

# Risk

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## FDA Requested Trial Data

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- **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**

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- **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

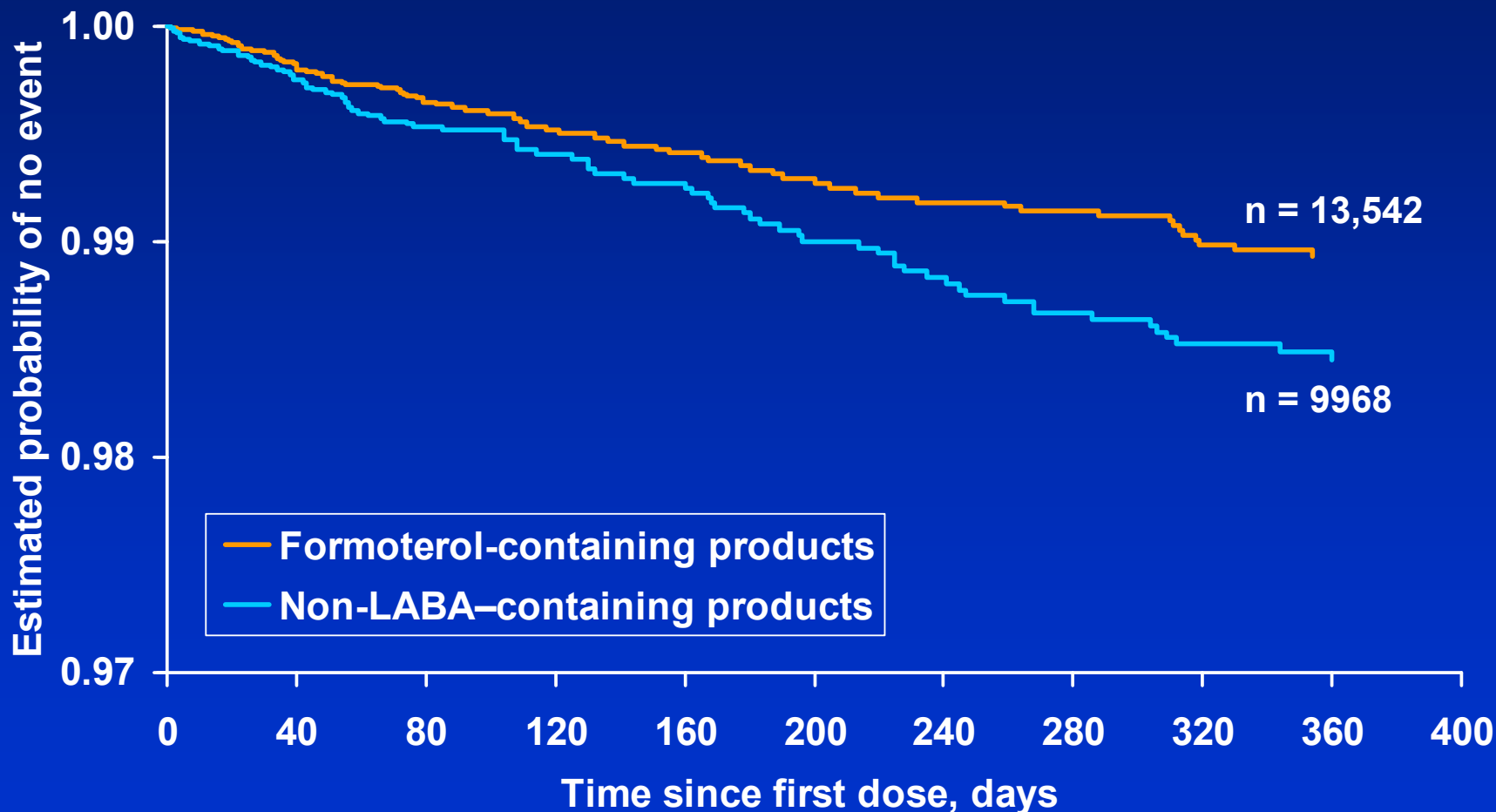
# No Increase in the Risk of Asthma-related Hospitalization

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 $\geq 1$ 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)	

