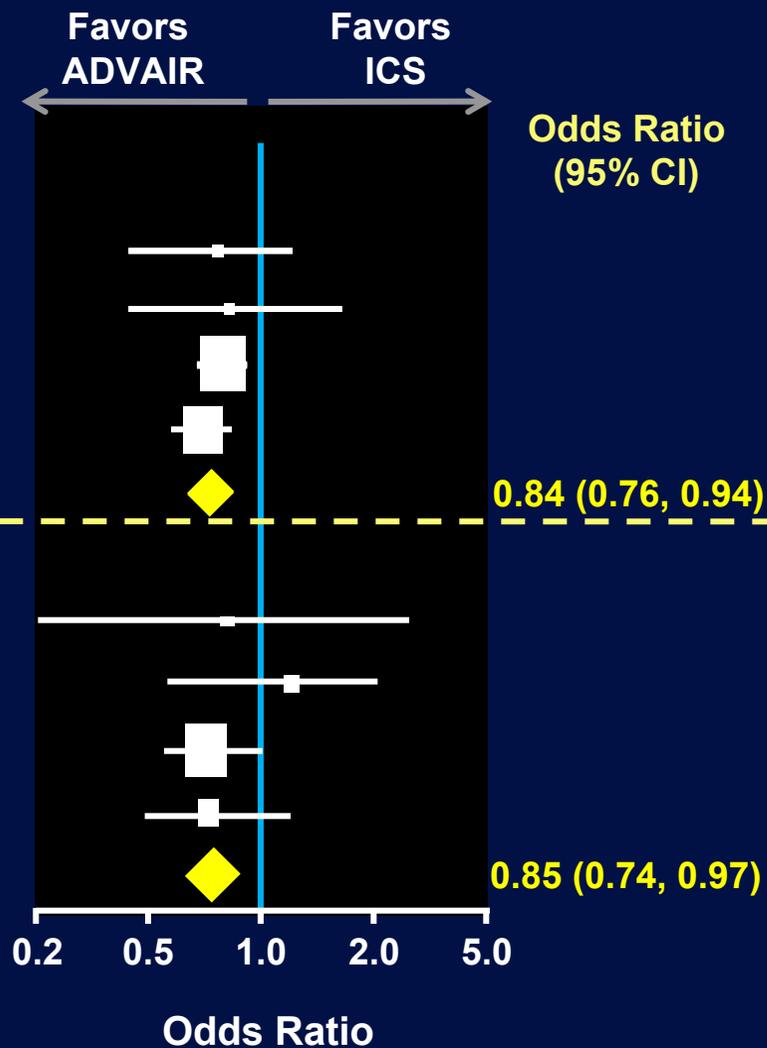
Presentation Outline

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

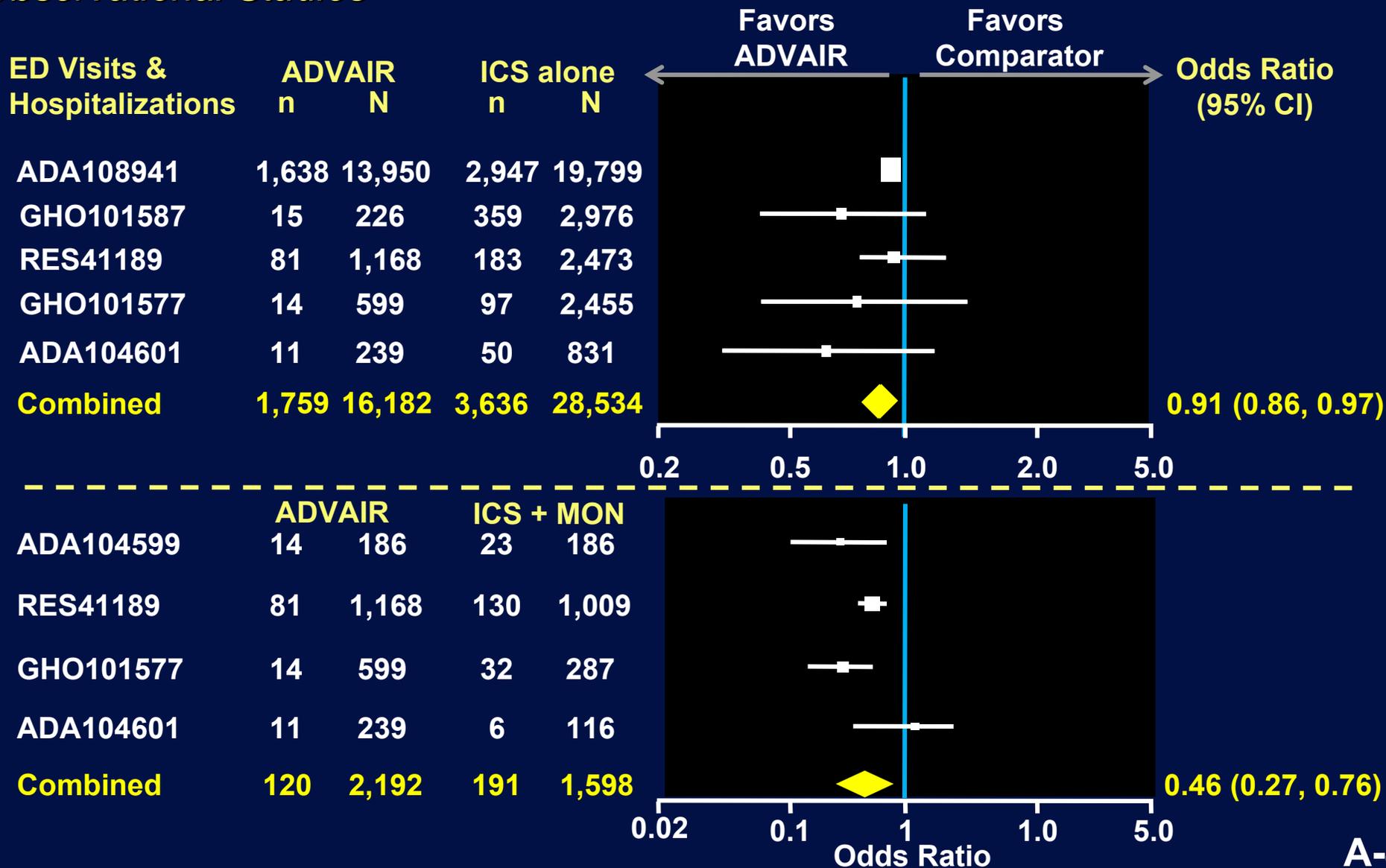
Reduction in Risk of ED and Hospitalizations with ADVAIR in Adults

Observational Studies

	ADVAIR		ICS alone	
	n	N	n	N
ED Visits				
Colice et al	25	414	26	319
Friedman & Yawn	18	1,818	24	1,818
ADA108941	2,786	14,285	1,375	6,072
Stanford et al	1,354	42,466	643	15,804
Combined	4,183	58,983	2,068	24,013
Hospitalizations				
Colice et al	5	414	5	319
Friedman & Yawn	20	1,818	18	1,818
ADA108941	389	14,285	183	6,072
Stanford et al	205	42,466	102	15,804
Combined	619	58,983	308	24,013



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 _{BK}	44	10135	4168	7	362
ICS _{SD}	96	14651	6387	0	72
Sal + ICS _{BK}	51	12881	5059	12	484
Sal + ICS _{SD}	109	21695	8056	1	82
Sal + ICS _{SI}	27	3804	1486	7	155
ADVAIR	86	17891	6571	0	65
SMART Sub-Groups (numbers included in categories above)					
Sal (without ICS)	1	6513	2993	27	184
Pla (without ICS)	1	6463	2930	0	140
Pla + ICS _{BK}	1	6716	3156	10	355
Sal + ICS _{BK}	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