

Foradil[®] **(formoterol fumarate inhalation powder)**

**Drug Safety and Risk Management,
Pulmonary-Allergy Drugs, and
Pediatric Advisory Committees**

December 10-11, 2008



Foradil®
**(formoterol fumarate
inhalation powder)**

Regulatory History

Mathias Hukkelhoven, PhD
Senior Vice President
Global Head of Drug Regulatory Affairs



Foradil[®] Approval History

	Foradil US		Foradil Ex-US	
	Aerolizer ^{®a}	Certihaler [®]	Aerolizer	Certihaler
	12 mcg BID	10 mcg BID	12/24 mcg BID ^b	10 mcg BID
	2001	2006	1990 (France)	2004 (Austria)
Asthma	√	√	√	√
EIB	√		√	
COPD	√		√	√

^a Novartis produces and is the NDA holder for Foradil Aerolizer. Schering-Plough Corporation markets Foradil Aerolizer in the United States.

^b 12 mcg in children; 12 or 24 mcg in adults.

US Regulatory History

- 2001** Foradil[®] Aerolizer[®] approved in US
- 2005** PADAC to discuss the safety of LABAs
- 2006** Labeling revision
- 2007** PAC meeting raised concerns about safety of LABAs in pediatric patients with asthma
- 2008** FDA requested information regarding controlled clinical trials conducted with LABAs

2006 Labeling Revision

◆ Addition of Boxed Warning

WARNING: Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, FORADIL AEROLIZER should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, including FORADIL AEROLIZER. Data from a large placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to formoterol (a long-acting beta₂-adrenergic agonist), the active ingredient in FORADIL AEROLIZER (see WARNINGS).

2006 Labeling Revision

- ◆ Addition of data for serious asthma exacerbations^a
 - Experience in children with asthma (Pivotal study)

Number and frequency of serious asthma exacerbations in patients 5-12 years of age from a 52-week trial

	Foradil 12 mcg BID	Foradil 24 mcg BID	Placebo
Serious asthma exacerbations	8/171 (4.7%)	11/171 (6.4%)	0/176 (0)

^a Differences in data between the Foradil label and the Novartis briefing document relate to the different duration of follow-up.

2006 Labeling Revision

- ◆ Addition of data for serious asthma exacerbations^a
 - Experience in adolescents and adults with asthma (Pivotal studies)

Number and frequency of serious asthma exacerbations in patients 12 years of age and older from two 12-week controlled clinical trials

	Foradil 12 mcg BID	Foradil 24 mcg BID	Albuterol 4 times daily	Placebo
Trial #1				
Serious asthma exacerbations	0/136 (0)	4/135 (3.0%)^a	2/134 (1.5%)	0/136 (0)
Trial #2				
Serious asthma exacerbations	1/139 (0.7%)	5/136 (3.7%)^b	0/138 (0)	2/141 (1.4%)

^a One patient required intubation.

^b Two patients had respiratory arrest, one of the patients died.

^a Differences in data between the Foradil label and the Novartis briefing document relate to the different duration of follow-up.

2006 Labeling Revision

- ◆ Addition of data for serious asthma exacerbations^a
 - Experience in adolescents and adults with asthma (Post-marketing commitment study)

Number and frequency of serious asthma exacerbations in patients 12 years of age and older from a 16-week trial

	Foradil 12 mcg BID	Foradil 24 mcg BID	Placebo
Serious asthma exacerbations	3/527 (0.6%)	2/527 (0.4%)	1/514 (0.2%)

^a Differences in data between the Foradil label and the Novartis briefing book relate to the different duration of follow-up.

Ongoing Risk Mitigation Strategies

- ◆ **Since approval of Foradil[®] Aerolizer[®], the following activities have been completed and/or continue to evaluate and minimize the risk of serious asthma exacerbations:**
 - **Post-marketing commitment study**
 - **Pharmacogenetic analysis**
 - **Epidemiological studies**
 - **Global pharmacovigilance**
 - **Labeling and Medication Guide**
 - **Education and communication of risk**

The Clinical Presentation Will Show That

Based on review of

- The totality of clinical data for formoterol, in the context of current treatment guidelines and the approved label, and
 - Post-marketing surveillance data (ARGUS and AERS)
-
- ◆ Foradil[®] continues to exhibit a favorable benefit/risk ratio
 - ◆ LABAs, including formoterol, remain an important therapeutic option in the treatment of patients with asthma
 - ◆ The continued availability of non-combined LABAs provides flexibility in choosing type and dose of inhaled corticosteroid
 - ◆ Appropriate use of Foradil is adequately outlined in the current labeling, which may be updated based on the discussions of this advisory committee

Foradil[®]
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inhalation powder)**

Clinical

Linda Armstrong, MD
Executive Medical Director



Overview

- ◆ **Selected individual trial results**
- ◆ **Results of formoterol (Foradil®) pooled analyses**
- ◆ **Spontaneous cases of asthma-related serious adverse events**
- ◆ **Foradil benefit-risk**

Timeline of Key Foradil® Studies (> 12 Weeks' Duration)



EPR = Expert Panel Report.

EPR 1 (1991- 1997)

EPR 2 (1997-2002)

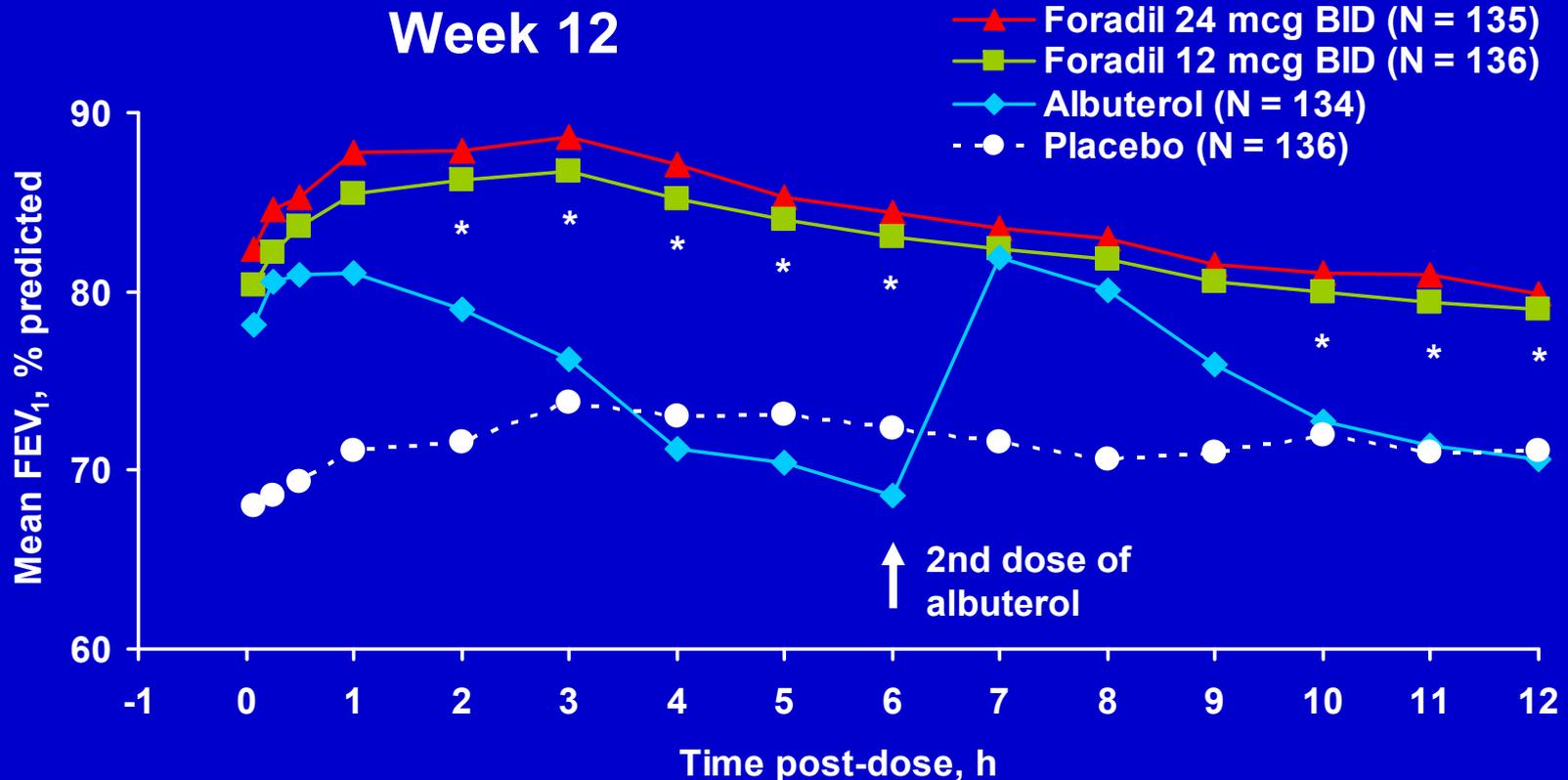
EPR Update (2002-2007)

