Risk-Benefit Assessment of Long-Acting Beta-Agonist Bronchodilators in the Treatment of Asthma

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Outline

- Introductory comments
- Risks of LABAs in adults and children
- Benefits of LABAs in adults and children
- Risk-benefit assessment of LABAs
- Reflections on FDA's Office of Surveillance and Epidemiology (OSE) assessment
- Concluding remarks

Differing Views on Managing LABA Risk

- Unanimous recommendations from OSE
  - Withdraw asthma indication for all LABAs for patients <18 years of age
  - Remove asthma indication and contraindicate use of single ingredient LABAs for all ages
- DPAP's position
  - Products containing LABAs should continue to be marketed
  - Safety risk should be managed through labeling

Asthma

- Asthma is a chronic inflammatory disease of the airways characterized by varying and recurring symptoms of shortness of breath, chest tightness, wheezing, and cough; airflow obstruction; bronchial hyperresponsiveness; and underlying inflammation
- Classified into four categories based on level of symptoms, nighttime awakening from symptoms, short-acting beta-agonist bronchodilator use for symptom control, interference with normal activity, and lung function
  - Intermittent asthma
  - Mild persistent asthma
  - Moderate persistent asthma
  - Severe persistent asthma

NAEPP ERP 3 2007; GINA 2007

Medications for Treating Asthma

- Quick-relief medications
  - Short-acting beta-agonist bronchodilators (SABA). e.g., inhaled albuterol
  - Systemic corticosteroids
- Long-term control medications
  - Cromones
  - Immunomodulators - omalizumab
  - Inhaled corticosteroids (ICSs)
  - Leukotriene modifiers
  - Long-acting beta-agonist bronchodilators (LABAs), e.g., inhaled salmeterol, inhaled formoterol
  - Methylxanthines
  - Systemic corticosteroids

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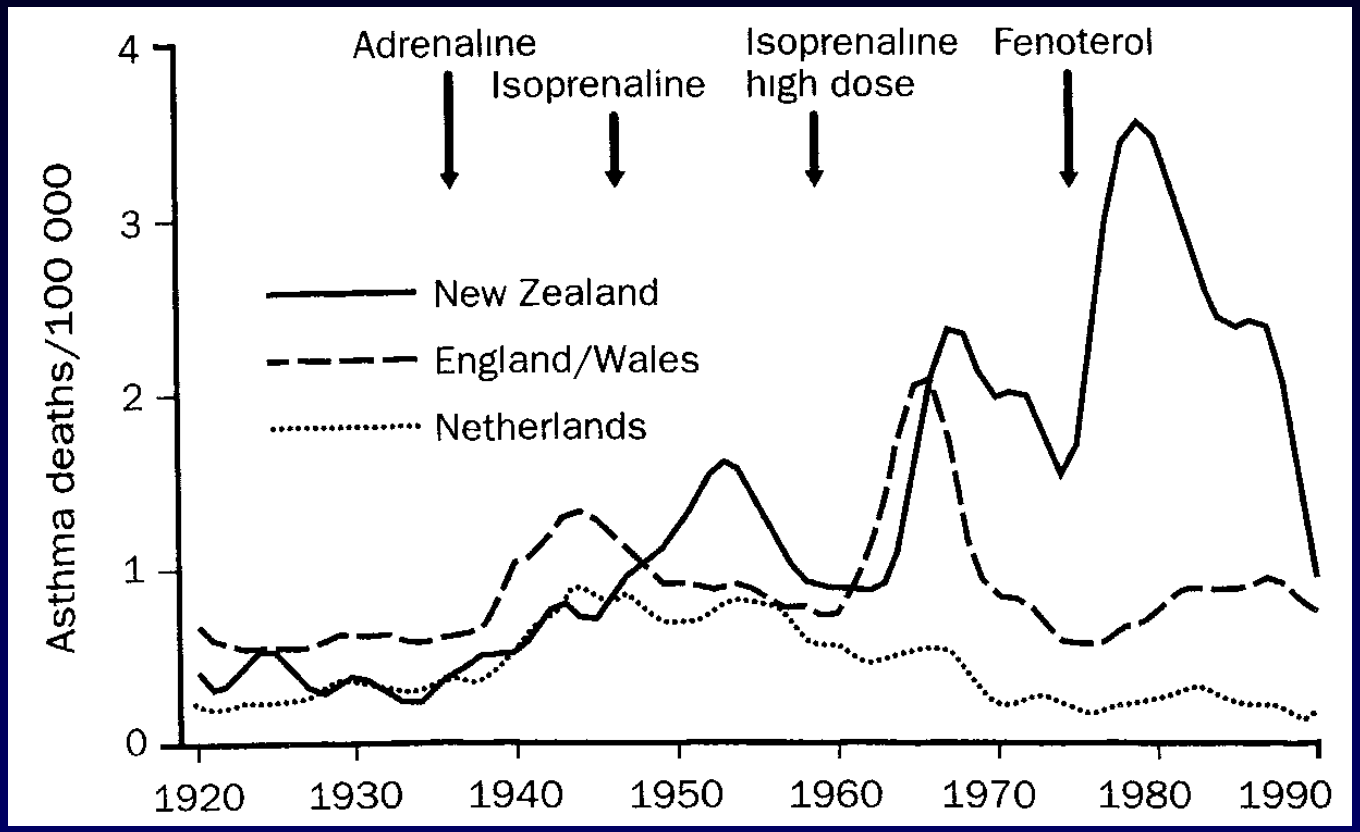
Asthma-Related Deaths with Short-Acting Beta-Agonists



1940s-1950s: Epinephrine or Isoprotenol
1950s: Isoprotenol
1960s: Isoprotenol
1970s: Fenoterol

J Allergy 1948; 19:429-440; Respir Dis 1972; 105:1837-1922
N Eng J Med 1949; 240:45-51; Lancet 1980; 1:883-892
J Allrgy 1969; 43:101-113 Thorax 1991; 46:105-111

