

Benefits and Risks of AstraZeneca Formoterol-Containing Products

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Vice President
Development Projects, SYMBICORT®
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Advisors Present for AstraZeneca

Gary Anderson, PhD

- Professor in Respiratory Pharmacology and Immunology, University of Melbourne, Australia

Gary Koch, PhD

- Professor of Biostatistics and Director of the Biometric Consulting Laboratory, University of North Carolina, Chapel Hill, NC

Craig La Force, MD

- Clinical Professor of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, NC

Harold Nelson, MD

- Professor of Medicine, Department of Medicine, National Jewish Health, Denver, CO

Malcolm Sears, MB

- Professor of Medicine, McMaster University, Hamilton, Ontario

Why We Are Here

- **ICS/LABA combination**
 - Preferred treatment option in evidence-based treatment guidelines
- **PADAC 2005**
 - Concerns triggered by SMART study
 - Boxed warning and appropriate use
- **PAC 2007**
 - New review of benefit/risk
- **AstraZeneca data not previously reviewed**

What We Will Show For SYMBICORT®

- **AstraZeneca products of relevance**
- **Review of benefits of SYMBICORT**
 - Reduction of asthma future risk
 - Improvement in current asthma control
- **Evaluation of SYMBICORT risk**
 - Analysis of FDA-requested dataset
 - No signal of increased risk for asthma-related severe events
 - Context for FDA analysis
- **Conclusions on SYMBICORT benefit and risk**
 - Important therapeutic option
 - Positive benefit/risk when used as indicated
 - Potential risks adequately labeled

Benefits

Tomas Andersson, MD, PhD
Medical Science Director, SYMBICORT®
AstraZeneca



SYMBICORT[®] Inhalation Aerosol (pMDI)

- **US approval: 2006**
- **Indication: long-term maintenance treatment of asthma in patients 12 years of age and older**
 - **Should only be used for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose ICS) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies**
- **Dose: 160/9 µg or 320/9 µg twice daily**

AstraZeneca Formoterol-Containing Products

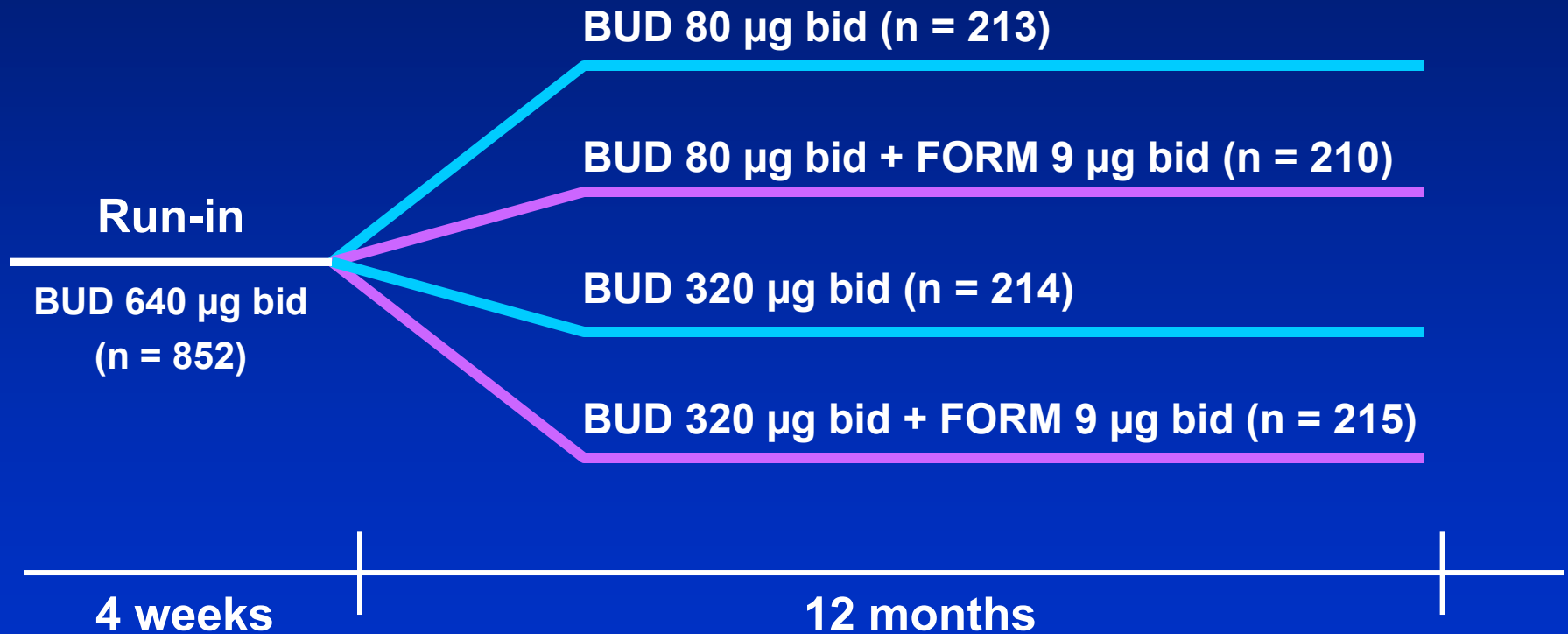
Product	First approval	Exposure (treatment days)	Approved daily formoterol dose
SYMBICORT[®] pMDI (BUD + FORM)	2006	> 48 mil	18 µg
SYMBICORT Turbuhaler[®] (BUD + FORM)	2000	> 4400 mil	9, 18, 36 µg (occasional use 54 µg)
OXIS[™] Turbuhaler (FORM)	1996	> 1400 mil	4.5, 9, 18, 36 µg (occasional use 54 µg)

Indicators of Benefit

- **Future risk**
 - **Asthma exacerbations**
 - **Asthma worsenings**
- **Current control**
 - **Asthma symptoms**
 - **Lung function (FEV₁ and morning PEF)**
 - **Asthma-related Quality of Life**

FACET: Study Design

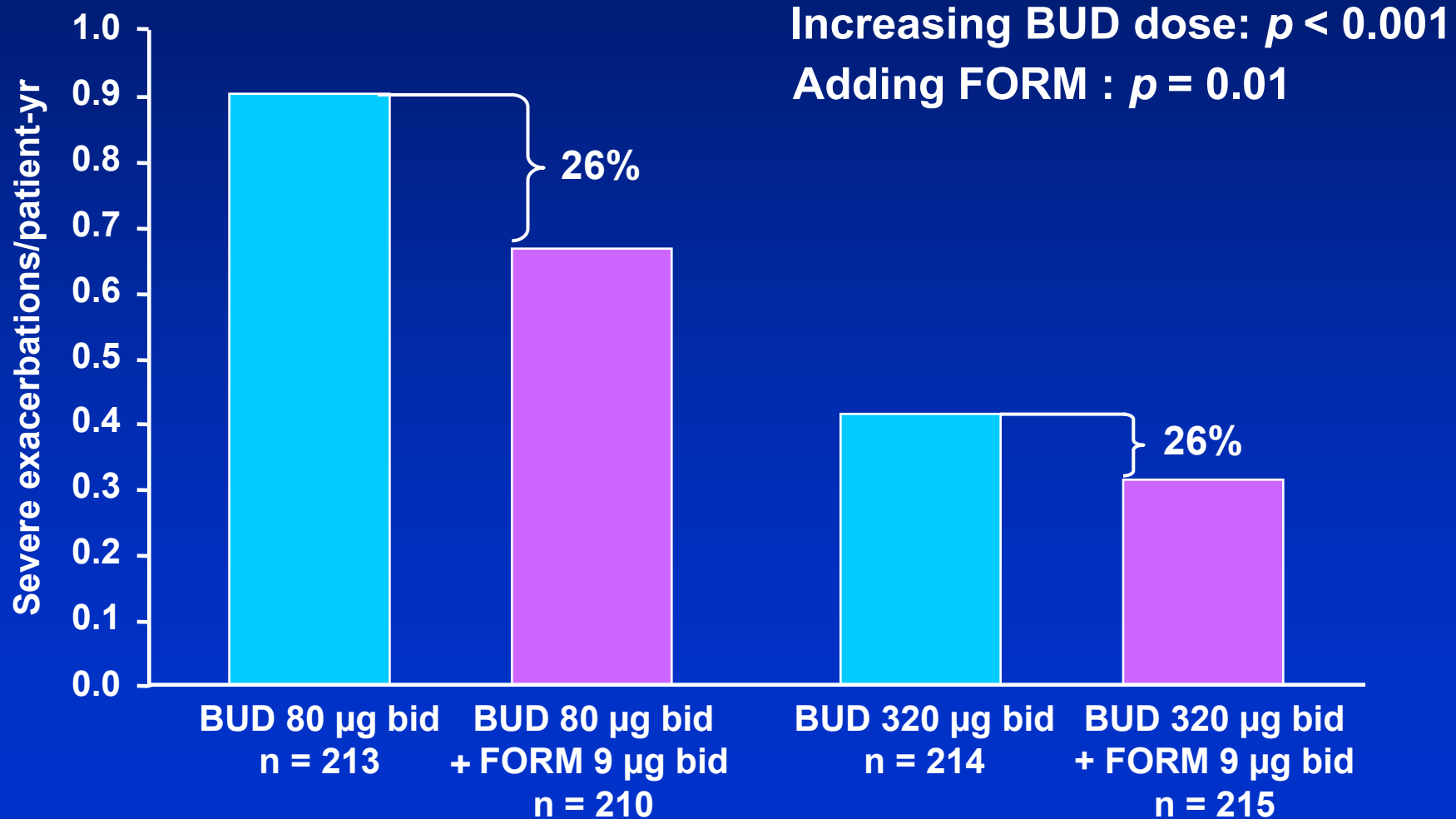
Study 3018—FACET



Note: Doses expressed as delivered doses.
Pauwels RA, et al. *N Engl J Med.* 1997;337:1405-1411.