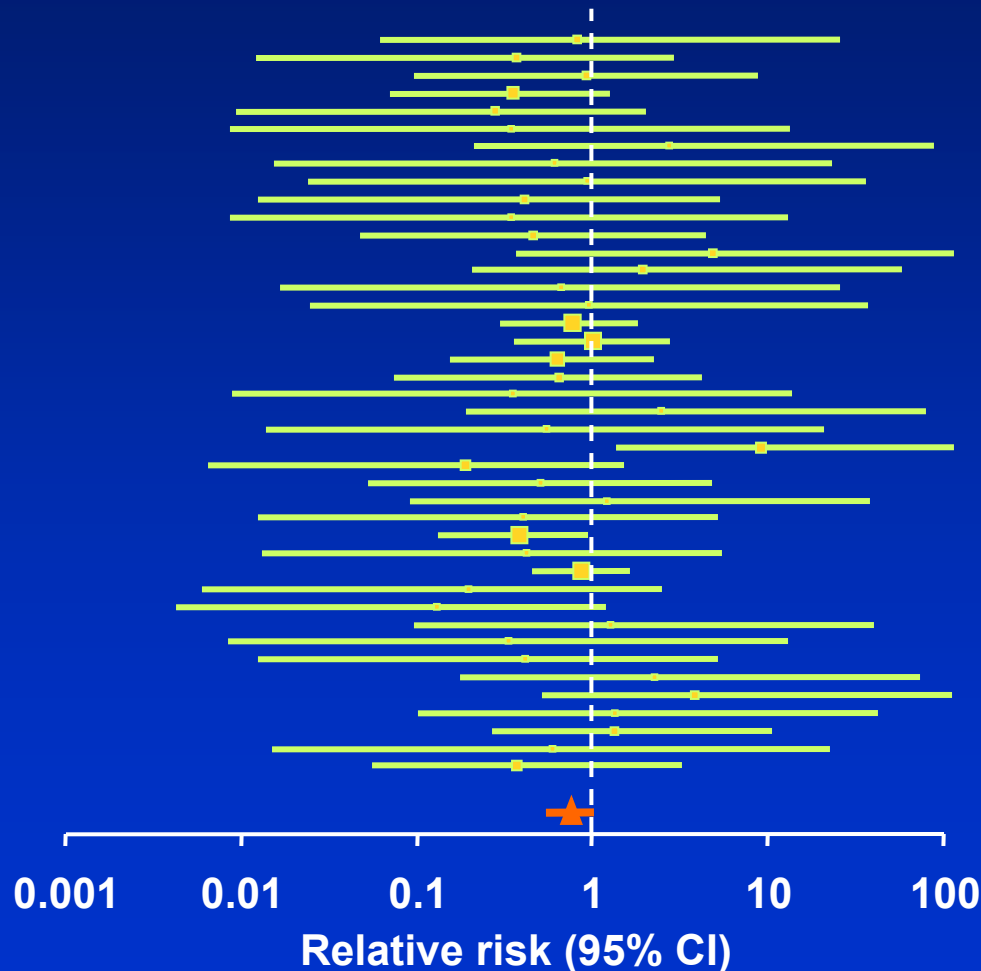
# No Increase in the Risk of Asthma-related Hospitalization

Overall Trial Data (N = 23,510)