Lancet 1995; 345:2-3

Possible Mechanism of Asthma-Related Death with Beta-Agonists

- Contributing factors
  - Use of high dose of beta-agonist drugs
  - Use of less selective beta-agonist drugs
- Hypothesized mechanisms
  - Reduction of protection against bronchoconstrictor stimuli
  - Masking symptoms of deteriorating asthma
- Genetic studies are preliminary and have not produced conclusive results
- Mechanisms by which inhaled SABAs and LABAs cause asthma-related death are not known, but the mechanism are likely to be similar, as the basic actions of both medication classes are the same

Risk of Inhaled LABAs in Adults

- Asthma-related death and serious asthma exacerbation
- Other effects
  - Cardiovascular effects, such as increased heart rate and increased blood pressure
  - Metabolic effects, such as increased blood glucose and decreased serum potassium
  - Muscle tremor
  - CNS excitability
  - Irritation of upper and lower airway

Salmeterol

- Safety finding for salmeterol came from two large phase 4 post-marketing studies conducted by GSK
  - SNS study (Brit Med J 1993; 306:1034-7)
  - SMART study (Chest 2006; 129:15-26)

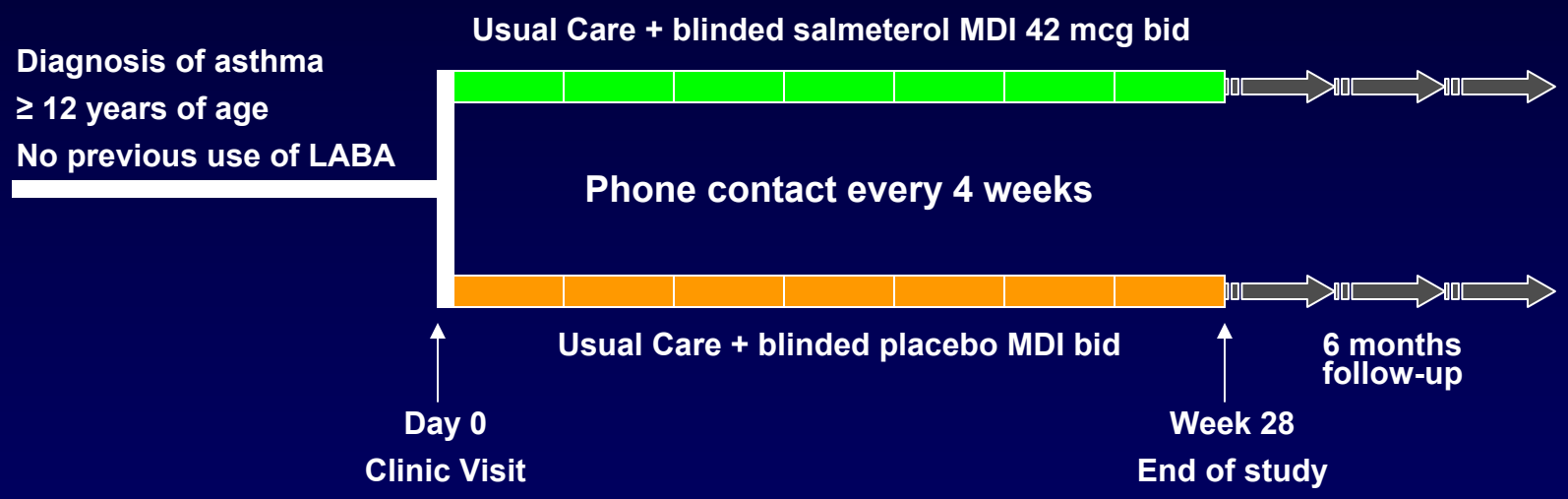
SNS Study

- Randomized, double-blind, active-controlled (salbutamol), parallel group, 16-week study in UK
- Clinic visits at 4, 8, and 16 weeks
- Outcome measures included serious adverse events and reasons for withdrawal

Outcome	Salmeterol (n=16,787)	Salbutamol (n=8,393)	Relative Risk	P-value
Respiratory and asthma related **deaths**	12 (0.07%)	2 (0.02%)	3	0.105
Respiratory and asthma related **hospitalizations**	193 (1.2%)	102 (1.2%)	0.95	0.65
Other respiratory and asthma related **serious events**	198 (1.2%)	100 (1.2%)	0.99	0.94
Respiratory and asthma related **withdrawals**	488 (2.9%)	318 (3.8%)	0.77	0.0002

BMJ 1993; 306:1034-7

SMART Study Design



www.fda.gov/ohrms/dockets/ac/cder05.html#PulmonaryAllergy
Chest 2006; 129:15-26

SMART Study Design

- Primary endpoint
  - Combined respiratory-related deaths and respiratory-related life threatening experiences (intubation and mechanical ventilation)
- Powered to rule out
  - 1.4 times increase in combined respiratory-related deaths and respiratory-related life-threatening experiences (intubation and mechanical ventilation)
  - 3 times increase in asthma-related deaths
- Sample size
  - Initially in 1996 planned to have 30,000 patients
  - Increased in 1999 to 60,000 patients
  - Terminated in 2003 with approximately 26,000 patients

www.fda.gov/ohrms/dockets/ac/cder05.html#PulmonaryAllergy

SMART Study Results

	Serevent MDI (n=13,176)	Placebo (n=13,179)	Relative Risk (95% CI)
Primary Endpoint: Respiratory-related deaths or life-threatening experiences			
Total	50 (<1%)	36 (<1%)	1.40 (0.91, 2.14)
Caucasians	29 (<1%)	28 (<1%)	1.05 (0.62, 1.76)
African Americans	20 (<1%)	5 (<1%)	4.10 (1.54, 10.90)
Secondary Endpoint: Asthma-related deaths			
Total	13 (<1%)	3 (<1%)	4.37 (1.25, 15.34)
Caucasians	6 (<1%)	1 (<1%)	5.82 (0.70, 48.37)
African Americans	7 (<1%)	1 (<1%)	7.26 (0.89, 58.94)