Adding Formoterol to Budesonide Reduces Severe Asthma Exacerbations

Study 3018—FACET

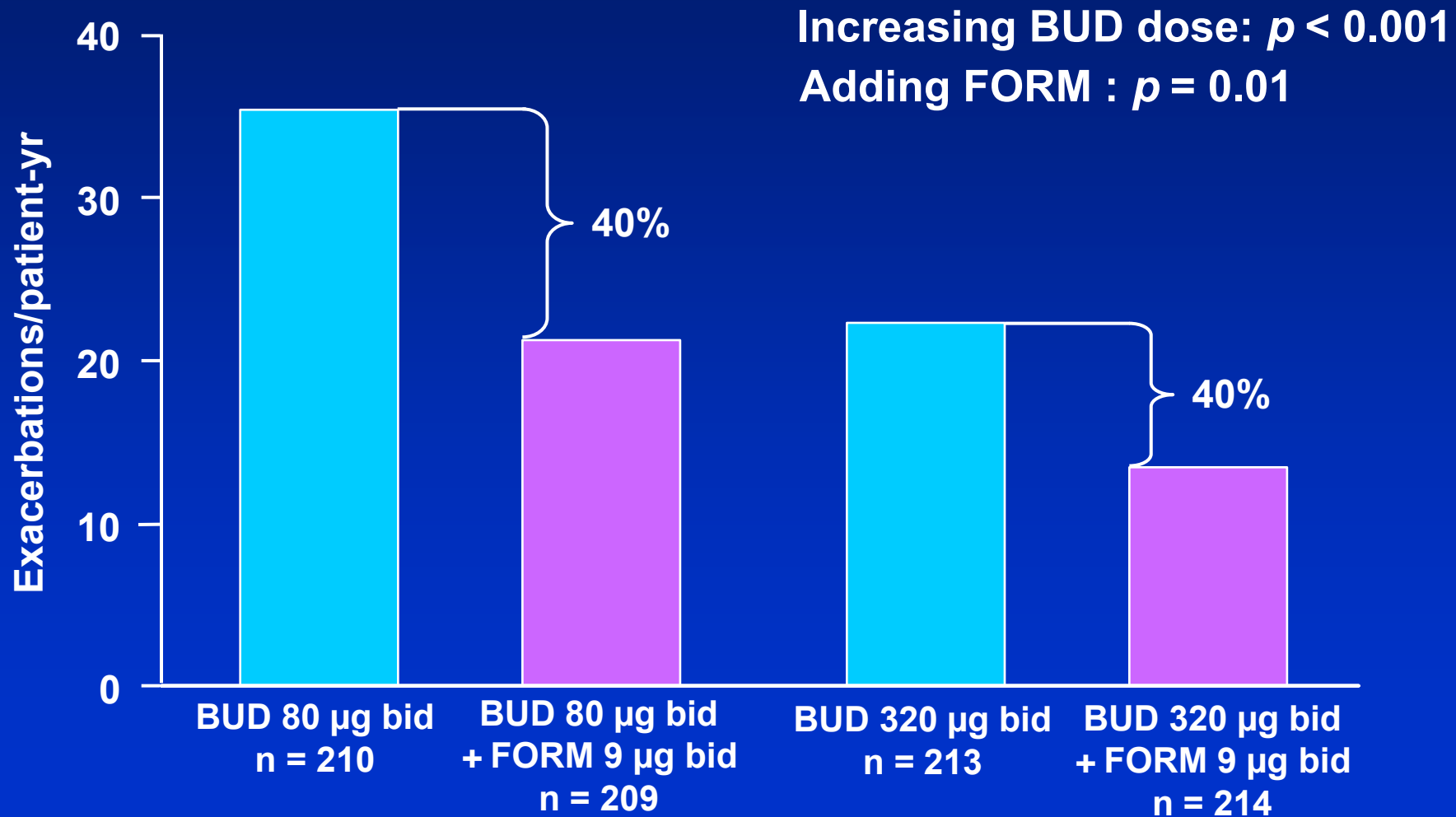


Note: Doses expressed as delivered doses.

Pauwels RA, et al. *N Engl J Med*. 1997;337:1405-1411.

Adding Formoterol to Budesonide Reduces *Mild* Asthma Exacerbations

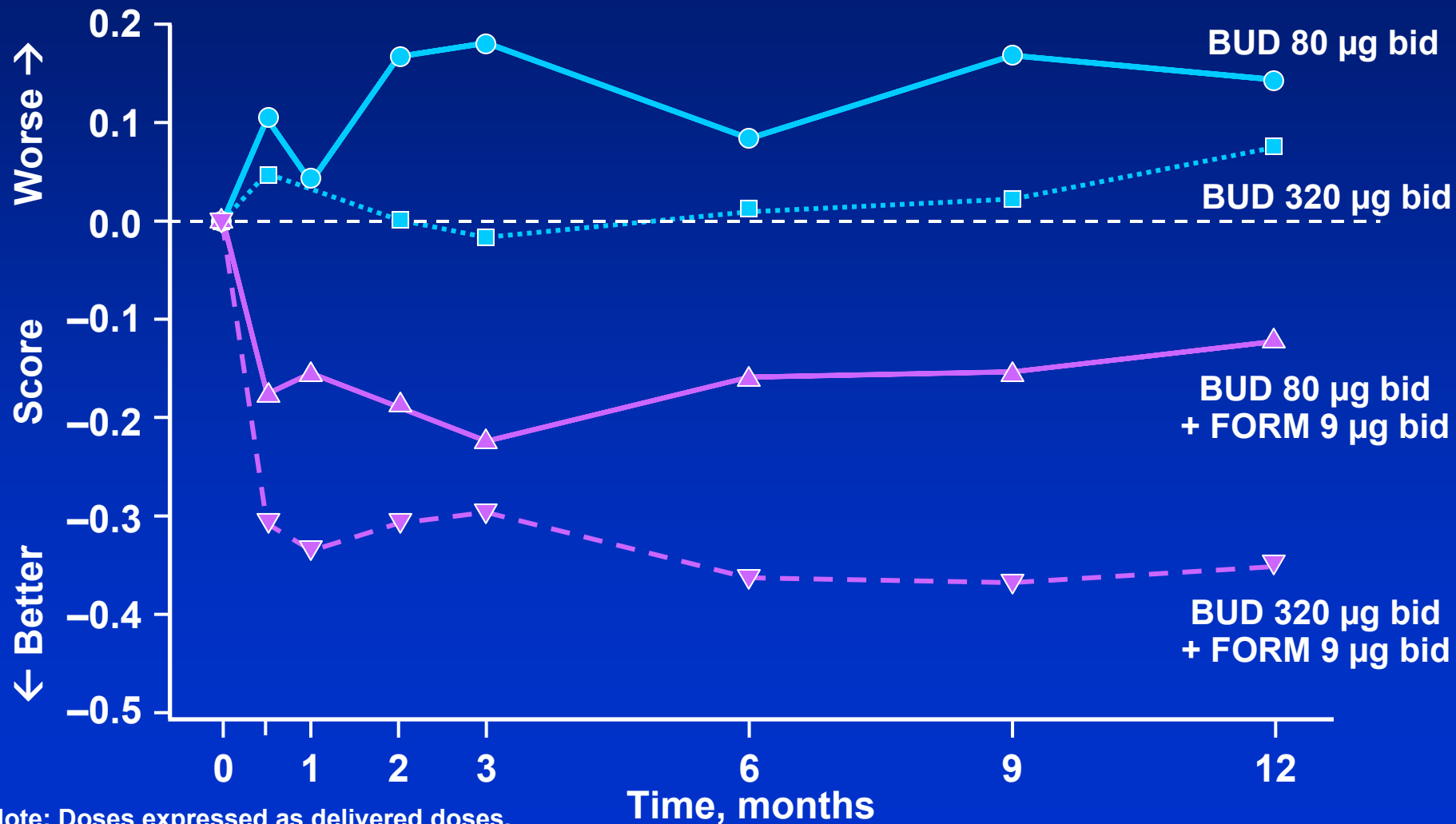
Study 3018—FACET



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Pauwels RA, et al. *NEJM* 1997;337:1405-1411.