EPR 3 (2007-

Pivotal Trials Supporting Foradil® Approval

Study number	n	Duration	Age	Treatment arms	Background ICS use
40	541	12 weeks	12-75	Foradil 12 mcg BID, 24 mcg BID, Albuterol 180 mcg QID, Placebo	50%
41	554	12 weeks	12-75	Foradil 12 mcg BID, 24 mcg BID, Albuterol 180 mcg QID, Placebo	50%
49	518	52 weeks	5-12	Foradil 12 mcg BID, 24 mcg BID, Placebo	75%

Efficacy of Foradil® in Study 40— Patients >12 Years of Age After 12 Weeks of Treatment

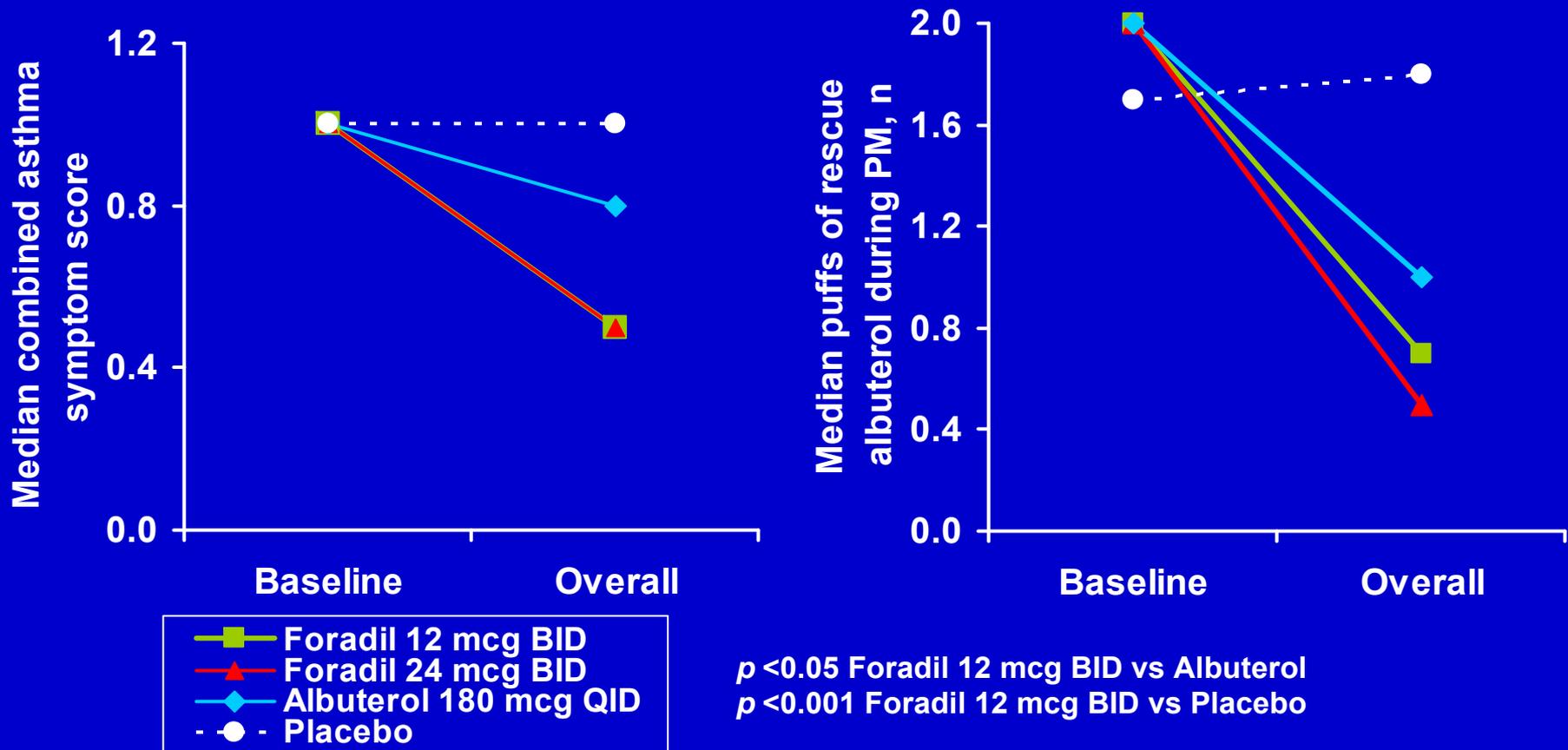


* $p < 0.05$ Foradil 12 mcg BID vs Albuterol

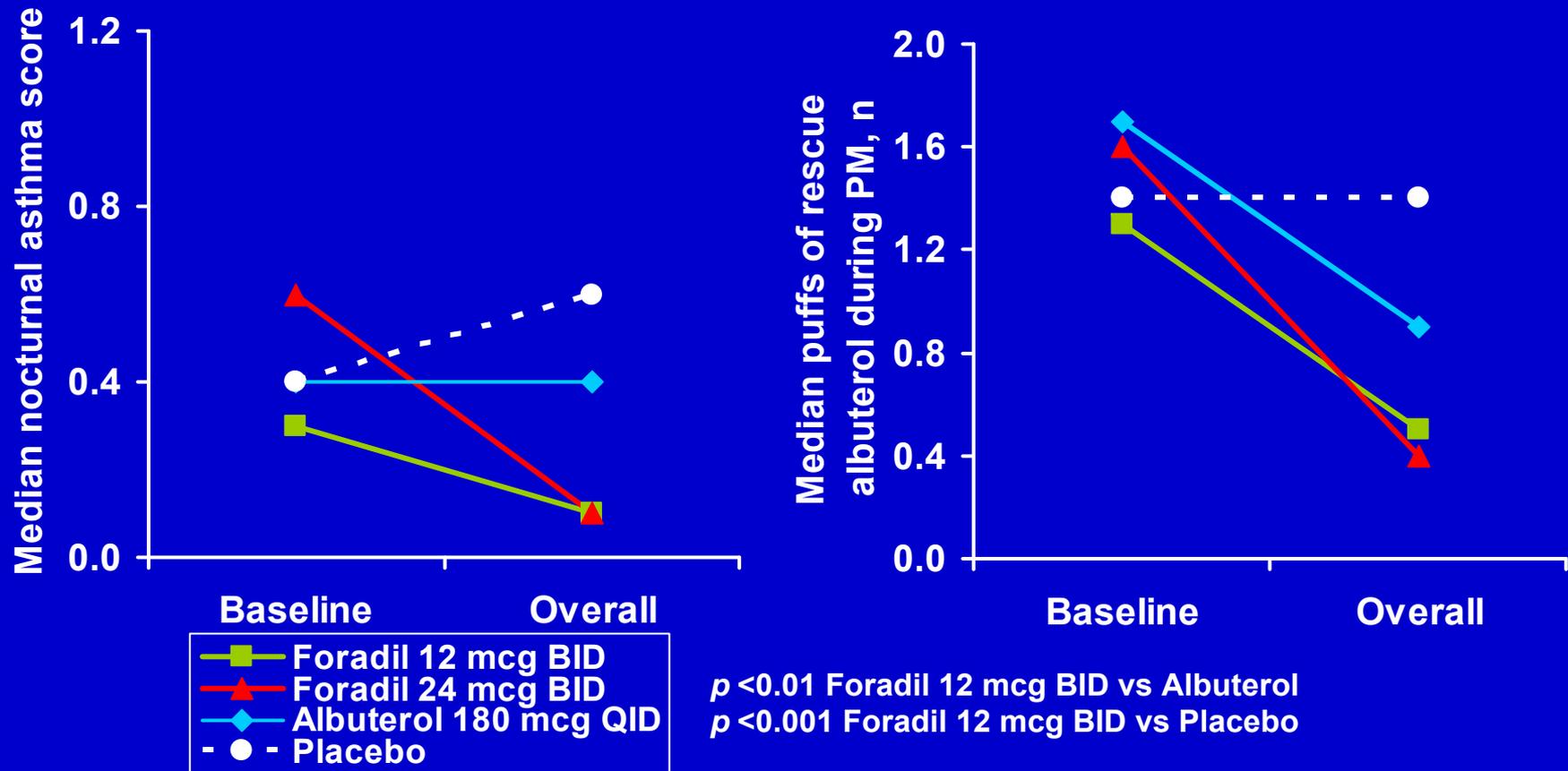
$p < 0.001$ Foradil 12 mcg BID vs Placebo (all time points)