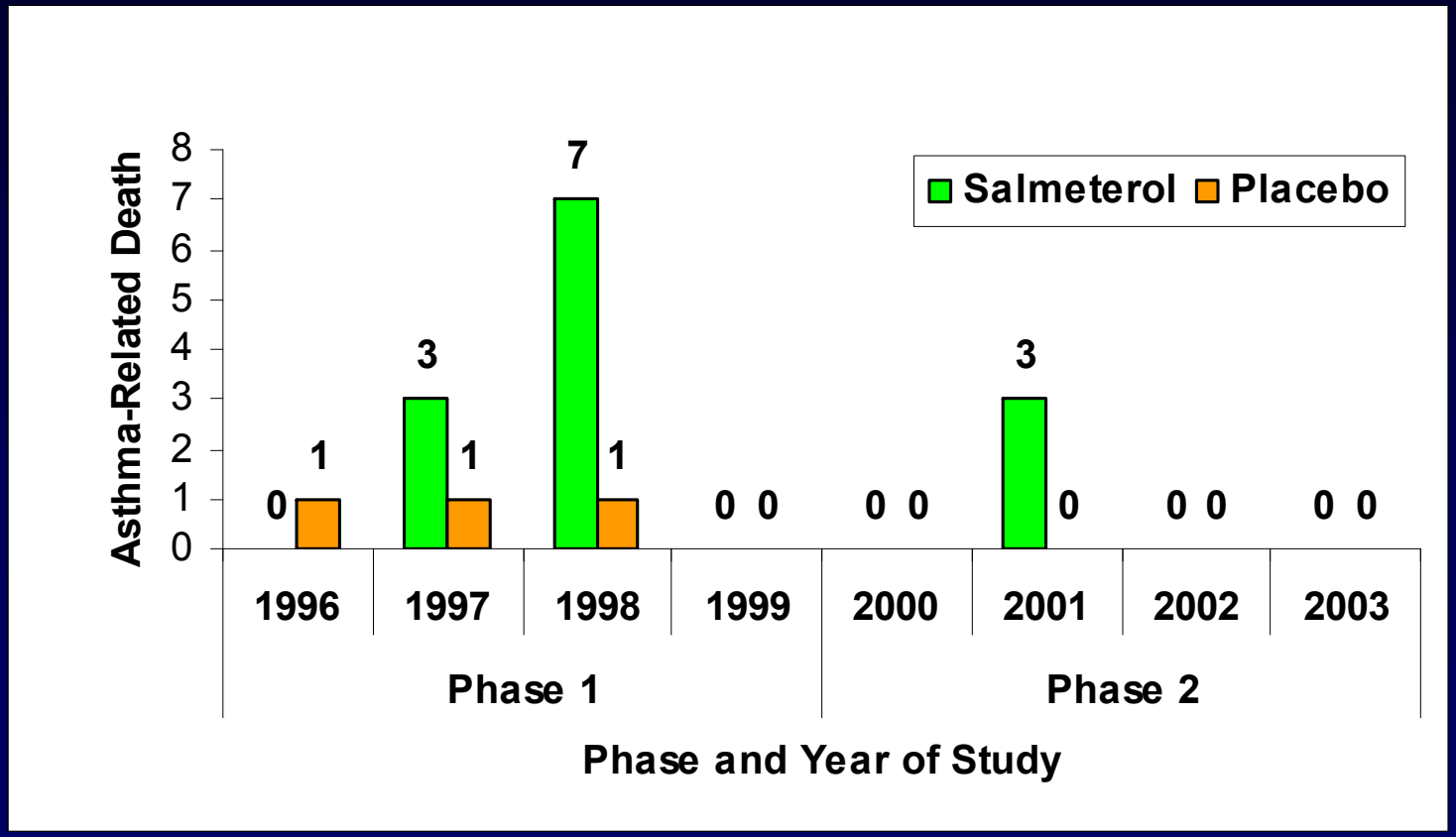
www.fda.gov/ohrms/dockets/ac/cder05.html#PulmonaryAllergy

SMART Study Results
- ICS Use at Baseline

	Inhaled Corticosteroids at baseline			No Inhaled Corticosteroids at baseline		
	Serevent	Placebo	Relative Risk	Serevent	Placebo	Relative Risk
Number of patients						
Total	6127	6138		7049	7041	
Caucasians	4586	4637		4695	4724	
African Americans	906	875		1460	1444	
Asthma-related deaths						
Total	4	3	1.35 (0.30, 6.04)	9	0	
Caucasians	1	1	0.96 (0.06, 15.35)	5	0	
African Americans	3	1	3.12 (0.33, 29.92)	4	0	

www.fda.gov/ohrms/dockets/ac/cder05.html#PulmonaryAllergy

SMART Study Results
- Phases of the Study



Chest 2006; 129:15-26

Formoterol

- Safety signal for formoterol was seen in relatively small studies conducted by Novartis
  - Two phase 3 placebo- and active-controlled 12-week studies in patients 12 years of age and older
  - One phase 3 placebo-controlled 1-year study in patients 5-12 years of age
  - One phase 4 placebo-controlled 16-week study in patients 12 years of age and older

www.fda.gov/ohrms/dockets/ac/cder05.html#PulmonaryAllergy
Chest 2003; 124:70-74
Chest 2006; 129:27-38

Formoterol Clinical Studies

	Number and Frequency of Serious Asthma Exacerbations *			
	Placebo	Albuterol 180 mcg BID	Formoterol 12 mcg BID	Formoterol 24 mcg BID
12-wk study in patients 12 years and older (Phase 3 study 040)	0/136 (0%)	2/134 (1.5%)	0/136 (0%)	4/135 † (3%)
12-wk study in patients 12 years and older (Phase 3 study 041)	2/141 (1.4%)	0/138 (0%)	1/139 (0.7%)	5/136 ‡ (3.7%)
1-yr study in patients 5-12 year of age(Phase 3 study 049)	0/176 (0%)	NA	8/171 (4.7%)	11/171 (6.4%)
16-wk study in patients 12 years and older(Phase 4 study)	1/514 (0.2%)	NA	3/527 § (0.6%)	2/527 § (0.4%)