Adding Formoterol to Budesonide Reduces Asthma Symptoms

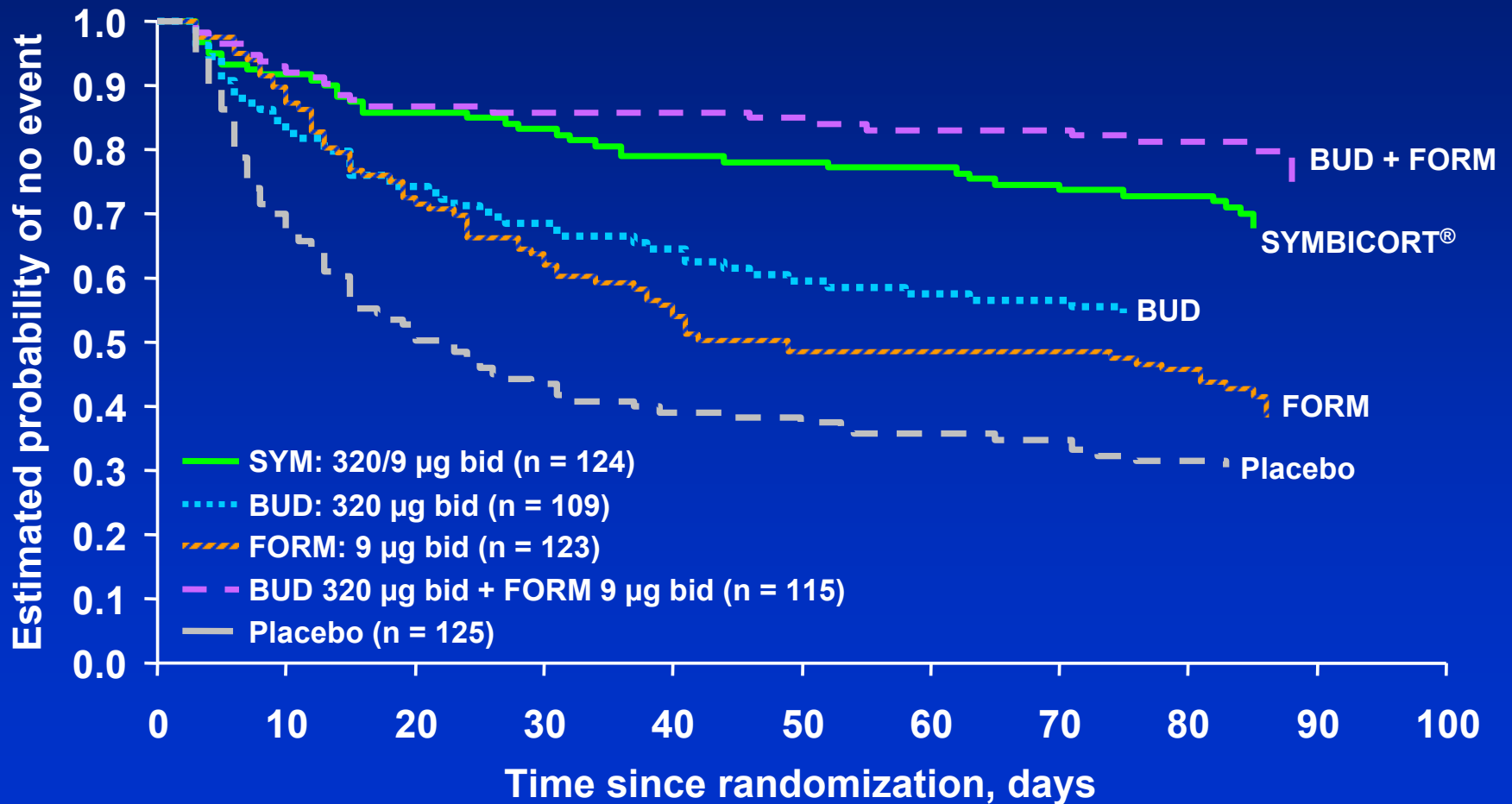
Study 3018—FACET



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Pauwels RA, et al. *NEJM* 1997;337:1405-1411.

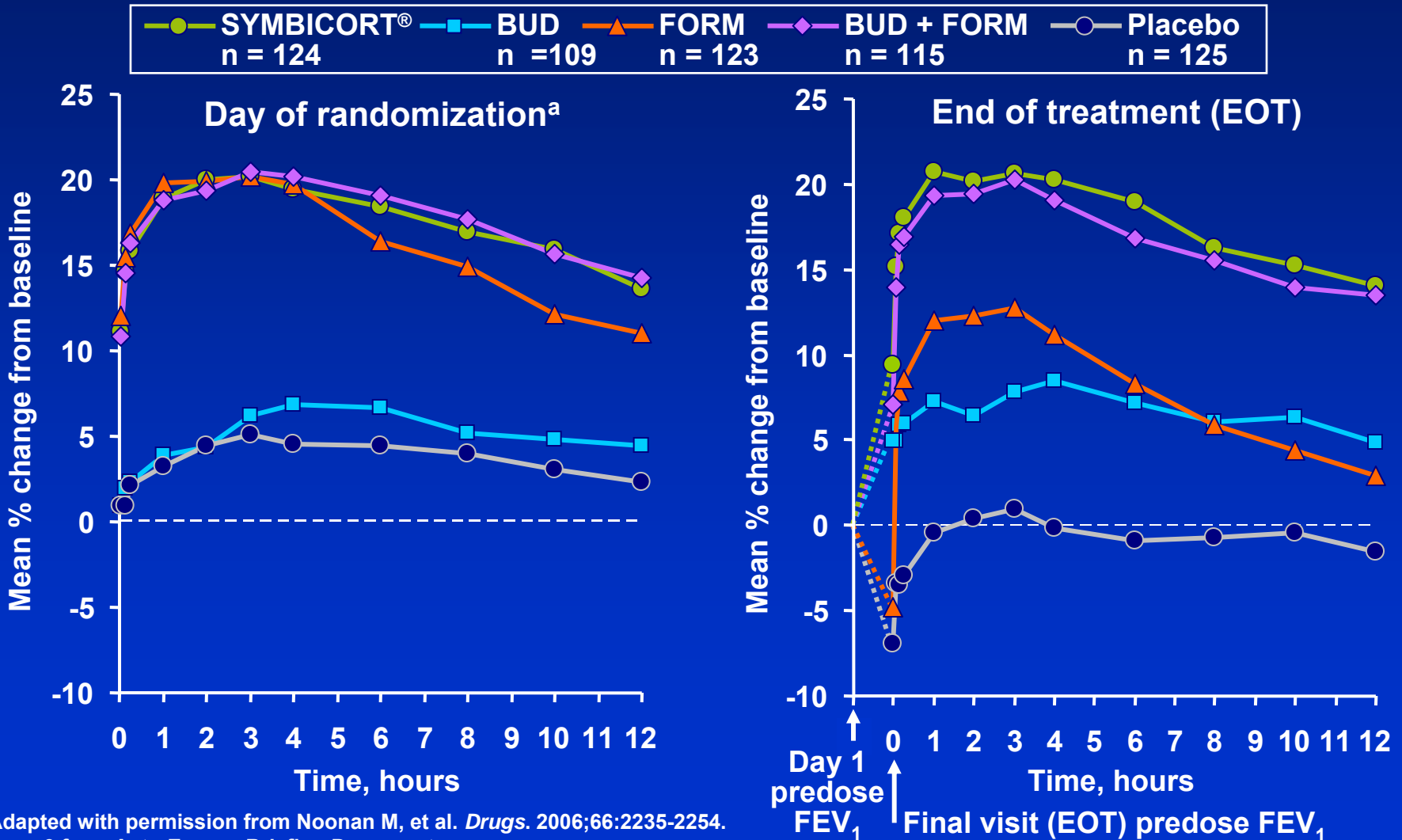
Adding Formoterol to Budesonide Reduces Risk of Asthma Worsening