- ◆ 22% improvement from baseline in mean FEV₁
- ◆ 89% of patients demonstrated a 12% improvement in FEV₁

Effect of Foradil[®] on Daytime Symptoms and Rescue Medication Use in Study 40



Effect of Foradil[®] on Nocturnal Symptoms and Rescue Medication Use in Study 40



- ◆ Treatment with Foradil 12 mcg BID resulted in a 20% decrease in nocturnal awakenings vs placebo and a 15% decrease vs albuterol QID

Serious Asthma Exacerbations in Pivotal Trials (Patients >12 Years of Age)

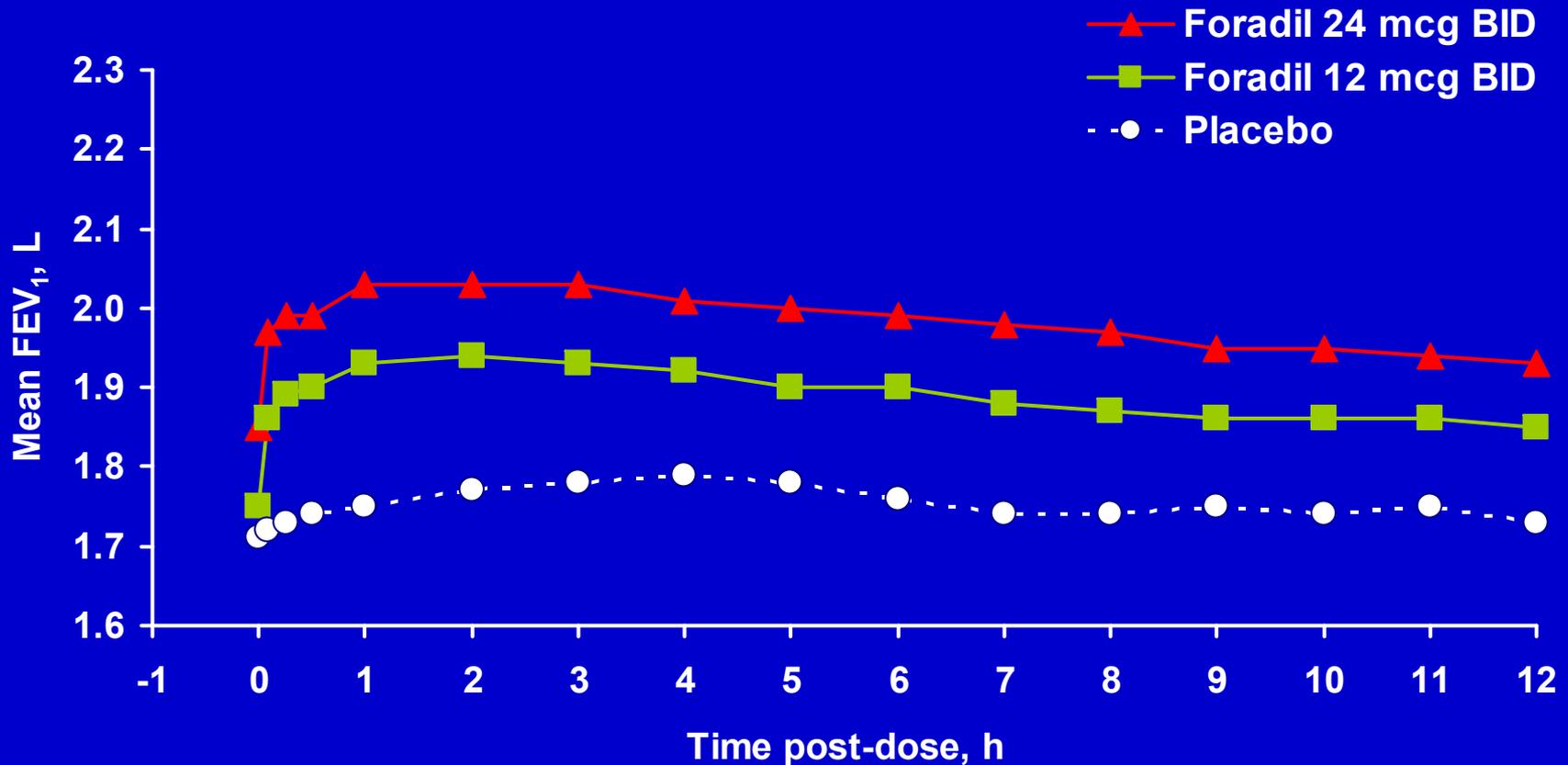
	Patients, n/N (%)			
	Foradil® 12 mcg BID	Foradil 24 mcg BID	Albuterol 180 mcg QID	Placebo
Study 40: Serious asthma exacerbations	0/136 (0)	4/135 (3.0)	2/134 (1.5)	0/136 (0)
Study 41: Serious asthma exacerbations	1/139 (0.7)	5/136 (3.7)	0/138 (0)	2/141 (1.4)

Pivotal Trials Supporting Foradil[®] Approval

Study number	n	Duration	Age	Treatment arms	Background ICS use
40	541	12 weeks	12-75	Foradil 12 mcg BID, 24 mcg BID, Albuterol 180 mcg QID, Placebo	50%
41	554	12 weeks	12-75	Foradil 12 mcg BID, 24 mcg BID, Albuterol 180 mcg QID, Placebo	50%
49	518	52 weeks	5-12	Foradil 12 mcg BID, 24 mcg BID, Placebo	75%

Efficacy of Foradil[®] in Patients With Asthma 5-12 Years of Age in Study 49— Primary Endpoint FEV₁