* Life-threatening experience, hospitalization, prolongation of hospitalization, persistent disability, or death

† 1 patient required intubation

‡ 2 patients had respiratory arrest, 1 of the patients died

§ 1 patient required intubation

www.fda.gov/ohrms/dockets/ac/cder05.html#PulmonaryAllergy
www.fda.gov/cder/drug/infopage/LABA/default.htm

Symbicort Phase 3 NDA studies

- Efficacy assessed in two 12-week US studies involving 1076 patients 12 years of age and older
  - Study 1: Moderate to severe asthma, FEV1 mean 68.1%
  - Study 2: Mild to moderate asthma, FEV1 mean 71.3%
- Co-primary efficacy endpoints
  - 12-hour-average post-dose FEV1 at week 2
  - Pre-dose FEV1 averaged over the course of the study
- Patients who satisfied a pre-defined asthma worsening criterion were required to be withdrawn

Product Label

Number (Percentage) of Subjects Meeting Asthma Withdrawal Criteria

Study 1	Symb n = 124	Bud n = 109	For n = 123	Bud + For n = 115	Pbo n = 115
Total	37 (29.8)	48 (44.0)	68 (55.3)	24 (20.9)	84 (67.2)
-- Decrease in FEV1	4 (3.2)	7 (6.4)	15 (12.2)	8 (7.0)	14 (11.2)
-- Rescue medication use	2 (1.6)	3 (2.8)	3 (2.4)	0 (0.0)	7 (5.6)
-- Decrease in AM PEF	2 (1.6)	5 (4.6)	17 (13.8)	5 (4.3)	15 (12.0)
-- Nighttime awakening	24 (19.4)	29 (26.6)	32 (26.0)	11 (9.6)	49 (39.2)
-- Clinical exacerbation	7 (5.6)	5 (4.6)	17 (13.8)	6 (5.2)	16 (12.8)

Study 2	Symb n = 123	Bud n = 121	For n = 114		Pbo n = 122
Total	23 (18.7)	26 (21.5)	48 (42.1)		69 (56.6)
-- Decrease in FEV1	3 (2.4)	3 (2.5)	11 (9.6)		9 (7.4)
-- Rescue medication use	1 (0.8)	3 (2.5)	1 (0.9)		3 (2.5)
-- Decrease in AM PEF	3 (2.4)	1 (0.8)	8 (7.0)		14 (11.5)
-- Nighttime awakening	17 (13.8)	20 (16.5)	31 (27.2)		52 (42.6)
-- Clinical exacerbation	1 (0.8)	3 (2.5)	5 (4.4)		20 (16.4)

Product Label

Risk of Inhaled LABAs in Children

- Ages 12 years and older
  - Same as older children and adults because the safety studies were conducted in this age cohort
- Ages 4 to 11 years
  - No large safety study
  - Phase 3 studies did not show asthma-related death
- Ages below 4 years
  - Not relevant because inhaled LABAs are not approved in this age group

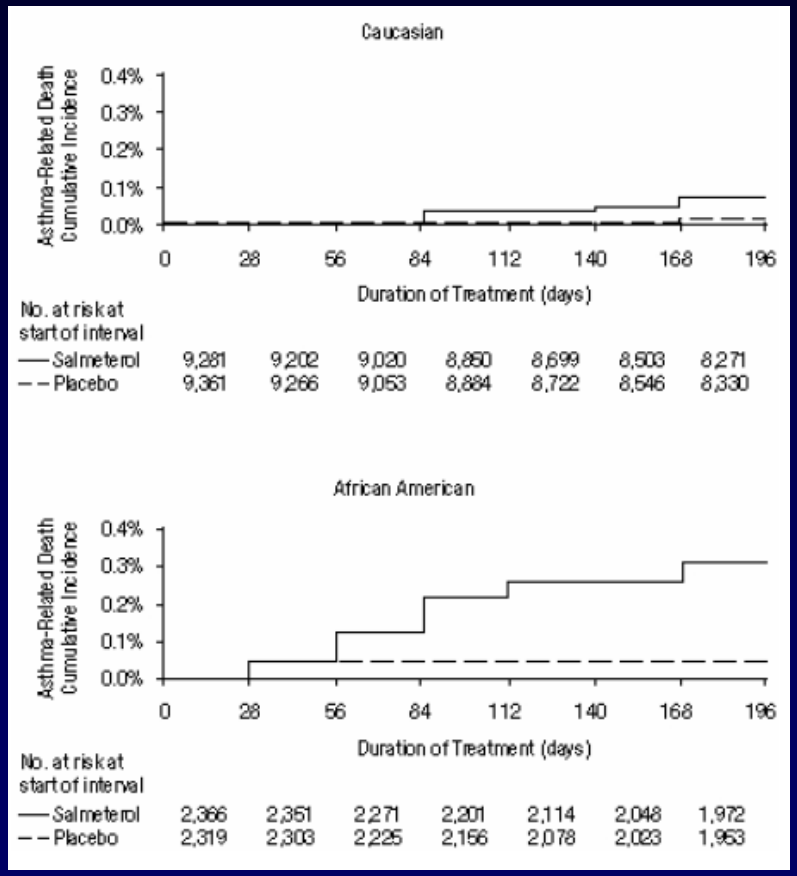
Risk of Inhaled LABAs in Children

- Available data do not suggest that safety risk with LABAs is higher in children 4 years and older compared to adults
- For children 4 years of age and older compared to adults
  - The pathophysiology of asthma is the same
  - The beta-receptors, target of LABAs, function similarly
  - Response to LABAs is expected to be the same
- Products containing inhaled LABAs carry the same labeling warning irrespective of age