# No Increase In the Risk of Asthma-Related Hospitalization

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

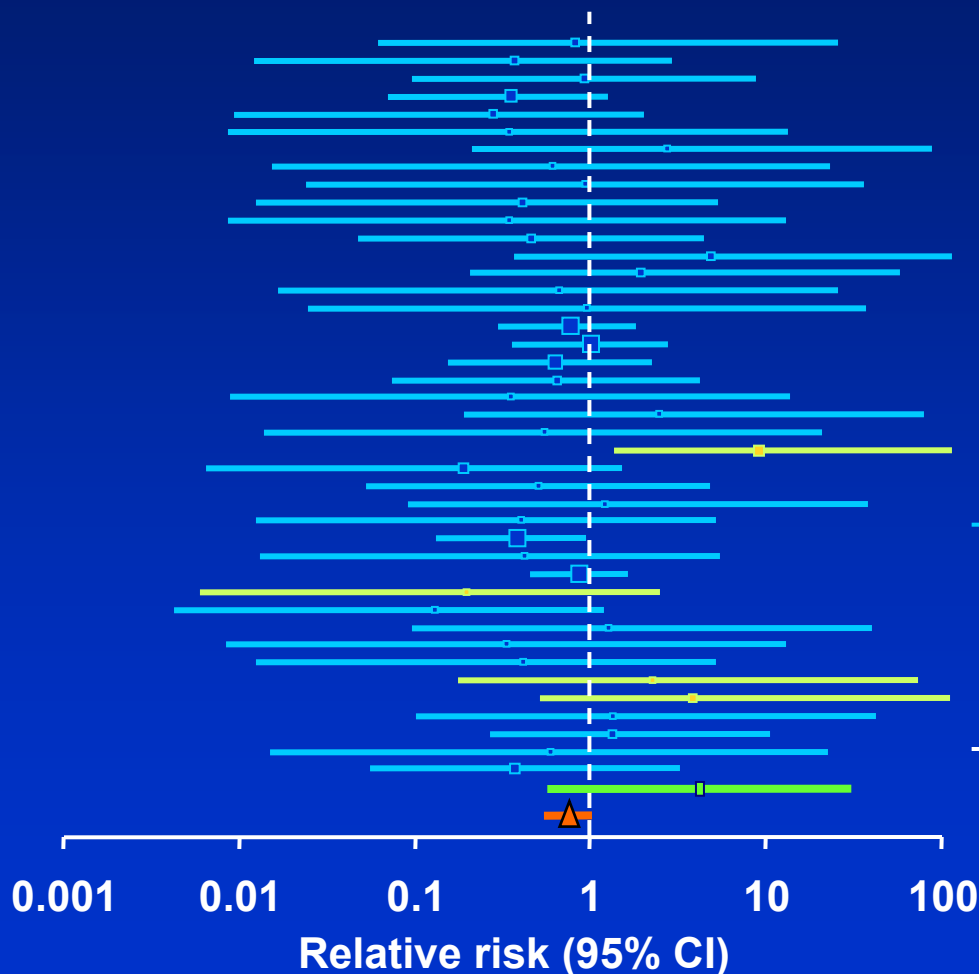


← Formoterol better Non-LABA better →



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