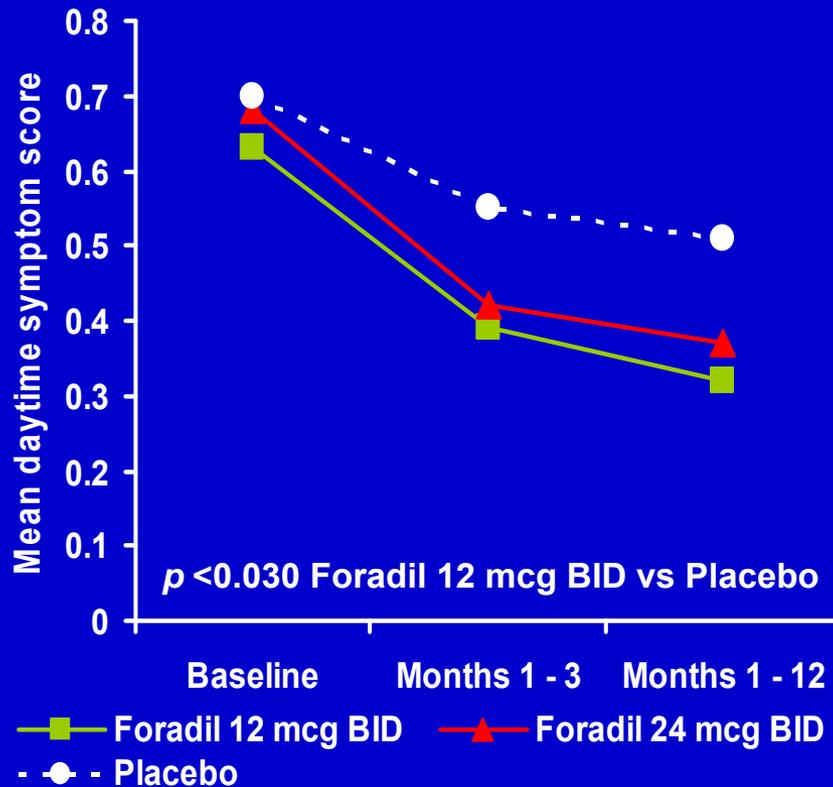
Week 12



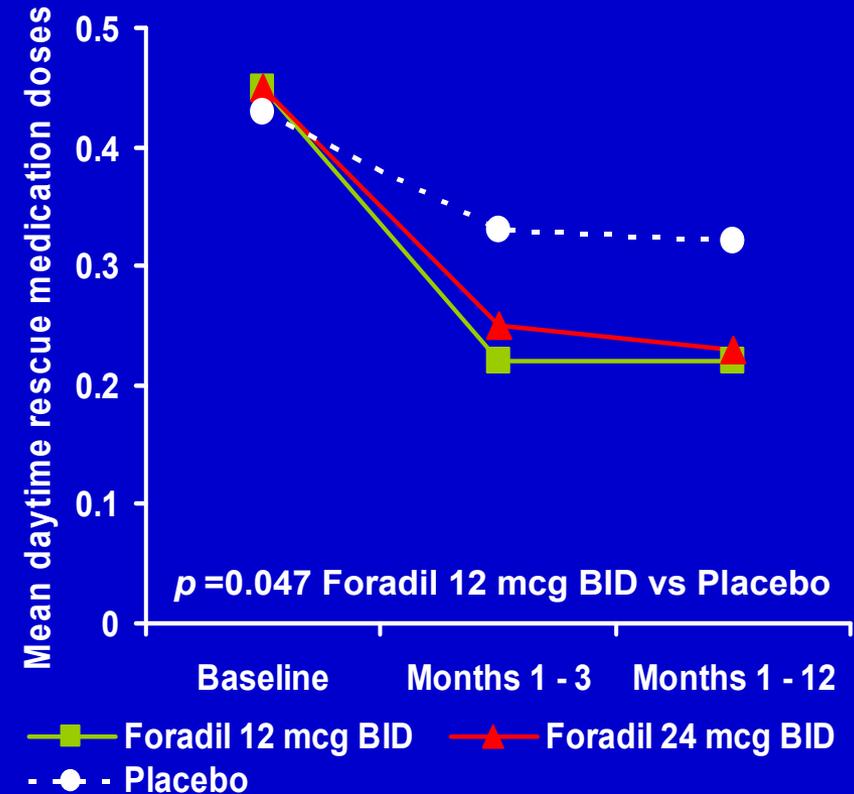
$p < 0.0001$ Foradil 12, 24 mcg BID vs Placebo (all time points)

Efficacy of Foradil® in Patients With Asthma 5-12 Years of Age in Study 49— Daytime Symptoms and Rescue Medication Use

Daytime symptom scores



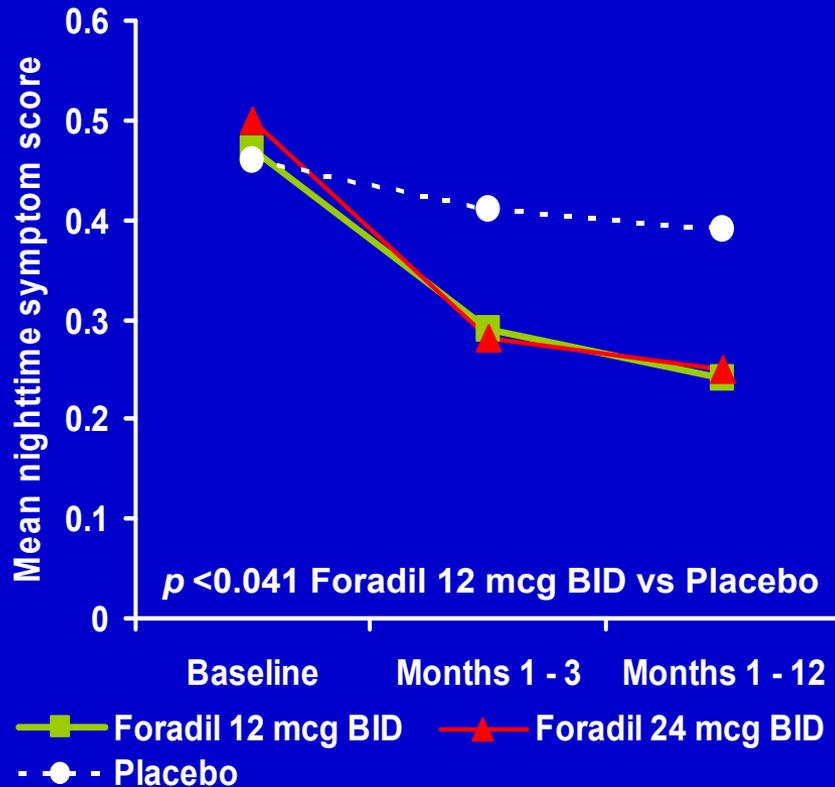
Daytime rescue use



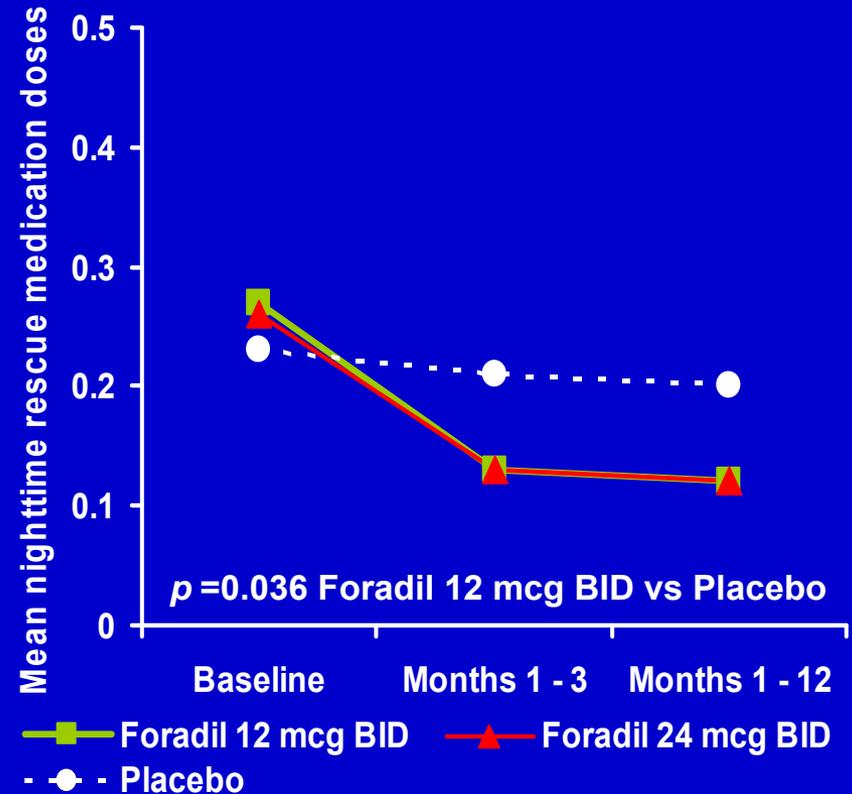
- ◆ Patients treated with Foradil 24 mcg BID experienced a 45% decrease in “deterioration days”