Risk Interpretation
- SMART Study

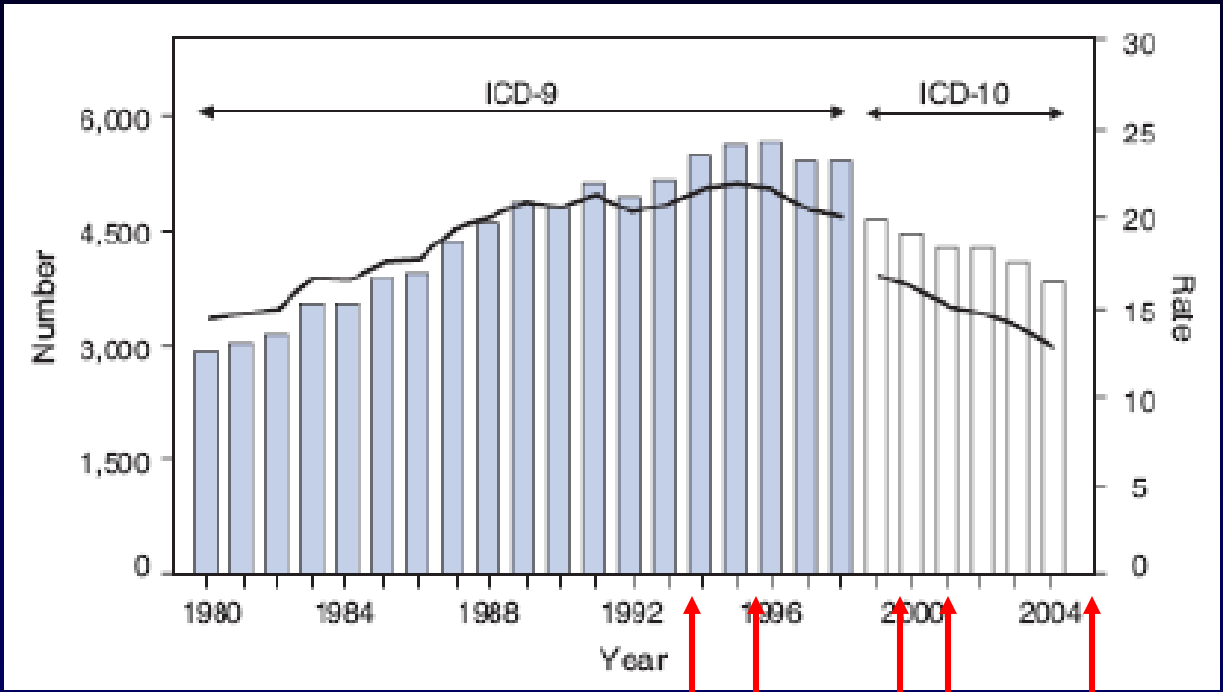
- Estimates of excess asthma-related deaths per 10,000 patients treated for 28 weeks (95% Confidence Interval)
  - Total population: 8 (3, 13)
  - Caucasian: 6 (1, 10)
  - African American: 27 (8, 46)

- "1 death was attributable to salmeterol for every 700 patient-years of treatment" (NEJM 2005; 353:2637)



Product Label

United States Asthma Mortality



1994 – Serevent Inhalation Aerosol

1996 – Serevent Diskus

2000 – Advair Diskus

2001 – Foradil Aerolizer

2006 – Advair HFA Inhalation Aerosol

2006 – Symbicort

MMWR 2007; 56:18-54

Benefit of Inhaled LABAs in Adults

- Bronchodilation resulting in improved pulmonary function, and decreased need for rescue short-acting bronchodilator use for asthma exacerbations
- Longer duration (12 hours) of bronchodilation compared to SABAs
- Labeled indications
  - Maintenance treatment of asthma and in the prevention of bronchospasm, including symptoms of nocturnal asthma, and for the prevention of exercise-induced bronchospasm

Benefit of Inhaled LABAs in Children

- Ages 12 years and older
  - Same as older children and adults because the efficacy studies were conducted in this age cohort
- Ages 4 to 11 years
  - Specific studies showed efficacy
- Ages below 4 years
  - Not relevant because inhaled LABAs are not approved in this age group

Benefit of Inhaled LABAs in Children

- Available data do not suggest that benefit with LABAs is less in children 4 years and older compared to adults
- For children 4 years of age and older compared to adults
  - The pathophysiology of asthma is the same
  - The beta-receptors, target of LABAs, function similarly
  - Response to LABAs are expected to be the same
- Products containing inhaled LABAs carry the same indication and usage labeling irrespective of age

Benefits of Inhaled LABAs

- LABAs are clearly effective in asthma in terms of improvements in FEV1, PEFR, rescue albuterol use, symptom control, nocturnal awakenings, etc.
  - NDA Studies (Serevent, Advair, Foradil, Symbicort): Product Labels
  - FACET (formoterol and budesonide): NEJM 1997;337:1405-11
  - SLIC (salmeterol and triamcinolone): JAMA 2001:285:2594
  - OPTIMA (formoterol and budesonide): AJRCCM 2001:164:1392
  - GOAL (salmeterol and fluticasone): AJRCCM 2004;170:836
  - STAY (formoterol and budesonide): AJRCCM 2005;171:129
  - GOAL follow-on (salmeterol and fluticasone): JACI 2006:117:563