Study 717—Pivotal US Study



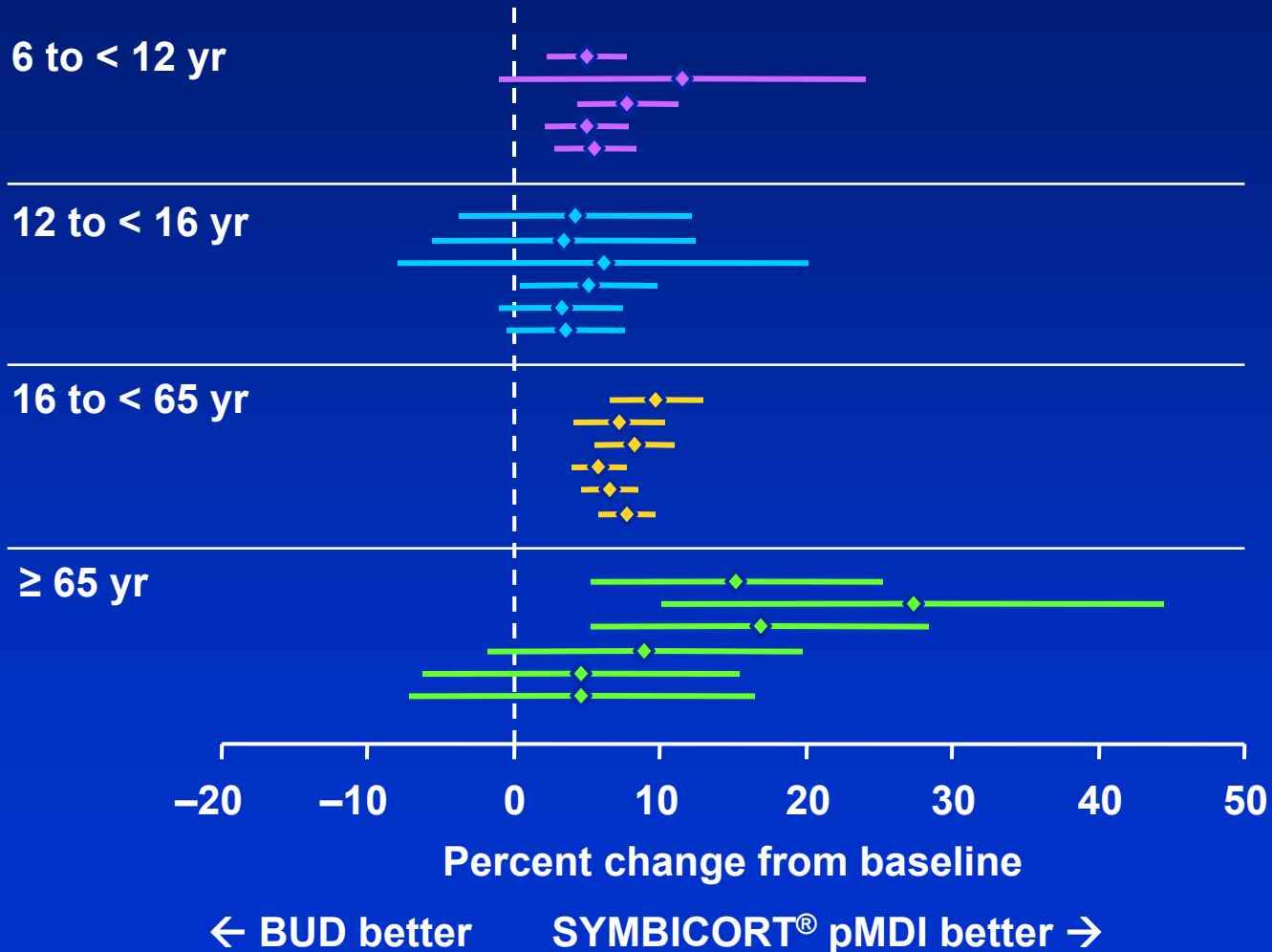
Adding Formoterol to Budesonide Improves FEV₁

Study 717—Pivotal US Study

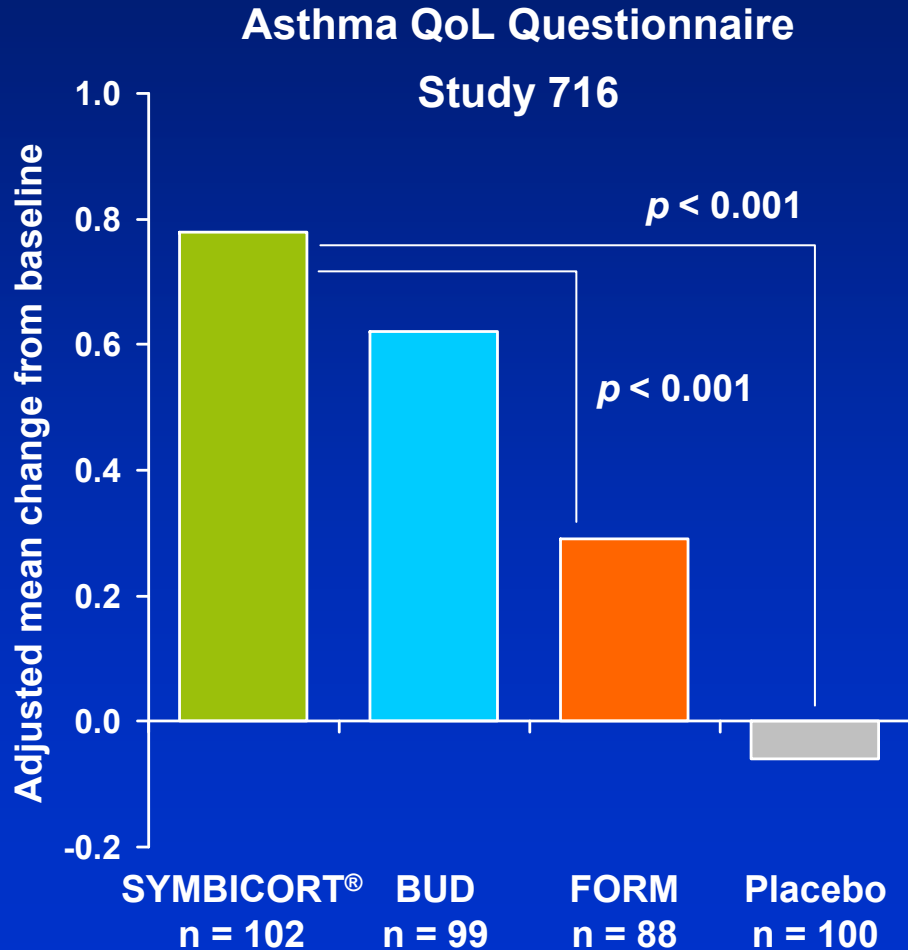


Adding Formoterol to Budesonide Improves Morning Predose PEF

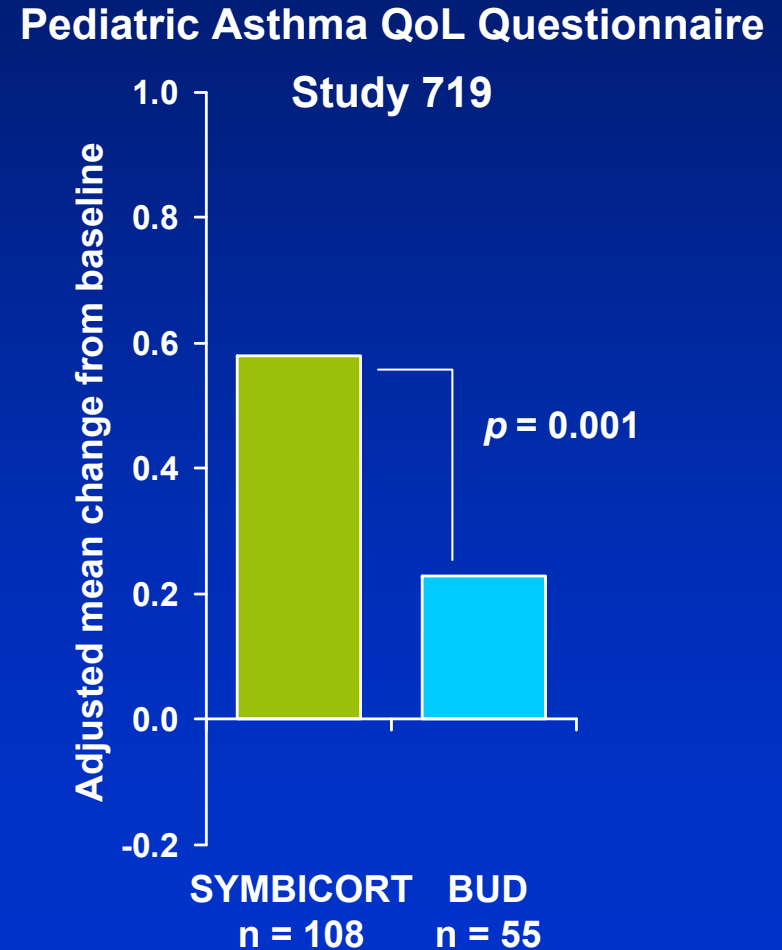
7 Trials



Formoterol Plus Budesonide Improves Asthma Quality of Life in Adults and Children



Note: Patients aged ≥ 18 years.



Note: Patients aged 7 - < 12 years.

SYMBICORT® Has a Positive Benefit Profile

- **Reduces future asthma risk**
 - **Worsenings**
 - **Exacerbations**
- **Improves current asthma control**
 - **Reduces asthma symptoms**
 - **Improves lung function**
 - **Improves quality of life**
- **Benefits in adults and children**

Risk

Kevin Carroll, MSc, BSc
VP Statistics & Chief Statistician
AstraZeneca



FDA Requested Trial Data

- All blinded, parallel-arm, randomized, controlled trials conducted with LABA in the treatment of asthma
 - LABA administered as randomized treatment with or without ICS or other adjunctive therapy
 - Placebo and active-controlled trials
- Blinded adjudication process for serious asthma related events occurring on treatment

Total of 23,510 Patients in 42 Trials Meeting FDA's Criteria

DPADP FDA criteria

N = 23,510 in 42 trials

FORM N = 13,542

Non-LABA N = 9,968



Additional exclusion criteria (QSPG)

FDA exclusion of data in 22,240 (95%) patients

- 1. LABA doses and/or comparators not approved in the US = 85.0% of data loss**
- 2. Pediatric patients = 14.6% of data loss**
- 3. N < 20 subjects in any arm = 0.4% of data loss**
- 4. Blinded duration < 7 days = 0% of data loss**



FDA analysis

N = 1270 in 4 trials

FORM N = 766

Non-LABA N = 504

Totally of the Trial Data Examined To Maximize Information On Possible Risks

- **All 23,510 patients in 42 trials included**
- **As per FDA request**
 - **All cause death**
 - **Asthma-related death**
 - **Asthma-related intubation**
 - **Asthma-related hospitalization**
- **Main comparison formoterol vs non-LABA**
 - **Refined comparisons**
 - **Formoterol + ICS vs ICS**
 - **Formoterol \geq 18 ug + ICS vs ICS**
- **Pediatrics**