Efficacy of Foradil® in Patients With Asthma 5-12 Years of Age in Study 49— Nocturnal Symptoms and Rescue Medication Use

Night-time symptom scores



Night-time rescue use



Serious Asthma Exacerbations (5-12 Years of Age)

	Patients, n (%)		
	Foradil® 12 mcg BID n = 171	Foradil 24 mcg BID n = 171	Placebo n = 176
Serious asthma exacerbations	8 (4.7)	11 (6.4)	0

Non-Serious Adverse Events and Premature Discontinuations

Study 49

	Patients, n (%)		
	Foradil [®] 12 mcg BID n = 171	Foradil 24 mcg BID n = 171	Placebo N = 176
Asthma-related non-serious AEs leading to discontinuation	1 (0.6)	3 (1.7)	7 (4)

Serious Asthma Exacerbations Postmarketing Safety Study (2307)

- ◆ 2085 patients >12 years of age were randomized to Foradil® 12 mcg BID, 24 mcg BID, 24 mcg and PRN dosing, or placebo
- ◆ All patients, including those who discontinued early, were followed for 16 weeks
- ◆ Patients were required to use concomitant anti-inflammatory medication; 70% used ICS

	Patients, n (%)			
	Foradil 12 mcg BID n = 527	Foradil 24 mcg BID + 12 mcg BID PRN n = 517	Foradil 24 mcg BID n = 527	Placebo n = 514
Serious asthma exacerbations	3 (0.6)	1 (0.2)	2 (0.4)	1 (0.2)

Overview

- ◆ Selected individual trial results
- ◆ **Results of formoterol (Foradil®) pooled analyses**
- ◆ Spontaneous cases of asthma-related serious adverse events
- ◆ Foradil benefit-risk

45 Clinical Trials Included in Current Analyses

- ◆ Randomized, blinded, Foradil[®]-controlled clinical studies in patients with asthma (N = 8231)
 - Foradil, 12/10 mcg TDD n = 585
 - **Foradil, 24/20 mcg TDD** n = **3129**
 - Foradil, 48 mcg TDD n = 1515
 - **Placebo** n = **2026**
 - **Albuterol** n = **976**
- ◆ As randomized treatment, albuterol administered 4 times per day
- ◆ All patients
 - Permitted to use albuterol as rescue medication
 - Continued to use background controller medications

Inconsistent Use of Concomitant Inhaled Corticosteroid in Novartis Foradil® Trials

- ◆ **ICS use permitted — 41 of 45 trials**
- ◆ **ICS use required — 4 of 45 trials**
 - **ICS included as study medication — 2 trials**
- ◆ **In trials for which ICS use was not randomized, compliance with ICS was not measured**

Studies not designed to assess whether ICS mitigate the risk of serious asthma exacerbations

Asthma Composite Endpoint Analyzed

- ◆ **Per FDA definition, events of interest included**
 - **Asthma-related deaths**
 - **Asthma-related intubations**
 - **Asthma-related hospitalizations**
- ◆ **Events identified through a blinded physician review and termed “Asthma Composite Endpoint”**
- ◆ **Search included events from randomization to last day of blinded treatment**
- ◆ **Separate comparisons made to placebo and albuterol**

Randomized Controlled Trials— Asthma-Related Death

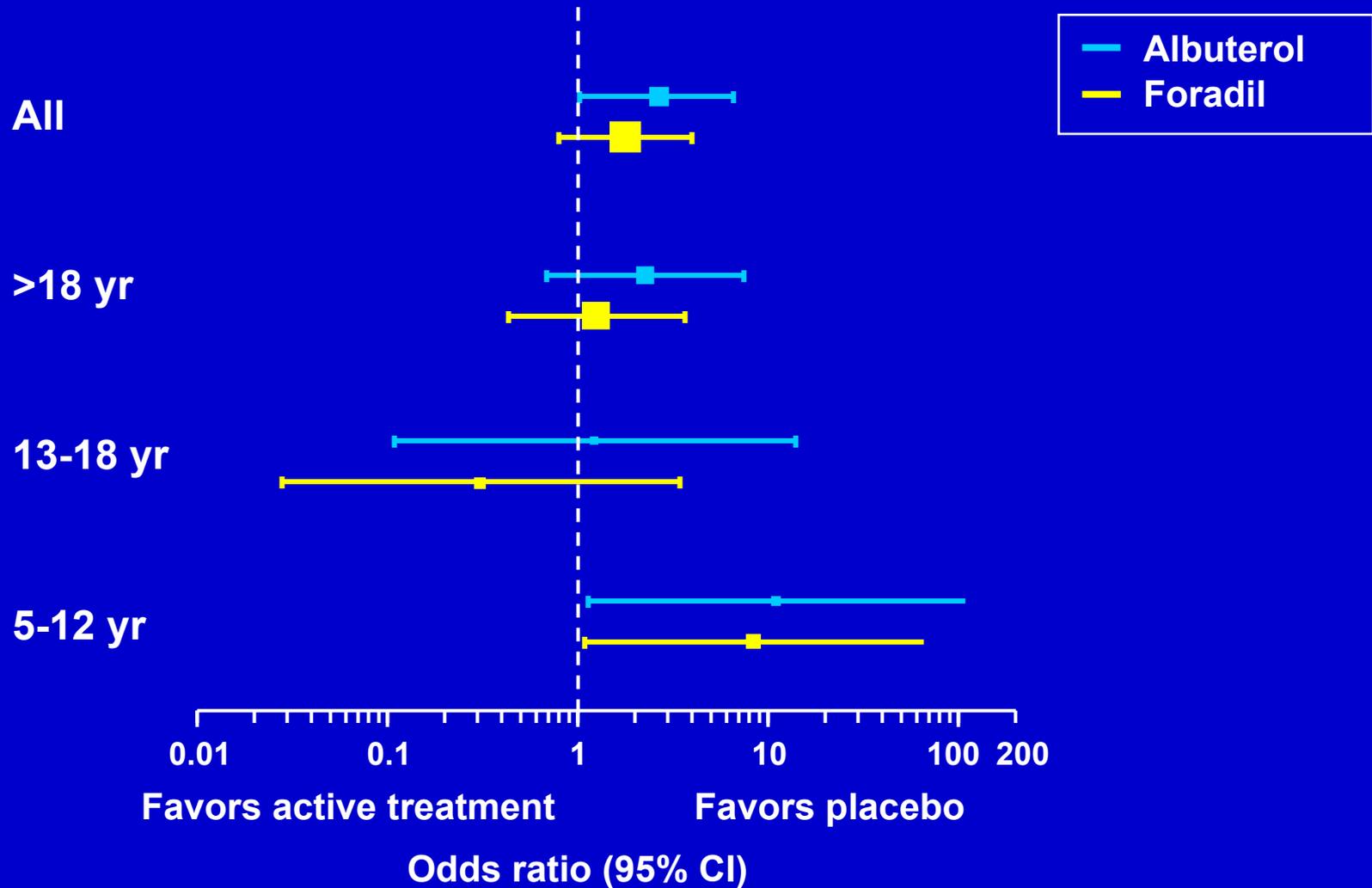
	Foradil® all doses n = 5367	Albuterol n = 976	Placebo n = 2026
Asthma-related deaths			
Total exposure, pt-yr	1399	568.4	222.2
Asthma-related deaths			
n (%)	1 (0.02)	0	0
n/100 pt-yr	0.07	—	—