N = 1270

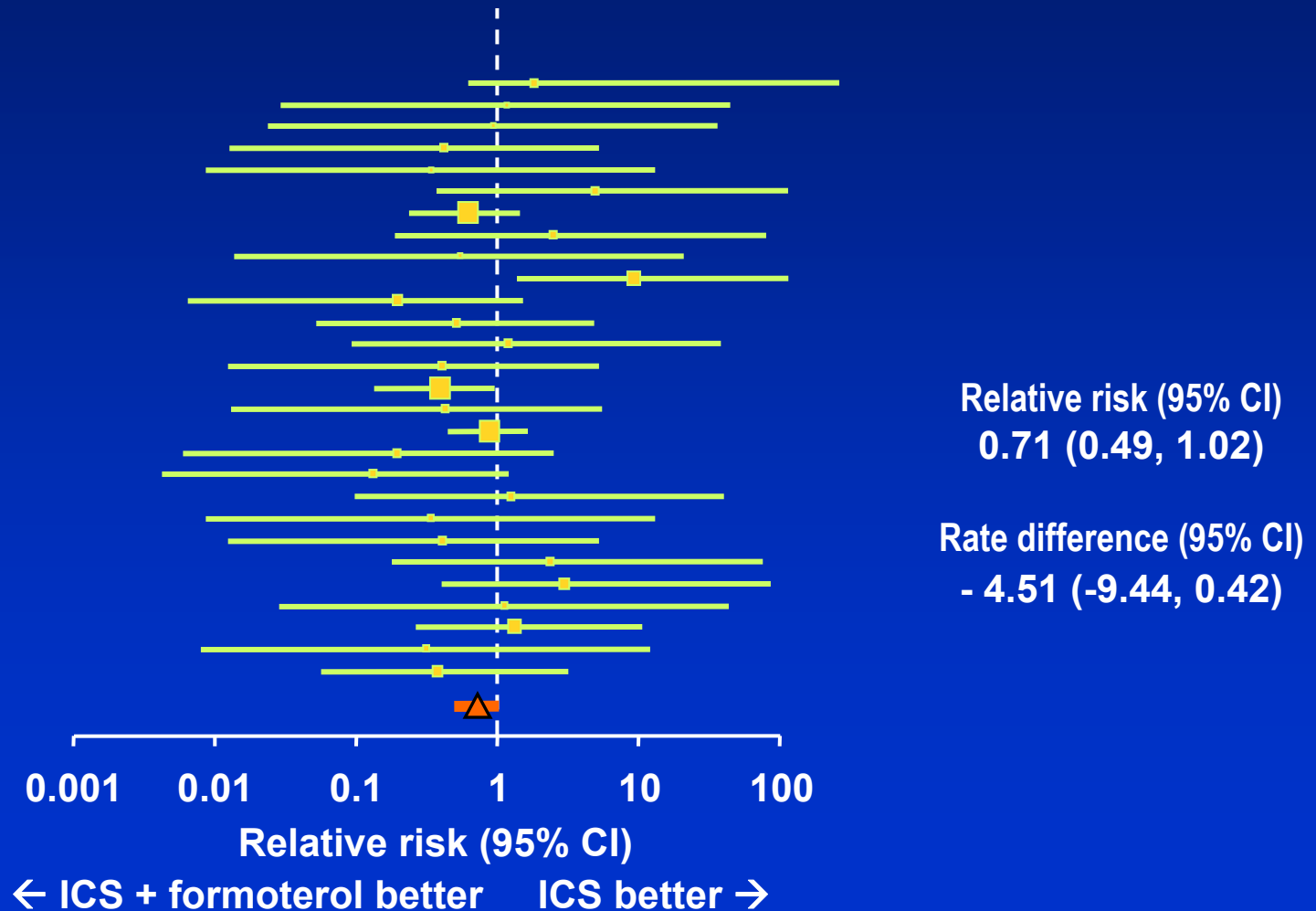


Trials included	Patients, n (%)
353:	115/286 = 40%
681:	678/679 = 100%
716:	244/511 = 48%
717:	233/596 = 39%
<b>4 trials</b>	<b>1270/2072 = 62%</b>