No Increase in the Risk of Death or Asthma-related Intubations

Overall Trial Data (N = 23,510)

	Formoterol exposed	Non-LABA exposed
Patients, n	13,542	9968
Total exposure (1000 treatment-yr)	6.49	4.92
All-cause deaths, n (%)	3 (0.02)	4 (0.04)
Death rate/1000 patients/yr	0.53	0.82
Relative risk (95% CI)	0.64 (0.14, 2.92)	
Rate difference (95% CI)	-0.29 (-1.31, 0.72)	
Patients with intubations, n (%)	1 (0.01)	0
Asthma-related deaths, n (%)	0	0

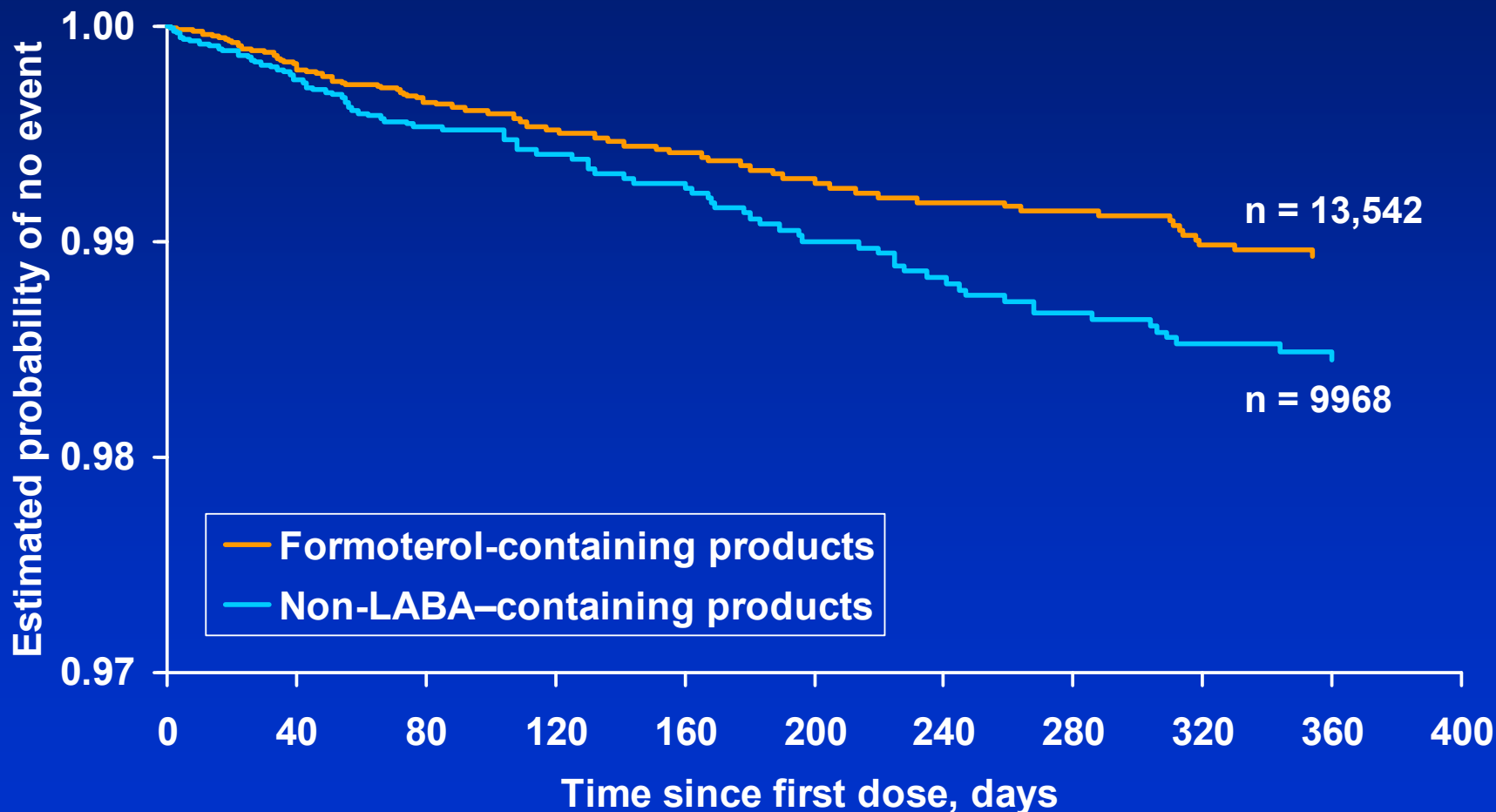
No Increase in the Risk of Asthma-related Hospitalization

Overall Trial Data (N = 23,510)

	Formoterol exposed	Non-LABA exposed
Patients, n	13,542	9968
Total exposure (1000 treatment-yr)	6.49	4.92
Patients with ≥ 1 asthma-related hospitalization, n (%)	78 (0.58)	83 (0.83)
Asthma-related hospitalizations/ 1000 patients/yr	12.05	16.40
Relative risk (95% CI)	0.73 (0.54, 1.01)	
Rate difference (95% CI)	-4.35 (-8.87, 0.18)	

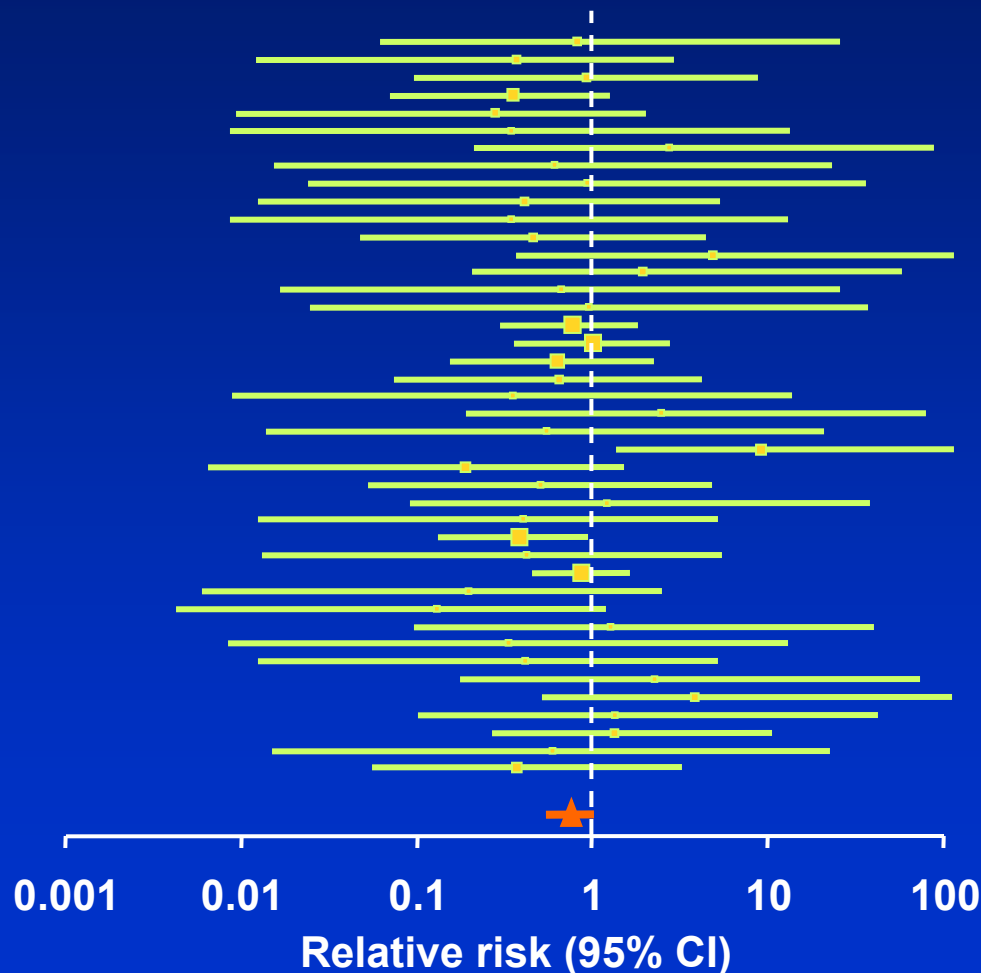
No Increase in the Risk of Asthma-related Hospitalization

Overall Trial Data (N = 23,510)



No Increase In the Risk of Asthma-Related Hospitalization

Overall Trial Data (N = 23,510), 42 Trials



Relative risk (95% CI)

0.73 (0.54, 1.01)