No deaths or intubations among pediatric patients

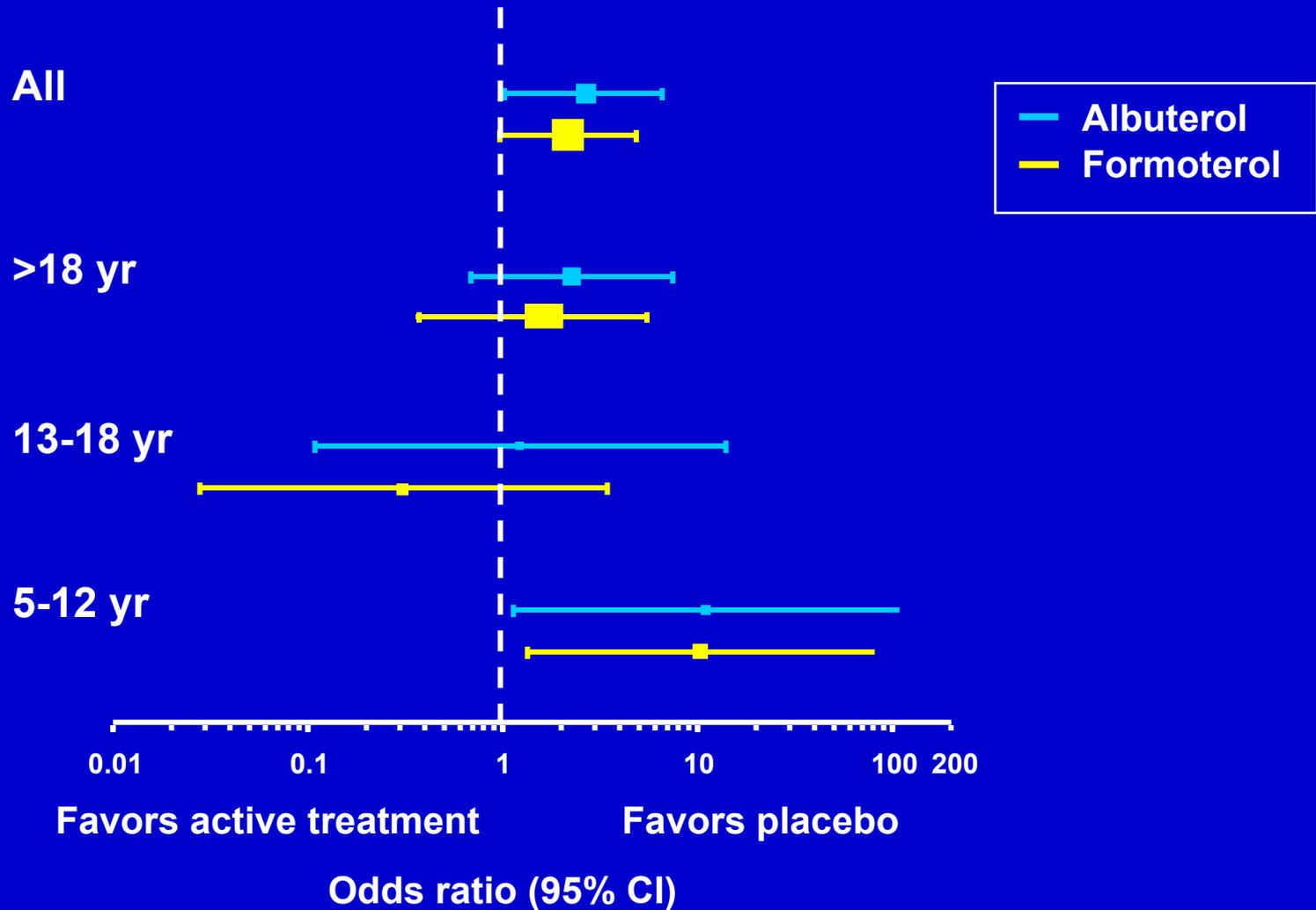
Asthma Composite Endpoint by Age

		Foradil 24 mcg TDD	Placebo	Albuterol
Overall	N	3129	2026	976
	n (%)	22 (0.7)	8 (0.4)	10 (1.0)
	n/100 pt-yr	2.7	1.4	4.5
>18 yr	N	2452	1546	825
	n (%)	10 (0.4)	5 (0.3)	6 (0.7)
	n/100 pt-yr	1.9	1.4	3.1
13-18 yr	N	215	135	55
	n (%)	1 (0.5)	2 (1.5)	1 (1.8)
	n/100 pt-yr	1.8	6.1	8.4
5-12 yr	N	462	345	96
	n (%)	11 (2.4)	1 (0.3)	3 (3.1)
	n/100 pt-yr	5.4	0.5	16.2

Odds Ratios for Asthma Composite Endpoint by Age



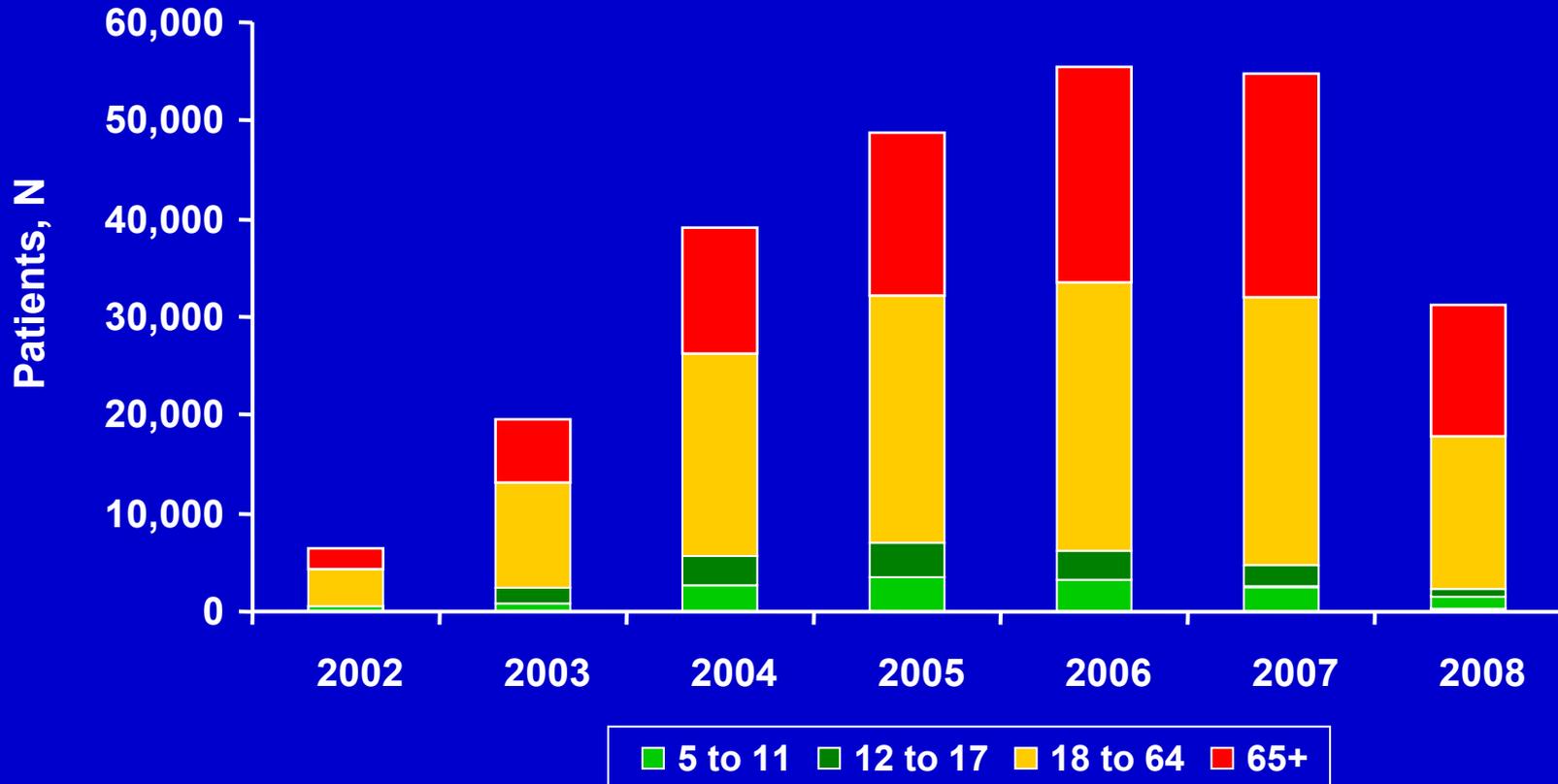
Odds Ratios for Asthma Composite Endpoint by Age to End of Observation Period