← Formoterol better    Non-LABA better →

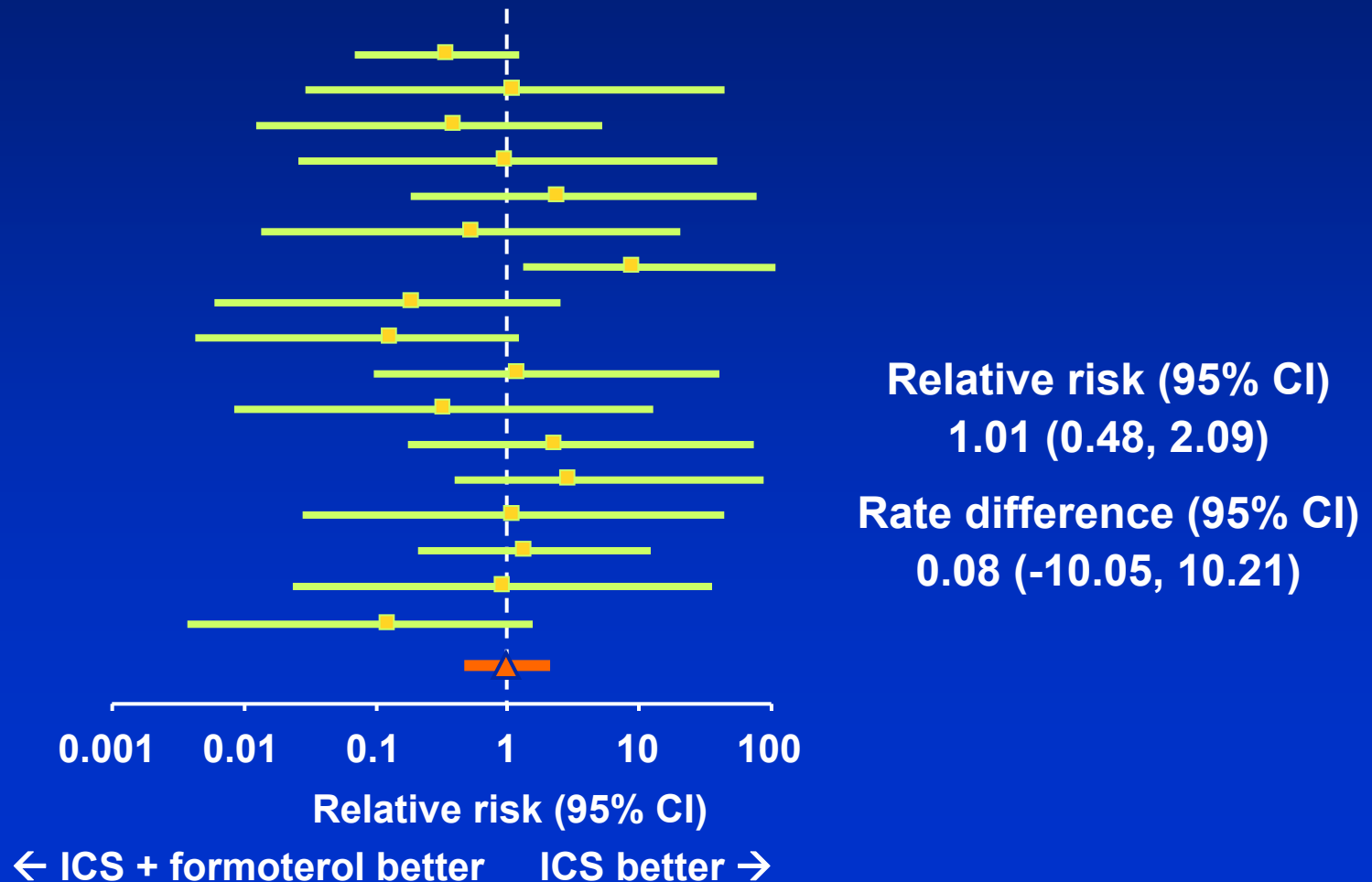
# Adding Formoterol to Budesonide Does Not Increase Risk of Asthma-related Hospitalization

## 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

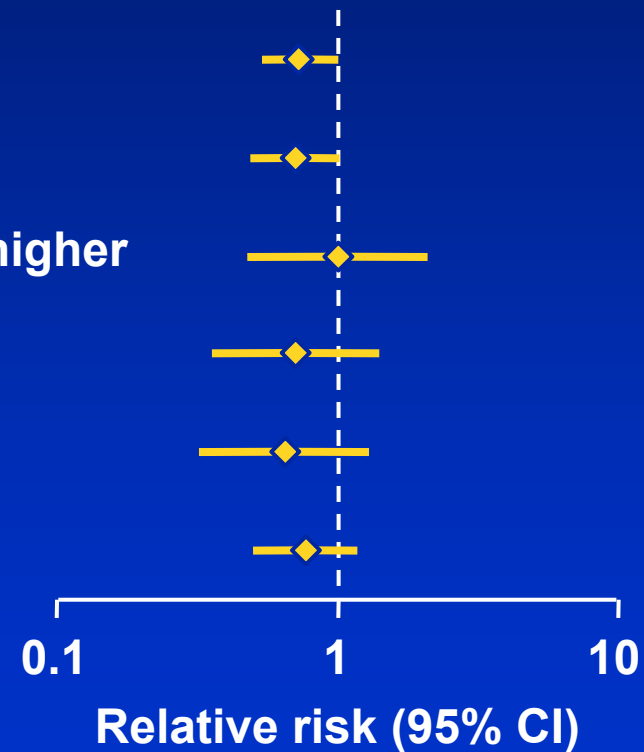
ICS+FORM<sub>free or comb</sub> vs ICS

ICS+FORM<sub>free or comb</sub> vs ICS; 18 µg or higher

ICS+FORM<sub>free</sub> vs ICS (ICS background)

ICS+FORM<sub>free</sub> 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 $\geq 1$ 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

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# No Deaths or Asthma-related Intubations in Pediatrics