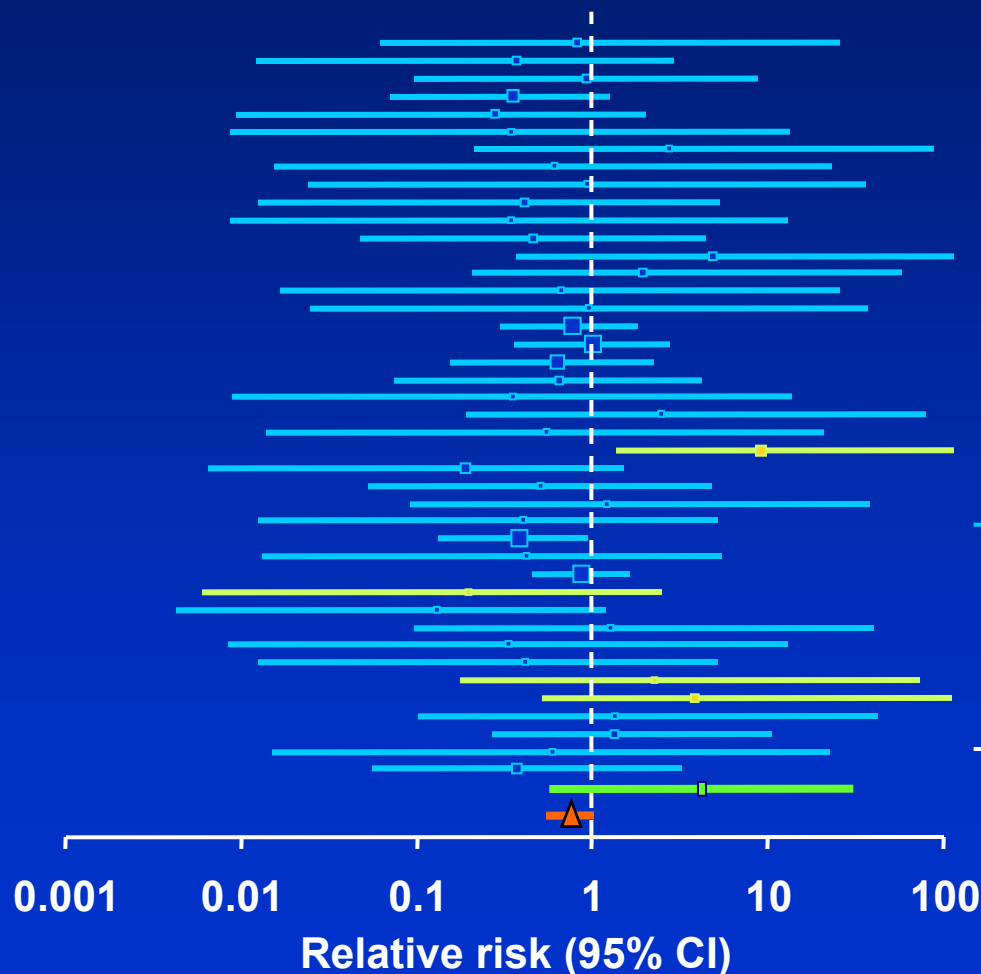
Rate difference (95% CI)

-4.35 (-8.87, 0.18)

← Formoterol better Non-LABA better →

FDA QSPG Criteria Result In Exclusion of 95% of Originally Requested Trial Data

N = 1270

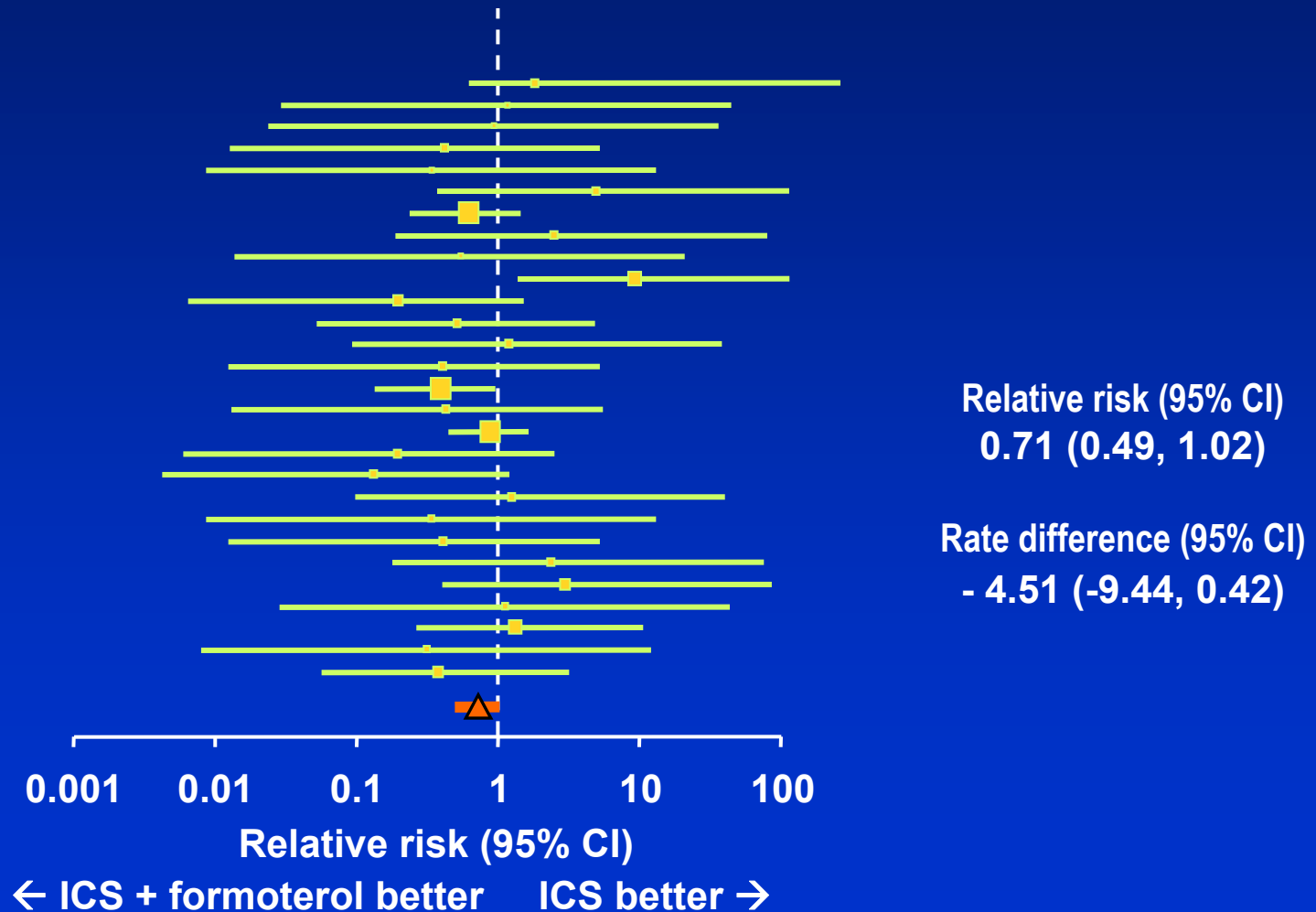


Trials included	Patients, n (%)
353:	115/286 = 40%
681:	678/679 = 100%
716:	244/511 = 48%
717:	233/596 = 39%
4 trials	1270/2072 = 62%

← Formoterol better Non-LABA better →

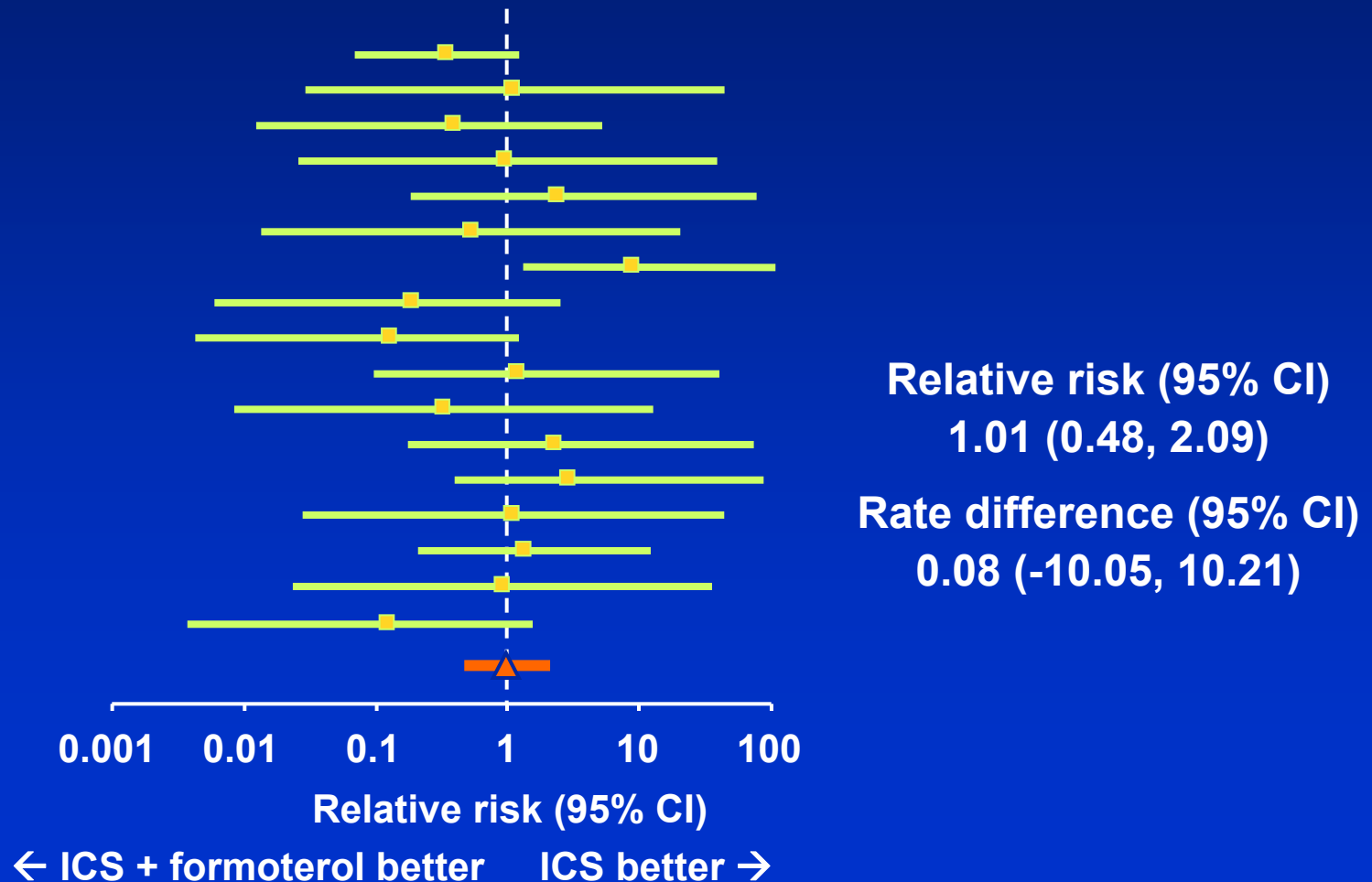
Adding Formoterol to Budesonide Does Not Increase Risk of Asthma-related Hospitalization