GOAL Study Design

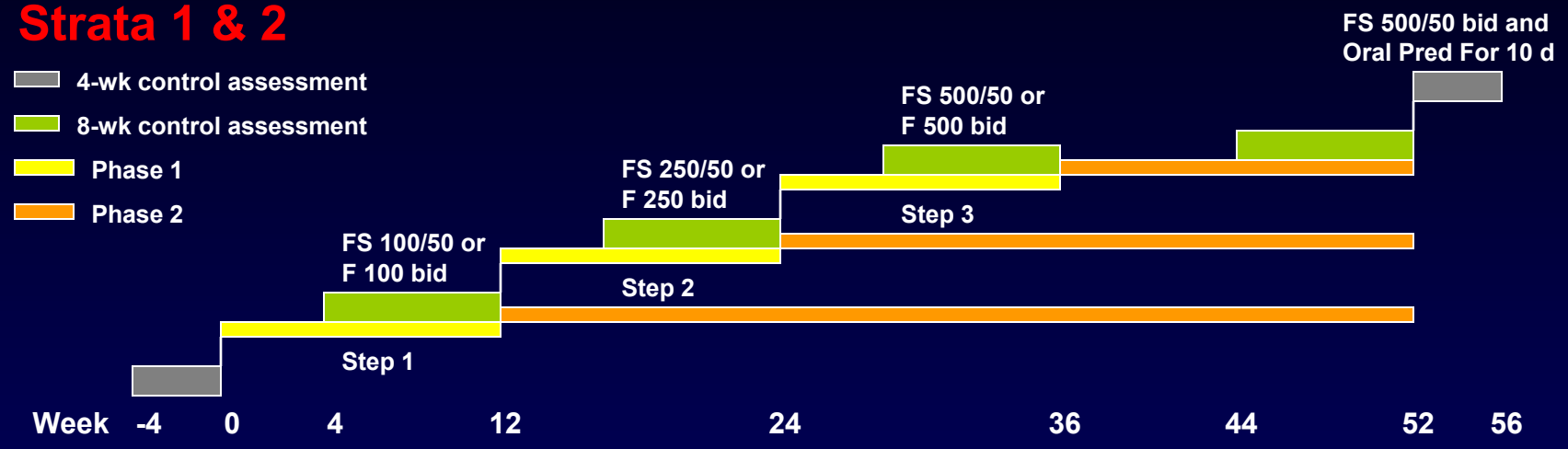
- One-year, double-blind, parallel-group, multinational study in 3416 patients, 12-80 years of age with asthma
- Compared step-wise increase of doses of fluticasone (F) or fluticasone+salmeterol (F+S) in achieving asthma control

	Well Controlled	Totally Controlled
Each week (maintained 7 of 8 wks)	**2 or more of:**	**All of:**
Daytime Symptoms	≤ 2 days with score >1	None
Rescue beta-agonist use	≤ 2 days and ≤ 4 occasions	None
Morning PEF	≥ 80% predicted every day	≥ 80% predicted every day
	All of:	**All of:**
Nighttime awakenings	None	None
Exacerbations	None	None
Emergency visits	None	None
Treatment-related AEs	None enforcing change in therapy	None enforcing change in therapy

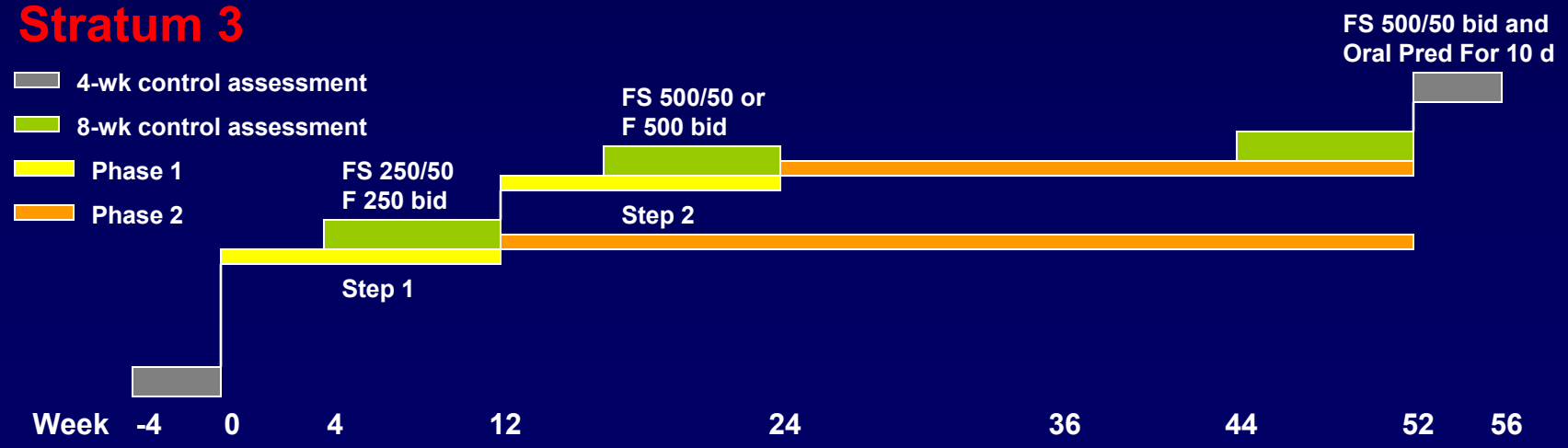
Am J Respir Crit Care Med 2004;170:836-844