Overview

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- ◆ Spontaneous cases of asthma-related serious adverse events
- ◆ Foradil benefit-risk

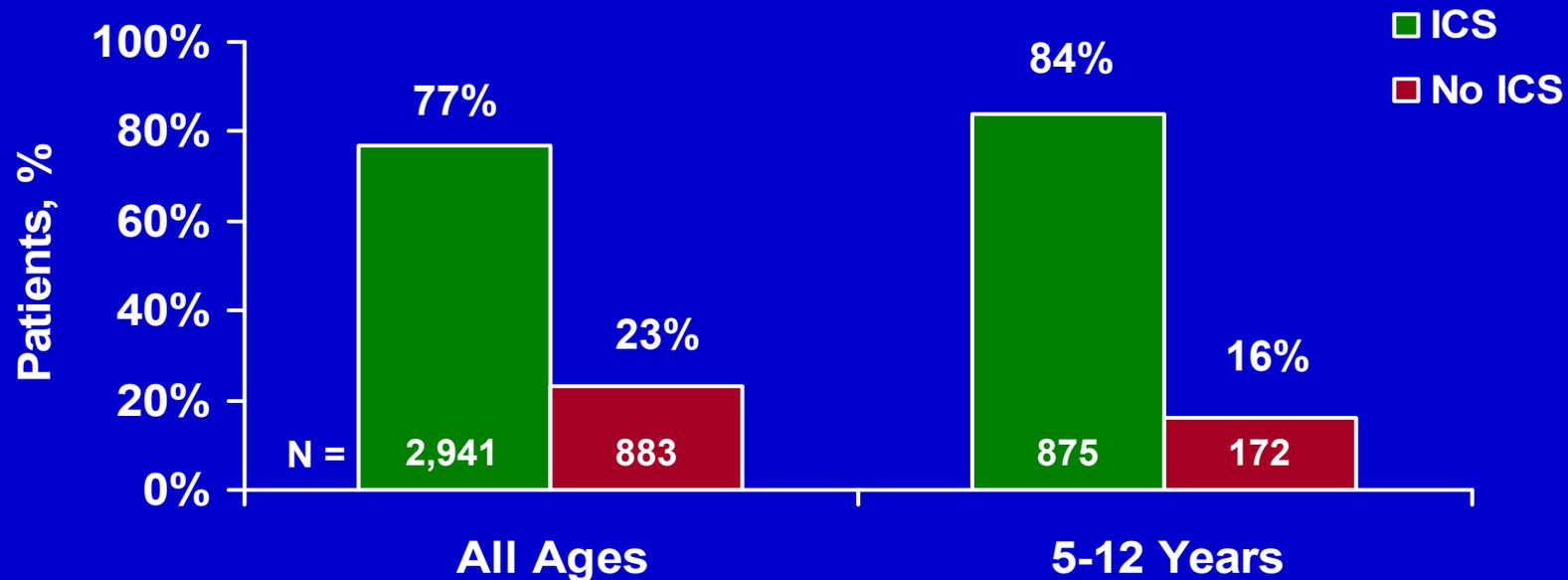
Foradil® Primarily Used in Patients ≥ 18 Years



20% of Foradil use is in patients with asthma

Majority of Patients With Asthma Use Foradil[®] with an Inhaled Corticosteroid

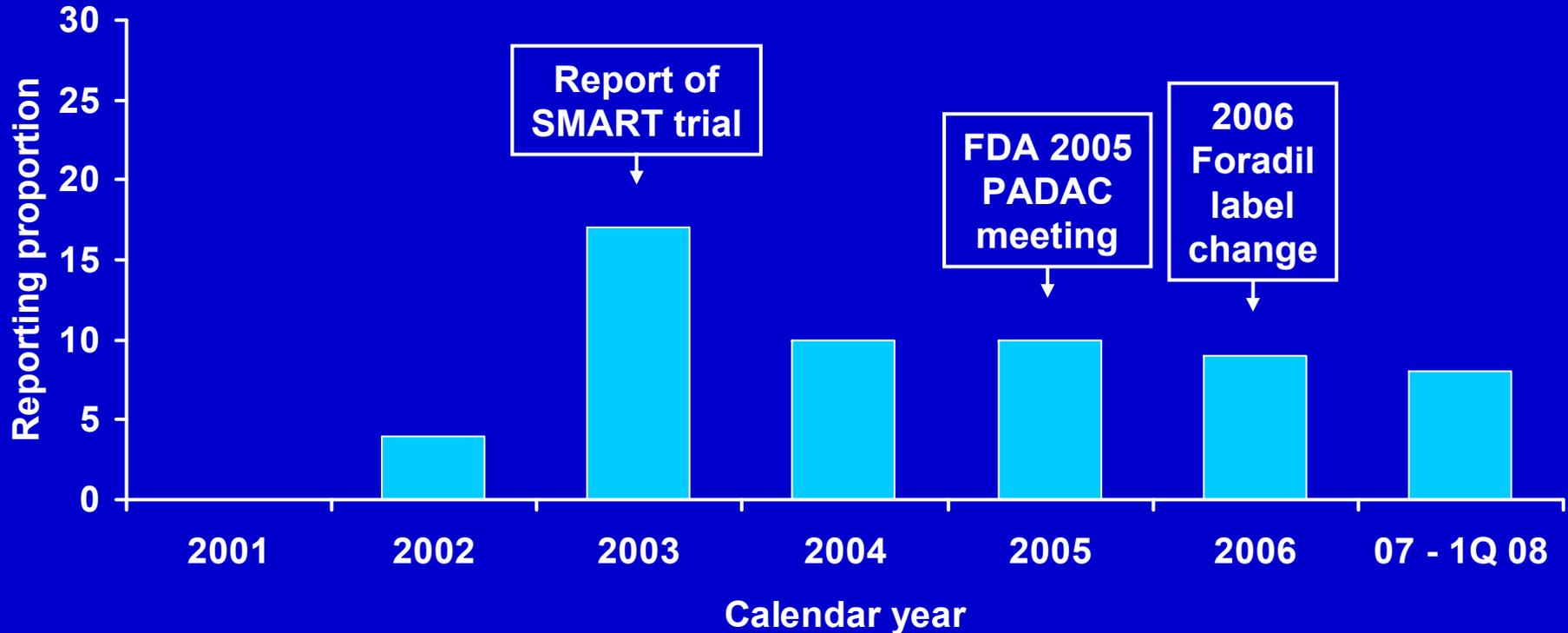
Concomitant ICS Prescribing in Patients < 40 Years



Analysis of FDA Adverse Events Reporting System (AERS)

- ◆ **AERS is a passive surveillance system that includes reports from manufacturers, consumers, and healthcare professionals**
- ◆ **AERS includes all spontaneous reports from US sources for all marketed drugs**
- ◆ **AERS database was searched for US reports in which Foradil[®] was identified as a medication *and***
 - **The event is an asthma-related SAE**

Reporting Proportions of Asthma-Related SAEs Among Patients of All Ages Using Foradil®



Number of asthma-related SAEs in children 5-12 yr

Year	2001	2002	2003	2004	2005	2006	2007	1Q 08
5 - 12	0	1	1	1	0	3	0	0

Note: 1 asthma-related SAE reported after 1Q 08 date cut-off.