ICS + Formoterol vs ICS, (N = 18,161), 29 Trials



Adding a Daily Dose of $\geq 18 \mu\text{g}$ Formoterol to Budesonide Does Not Increase Risk of Asthma-related Hospitalization

N = 7213, 17 Trials



Data Consistently Show No Increase in the Risk of Asthma-Related Hospitalization

FORM vs non-FORM

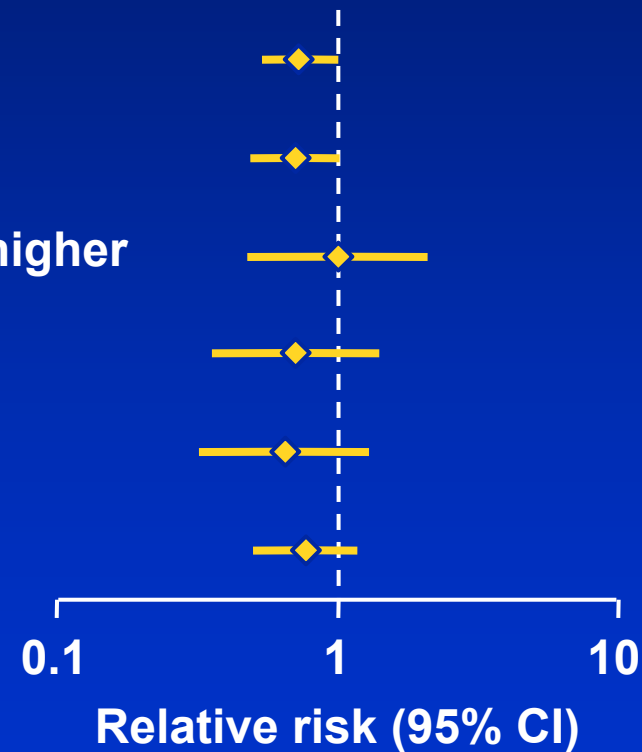
ICS+FORM_{free or comb} vs ICS

ICS+FORM_{free or comb} vs ICS; 18 µg or higher

ICS+FORM_{free} vs ICS (ICS background)

ICS+FORM_{free} vs ICS (ICS randomised)

SYMBICORT® vs ICS (ICS randomised)



← Formoterol better Comparator better →

No Dose-Related Increase In Asthma-Related Hospitalizations With Formoterol

Daily dose of formoterol	Patients, n	Patients reporting ≥ 1 asthma-related hosp, n (%)	Hospitalization per 1000 treatment-yr
$\geq 4.5 \mu\text{g}$	12,522	67 (0.54)	11.59
Non-LABA	8945	69 (0.77)	16.16
$\geq 9 \mu\text{g}$	12,285	60 (0.49)	10.71
Non-LABA	8945	69 (0.77)	16.16
$\geq 18 \mu\text{g}$	5653	25 (0.44)	13.81
Non-LABA	4160	18 (0.43)	15.25
$\geq 36 \mu\text{g}$	1088	1 (0.09)	1.89
Non-LABA	561	2 (0.36)	9.52

Pediatric Patients



No Deaths or Asthma-related Intubations in Pediatrics

Overall Trial Data, Patients < 12 Years (N = 3423)

	Formoterol exposed	Non-LABA exposed
Patients, n	2155	1268
Total exposure (1000 treatment-yr)	0.77	0.48
All-cause deaths, n (%)	0	0
Deaths/1000 treatment-yr	0	0
Asthma-related deaths, n (%)	0	0
Deaths/1000 treatment-yr	0	0
Patients with intubations, n (%)	0	0
Intubations/1000 treatment-yr	0	0

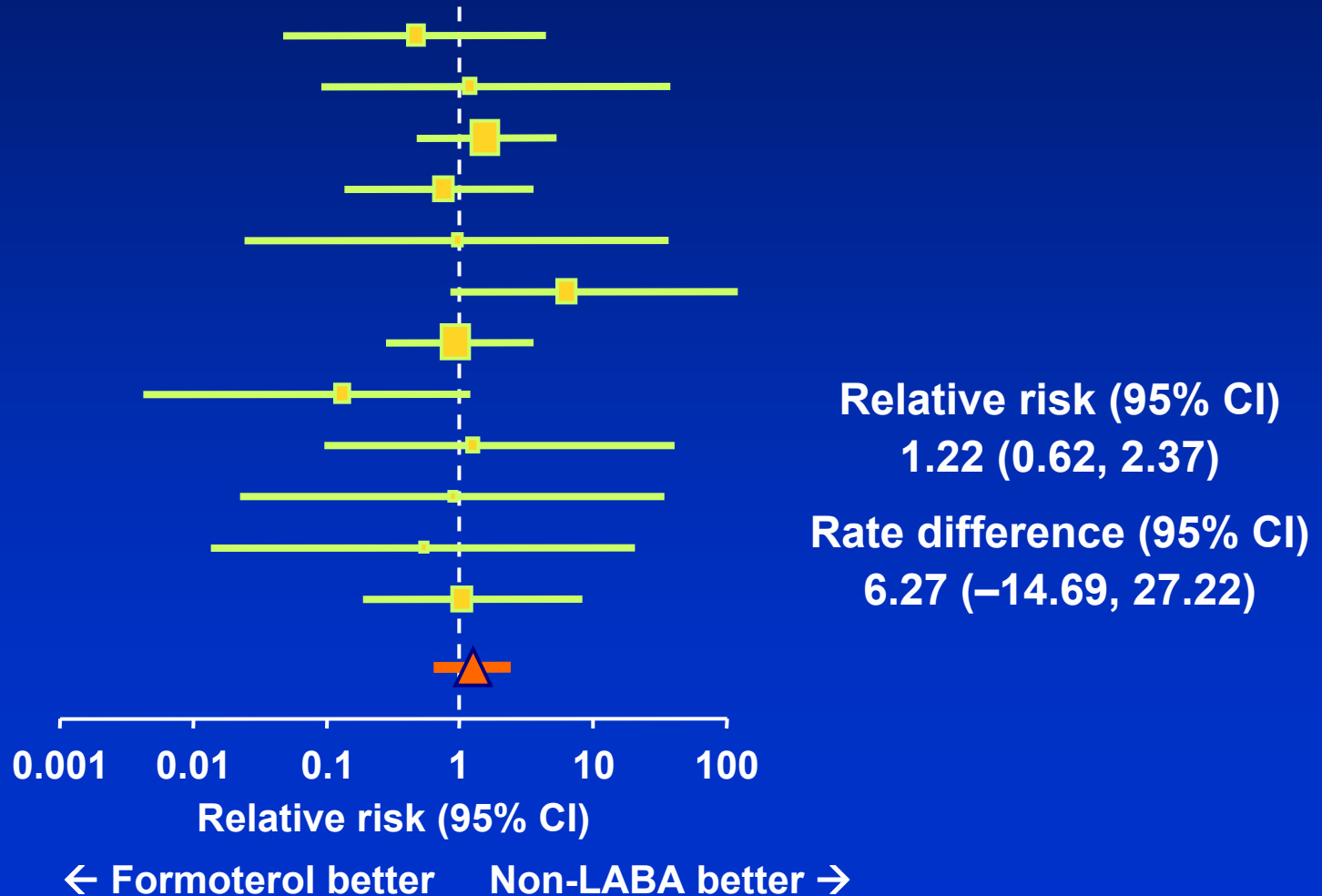
Patients With ≥ 1 Asthma-Related Hospitalization

Overall Trial Data, Patients < 12 Years (N = 3423)