GOAL Study Design

Strata 1 & 2

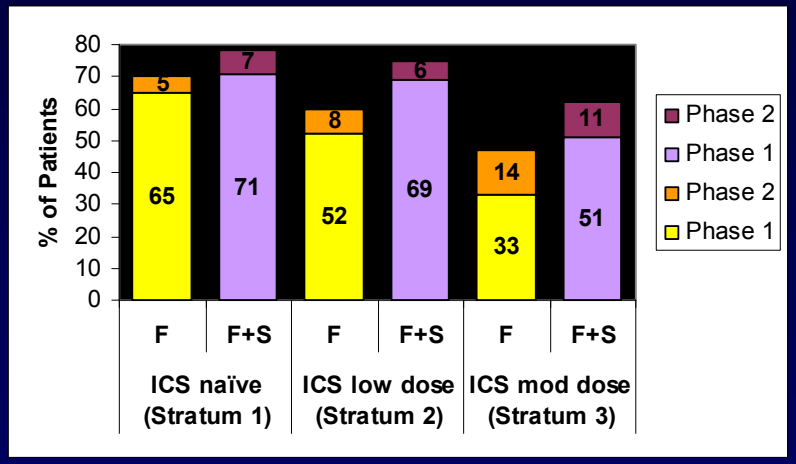


Stratum 3



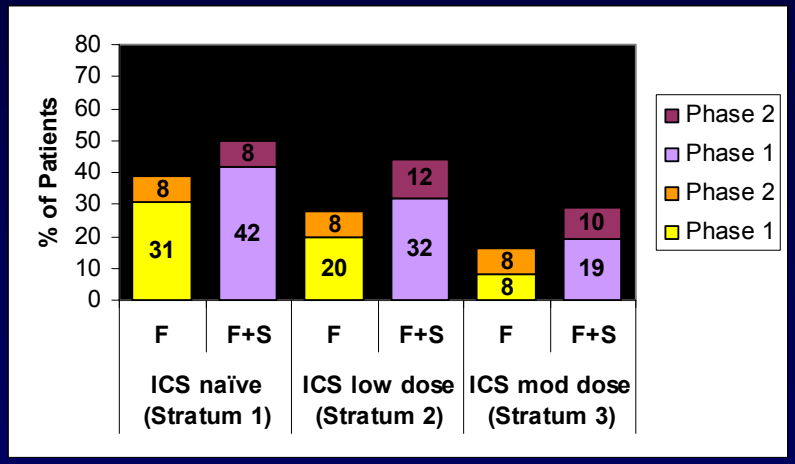
Asthma Control in GOAL Study

Percentage of Patients Achieving Well Controlled Asthma



F+S > F by 8-15%

Percentage Patients Achieving Totally Controlled Asthma



F+S > F by 11-14%

Am J Respir Crit Care Med 2004;170:836-844

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Risk-Benefit Assessment of LABAs

- Risk
  - Serious risk of asthma-related death and asthma exacerbation in a small number of patients
- Benefit
  - Most patients derive symptomatic benefit in the form of improved lung function, reduced nocturnal awakening from asthma symptoms, and decreased use of rescue SABA for asthma exacerbations

Risk-Benefit Assessment of LABAs

- Patients, health care providers, and society have accepted serious adverse reactions, and even death, in a small number of patients, for symptom control in a large number of patients
- DPAP's position: The safety risk of LABAs can be managed through labeling to inform health care providers and patients of the risk, thereby directing use of inhaled LABAs to the appropriate patient population

Consequence of Removal of Asthma Indication for LABAs

- Reduce choices for clinicians unable to control patients' asthma on ICS alone
- Alternate treatments will be:
  - Inhaled SABAs chronically and at high doses
  - Sustained release albuterol tablets
  - Cromones
  - Leukotriene modifying drugs
  - Omaluzimab
  - Theophylline
  - Oral corticosteroids

Consequences of Removing the Asthma Indication for LABAs

- Increased concern of inappropriate use of LABAs in patient with asthma, because
  - Single ingredient LABAs will remain in the market for the COPD indication, therefore, health care providers and patients will have access to these medications and use of these medications (i.e., off-label use) may continue
  - With the removal of the asthma indication, specific recommendations regarding appropriate use of LABAs in asthma will also be removed

Removal of Asthma Indication for Single Ingredient LABAs in Favor of Combination Products Containing LABA+ICS

- Reduce choices for clinicians
  - Reduce choices of ICS for patients who need treatment with an ICS and an inhaled LABA
  - Preclude combination use of inhaled LABA with long-term control medications other than ICS
- No data to show that combination products containing an inhaled LABA and an ICS abolish the risk of asthma-related death with an inhaled LABA

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Limitations of Meta-Analysis

- Meta-analyses are usually done to overcome the problem of reduced statistical power in studies with small sample sizes by pooling similar studies in an appropriately orderly way
- A weakness of meta-analysis is that any source of bias in the various studies is carried to the meta-analysis
- Critical issues in meta-analysis
  - Identification and selection of studies
  - Heterogeneity of results
  - Availability of information
  - Analysis of the data
- Large randomized controlled clinical study is the gold-standard for obtaining information on a specific question

Meta-Analysis: Its Strengths and Limitations; Clev Clin Med 2008: 431-439

Difficulties of Meta-Analysis for Rare Events

- In meta-analysis of rare events, such as adverse events
  - Small changes in data can cause dramatic changes in the results
  - Heterogeneity in studies makes it difficult to assess risks
  - Risk can vary with treatment duration
  - Risk can vary with study subjects enrolled in different studies
- Rare risk signals can emerge from meta-analysis, however
  - Conclusions should be based on valid endpoints
  - Require good understanding of all potential bias introduced in the analysis

Issues in OSE Meta-Analysis of LABA Studies

- Patient dropout information not obtained, and findings not corrected for possible differential dropouts
- Non-LABA is not an appropriate comparator group for some analyses
- Many studies included in the meta-analysis were not designed to address the objective of the meta-analysis
- SMART contributed a large percentage of subjects and is expected to have a large influence on the finding

Meta-Analysis for Asthma-Related Death

- What is the role of a meta-analysis when large randomized controlled studies, e.g., SMART and SNS, have already demonstrated an increased risk of asthma-related death?
- Risk difference can be diluted by
  - Inclusion of studies with limited duration of exposure and low event rate
  - Heterogeneity of patient population in some studies (e.g., including milder patients or including patients adequately controlled on controller drugs who have low risk)
  - Combination of non-LABA (placebo, SABA, ICS, etc) as comparator