Commitment to Ongoing Risk Evaluation and Mitigation Strategies

- ◆ Ongoing epidemiological study
- ◆ Medication guide and label
- ◆ Communication of appropriate use and risk
 - Physician education consistent with NHLBI guidelines (step-up and step-down)
 - Patient asthma education on Foradil.us Web site and through patient literature (print and CD-ROM)
- ◆ Global pharmacovigilance
 - Targeted data capture for concurrent inhaled medications

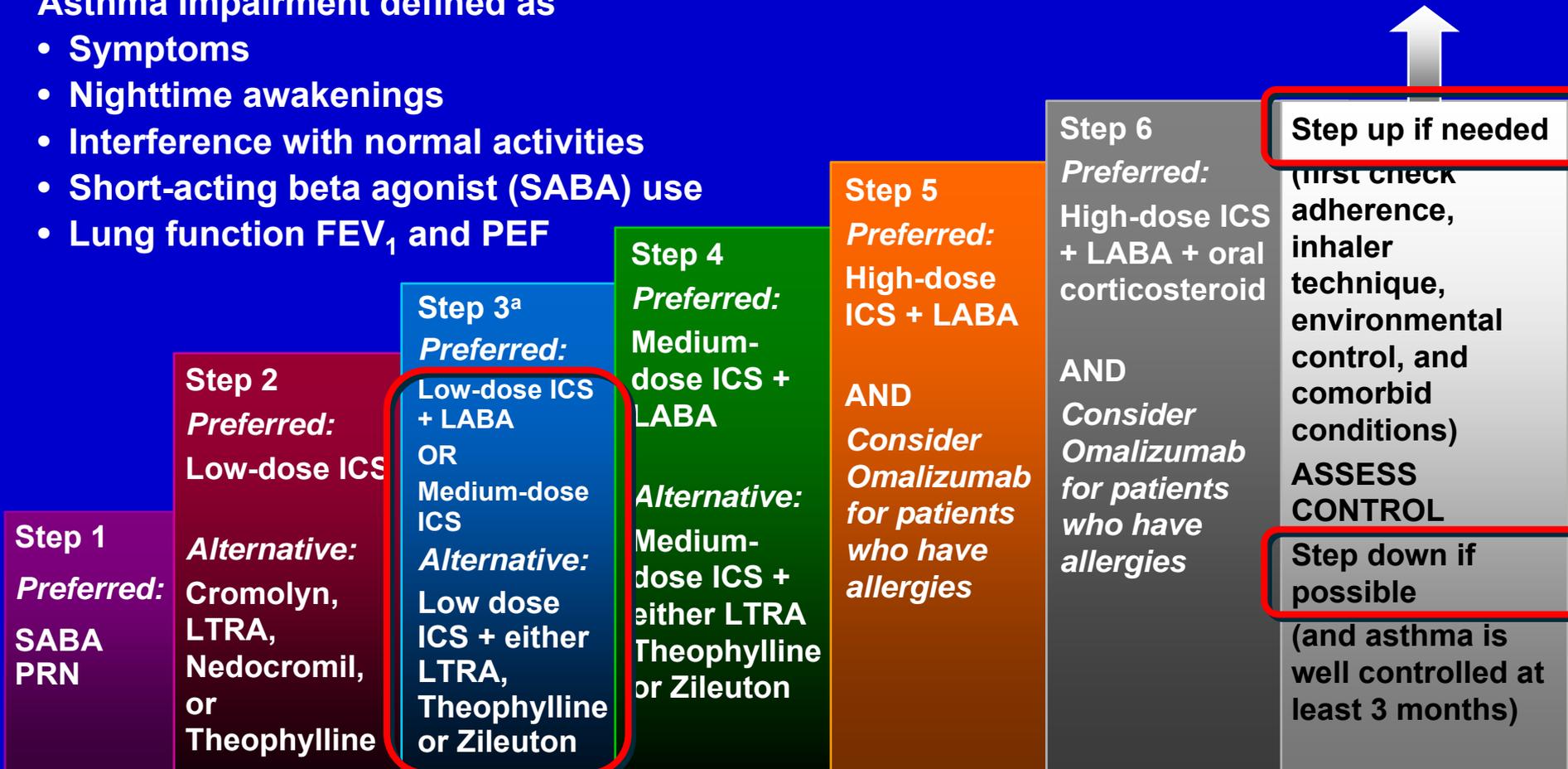
Overview

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Stepwise Approach for Managing Asthma

Asthma Impairment defined as

- Symptoms
- Nighttime awakenings
- Interference with normal activities
- Short-acting beta agonist (SABA) use
- Lung function FEV₁ and PEF



^a NHLBI Expert Panel Report. NIH Publication. October 2007. No 08-5846. For pts <12 years old, LABA alternative add on to ICS in Step 3

Comparison of LABAs to Other Add-on Therapies

- ◆ As add-on therapy, LABAs demonstrate greater improvements in symptoms, lung function, and rescue medication use compared with
 - Montelukast^a
 - Increased ICS dose^b
 - Theophylline^c
- ◆ Safety factors for alternate medications include
 - Seizures, arrhythmias—Theophylline
 - Liver toxicity—Zileuton
- ◆ Pediatric data on alternatives is limited

^a Nelson HS. *J Allergy Clin Immunol*. 2000.

^b Pauwels RA, et al. *N Engl J Med*. 1997; Russel G, et al. *Ann Allergy Asthma Immunol*. 1995.

^c Tee A, et al. *The Cochrane Collaboration*. 2008.

Approved ICS (US) for the Treatment of Asthma

Brand and Formulation		Approved Age
Marketed in Fixed Combination With LABA in Addition to Monotherapy		
Fluticasone propionate	Flovent Diskus	≥ 4 yrs
	Flovent HFA MDI	≥ 4 yrs
	Advair Diskus ^a	≥ 4 yrs
	Advair HFA MDI ^a	≥ 12 yrs
Budesonide	Pulmicort Flexihaler MDI	≥ 6 yrs
	Pulmicort Respules	≥ 12 mo-8 yrs
	Symbicort MDI ^b	>12 yrs
ICS Not Approved in Fixed Combination (Only Available as Monotherapy)		
Ciclesonide	Alvesco HFA MDI	≥ 12 yrs
Mometasone furoate	Asmanex Twisthaler	≥ 4 yrs
Beclomethasone dipropionate	QVAR HFA MDI	≥ 5 yrs
Triamcinolone acetonide	Azmacort CFC MDI	≥ 6 yrs
Flunisolide EQ	Aerospan HFA MDI	≥ 6 yrs

^a Advair Diskus and Advair HFA are fixed combinations with salmeterol 50 mcg/inhalation.

^b Symbicort HFA is fixed combination with formoterol 6 mcg/inhalation.

Foradil[®] Benefit Conclusions

- ◆ **Foradil improves lung function, reduces rescue bronchodilator use, reduces symptoms in all populations**
- ◆ **Foradil remains important treatment option as add-on therapy for patients not controlled on ICS alone (Steps 3 and 4 EPR-3)**
- ◆ **Foradil provides physicians and patients the choice of adding Foradil delivered via dry powder inhaler to a variety of inhaled corticosteroids over the range of approved doses**

Foradil® Safety Conclusions (1/2)

- ◆ Foradil, like all long-acting beta agonists, may be associated with an increased risk of asthma-related hospitalizations
 - This risk is reflected in the current label
- ◆ Data from key trials were previously presented at the 2005 PADAC Meeting
- ◆ Analysis of the pooled Novartis clinical trial data shows an imbalance in asthma-related hospitalizations in patients 5-12 years of age
 - The imbalance was primarily based on findings from the 1-year safety study in which more patients treated with placebo discontinued prematurely
 - This study was the basis for approval of the indication in 2001

Foradil® Safety Conclusions (2/2)

- ◆ **There have been no reports of asthma-related pediatric deaths since US approval in 2001**
- ◆ **Spontaneous reports from postmarketing data show no additional risk of asthma-related hospitalization in the pediatric population**

Overall Conclusions

- ◆ **Benefit-risk profile for Foradil[®] remains positive for patients with asthma**
 - **Indicated as a long-acting bronchodilator**
 - **Highly effective**
 - **Risks well described in label**
- ◆ **Foradil remains an important option for physicians and patients**

Planned Epidemiology Study—Multi-State Medicaid Database

- ◆ 870,000 asthmatics
 - 436,000 <12 years
- ◆ Data through 2007 (potentially extend to 2009)
- ◆ Outcomes: asthma-related mortality, asthma-related ER visits, asthma-related hospitalizations, and intubations
- ◆ Permits for analyses for:
 - Foradil-specific estimates
 - Young users
 - Contemporary standards of care
 - Address confounding factors
- ◆ Study report to become available 2009