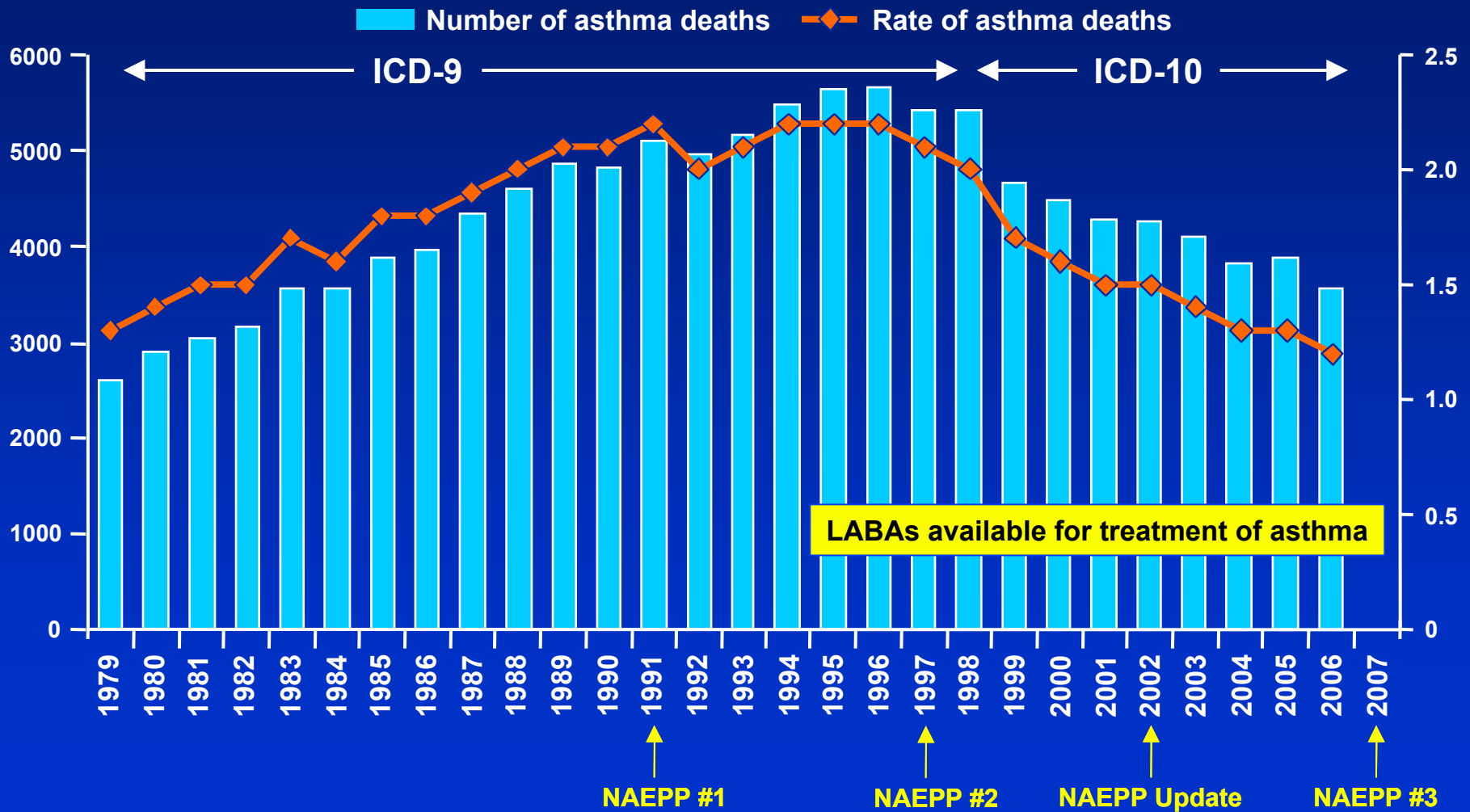
	Formoterol exposed	Non-LABA exposed
Patients < 12 y, n	2155	1268
Total exposure (1000 pt-yr)	0.77	0.48
Patients with ≥ 1 asthma-related hospitalization, n (%)	25 (1.16)	14 (1.10)
Asthma-related hospitalizations/ 1000 patients/yr	35.3	29.1
Relative risk (95% CI)	1.22 (0.62, 2.37)	
Rate difference (95% CI)	6.27 (-14.69, 27.22)	

Asthma-Related Hospitalizations

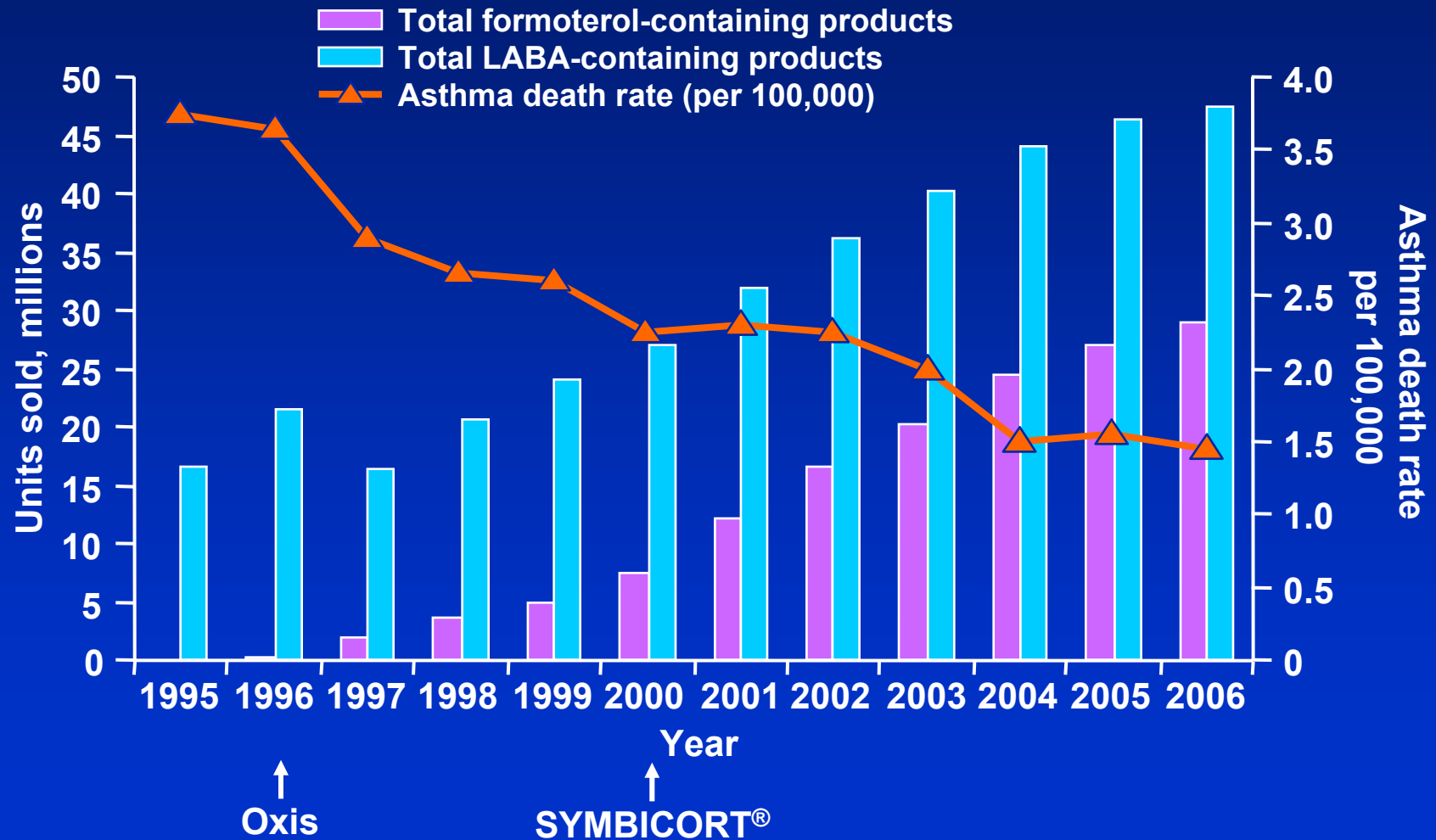
Overall Trial Data, Patients < 12 Years (N = 3423) 12 Trials



Changing Pattern in Asthma Mortality in the US



Asthma Deaths and Sales of LABA-containing Products in Sweden



Conclusions

Catherine Bonuccelli, MD
Vice President
Development Projects, SYMBICORT[®]
AstraZeneca



Positive Benefit/Risk for SYMBICORT® pMDI

- **Unequivocal benefits for SYMBICORT**
 - Improves asthma control by improving lung function, reducing symptoms and improving QoL
 - Reduces the risk of asthma worsenings and exacerbations
- **In 23,510 patients from 42 controlled, randomized, blinded, parallel-group trials**
 - No increased risk of asthma-related deaths, intubations, or hospitalizations
 - Asthma hospitalizations occurred less frequently in formoterol-treated patients
 - Results are comprehensive and more precise than the FDA analysis

Positive Benefit/Risk for SYMBICORT® pMDI

- Safe, effective, and important treatment for patients not well controlled with inhaled corticosteroids alone
- Current labeling reflects appropriate use of LABAs always with inhaled corticosteroids
- Potential risks are adequately described in current SYMBICORT pMDI label
- Clinical evidence supports that SYMBICORT should remain a therapeutic option

Relative Risk Estimates of Hospitalizations by Trial and Overall ICS + Formoterol vs ICS, Patients < 12 Years