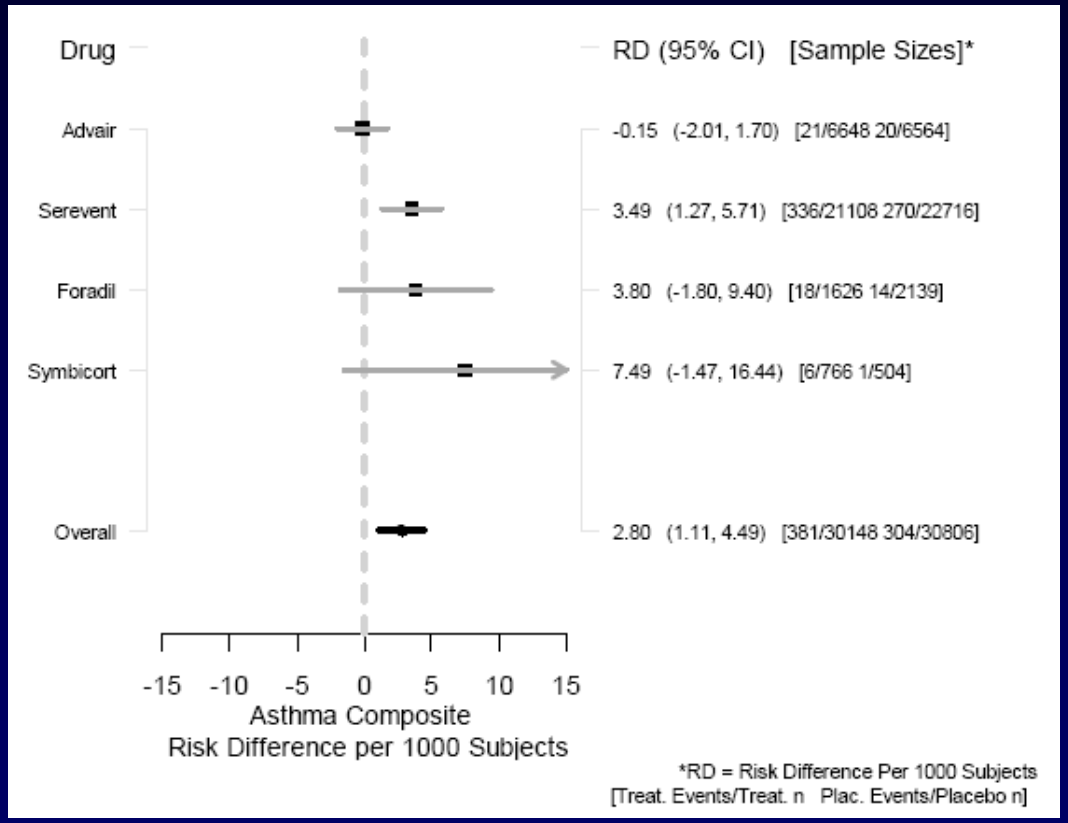
Meta-Analysis for Asthma-Related Hospitalization

- Asthma-related hospitalization may not be informative for asthma-related death
  - Increased hospitalization in children in OSE meta-analysis did not track with asthma-related death or intubation
- Potential biases
  - Early dropouts due to lack of efficacy in placebo arms can lead to shorter duration of treatment and therefore less events in placebo arms compared to LABA arms
  - Decision to hospitalize may vary across hospitals
- Number of hospitalization events, without accounting for underlying cause of hospitalization, does not provide a complete picture of the risk

OSE Meta-Analysis
- Primary Endpoints Stratified by Age
- Risk Difference (95% CI) per 1000 subject, LABA vs no LABA

Age in years (number)	Asthma Composite	Asthma Death	Asthma Death/Intubation	Asthma Hospitalization
4-11 (3,415)	**14.83** (3.24, 26.43)	**-0.63** (-1.86, 0.6)	**-1.25** (-2.97, 0.47)	**15.46** (3.92, 27.01)
12 to 17 (6,392)	**5.57** (0.21, 10.92)	**0.32** (-0.31, 0.95)	**-0.02** (-1.28, 1.25)	**5.25** (-0.07, 10.57)
18 to 64 (46,878)	**2.13** (0.34, 3.91)	**0.52** (0.18, 0.87)	**0.88** (0.24, 1.52)	**1.86** (0.1, 3.63)
65 and above (4,214)	**-3.58** (-10.47, 3.32)	**-0.01** (-1.36, 1.33)	**-0.56** (-3.42, 2.3)	**-4.04** (-10.74, 2.66)

OSE Meta-Analysis
- Asthma Composite Endpoint by Drugs
- Risk Difference (95% CI) per 1000 subject



Reflection on Unanimous OSE Recommendations

- Withdraw asthma indication for all LABAs for patients <18 years of age
- Remove asthma indication and contraindicate use of single ingredient LABAs for all ages

Reflection on Some Other OSE Comments

- “Which benefits might outweigh the risks”
- “The younger patients show a higher risk difference”
- “LABA use in children <18 years of age may not be even as safe as it is in adult asthmatic patients”
- “Paucity of data on benefit in children <18 years of age”
- “Show what the long-acting drugs offer above what is offered by the short-acting beta agonists”

Reflection on Some Other OSE Comments

- Two large remaining questions
  - How does the safety and efficacy of SABA+ICS compare with safety and efficacy of LABA+ICS?
  - Does concomitant ICS use mitigate LABA-associated risk in asthma patients?
- Proposed large safety studies of Advair and Symbicort in adults
  - SABA+ICS as a control arm
  - ICS as a control arm

Concluding Remarks
- Risk-Benefit Analysis of Inhaled LABAs in the Treatment of Asthma

- Risk in a small number of patients, whereas, benefit in most patients
- Accept and manage safety risk
  - Labeling, including Boxed Warning and Medication Guide, to inform patients and health care providers of the risk
  - Labeling to direct use of LABA for appropriate patients

Concluding Remarks
- Risk-Benefit Analysis of Inhaled LABAs in the Treatment of Asthma

- Patients 4 years of age and older
  - LABAs should be used in patients not adequately controlled on other asthma-controller medications (e.g., low to medium dose ICSs) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies
  - LABAs should not be used in patients whose asthma can be managed by ICS along with occasional use of inhaled short acting beta2-agonists
- Patients less than 4 years of age
  - LABAs not approved in this age group