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

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

# Patients With $\geq 1$ Asthma-Related Hospitalization

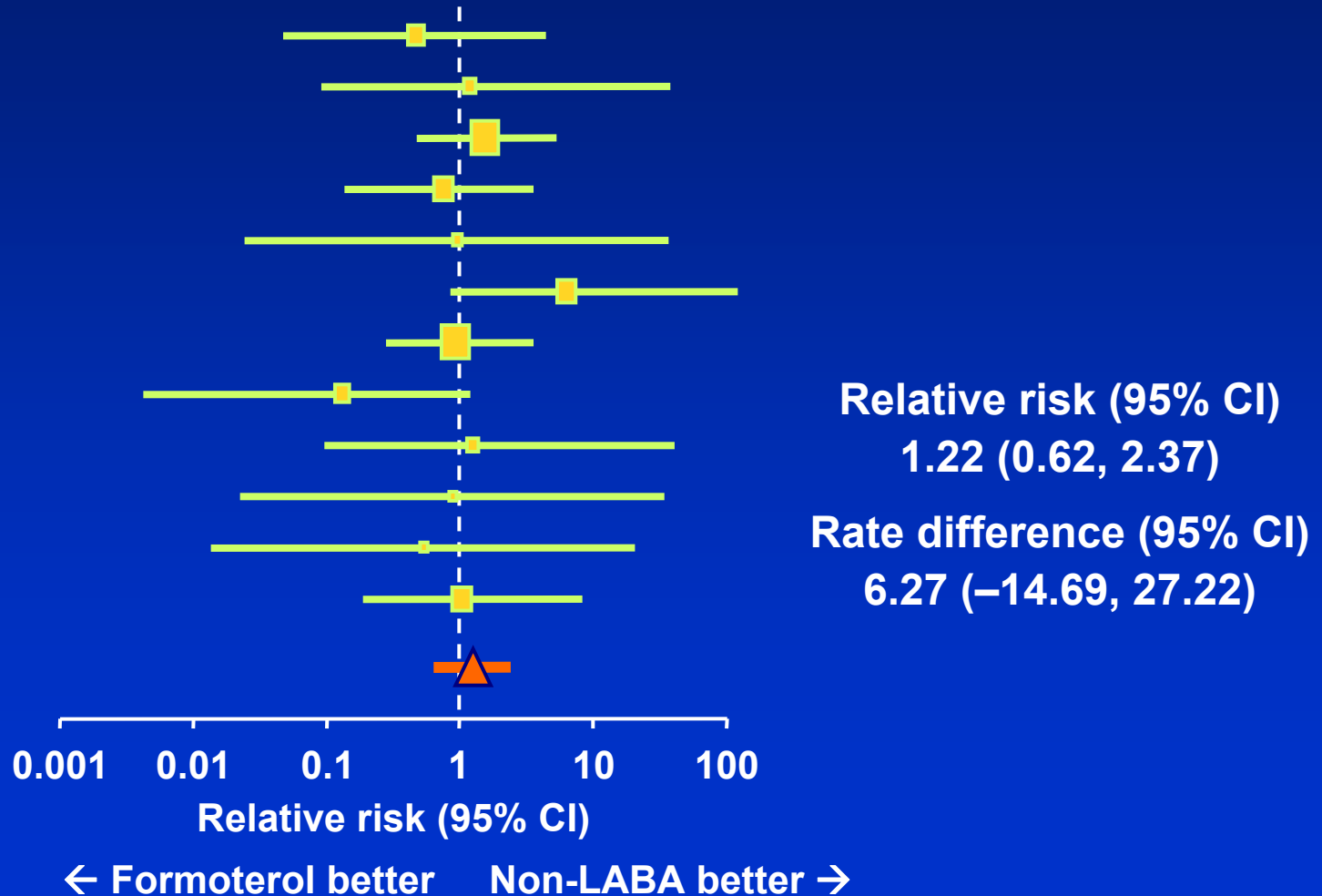
Overall Trial Data, Patients < 12 Years (N = 3423)

	Formoterol exposed	Non-LABA exposed
Patients < 12 y, n	2155	1268
Total exposure (1000 pt-yr)	0.77	0.48
Patients with $\geq 1$ 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)	

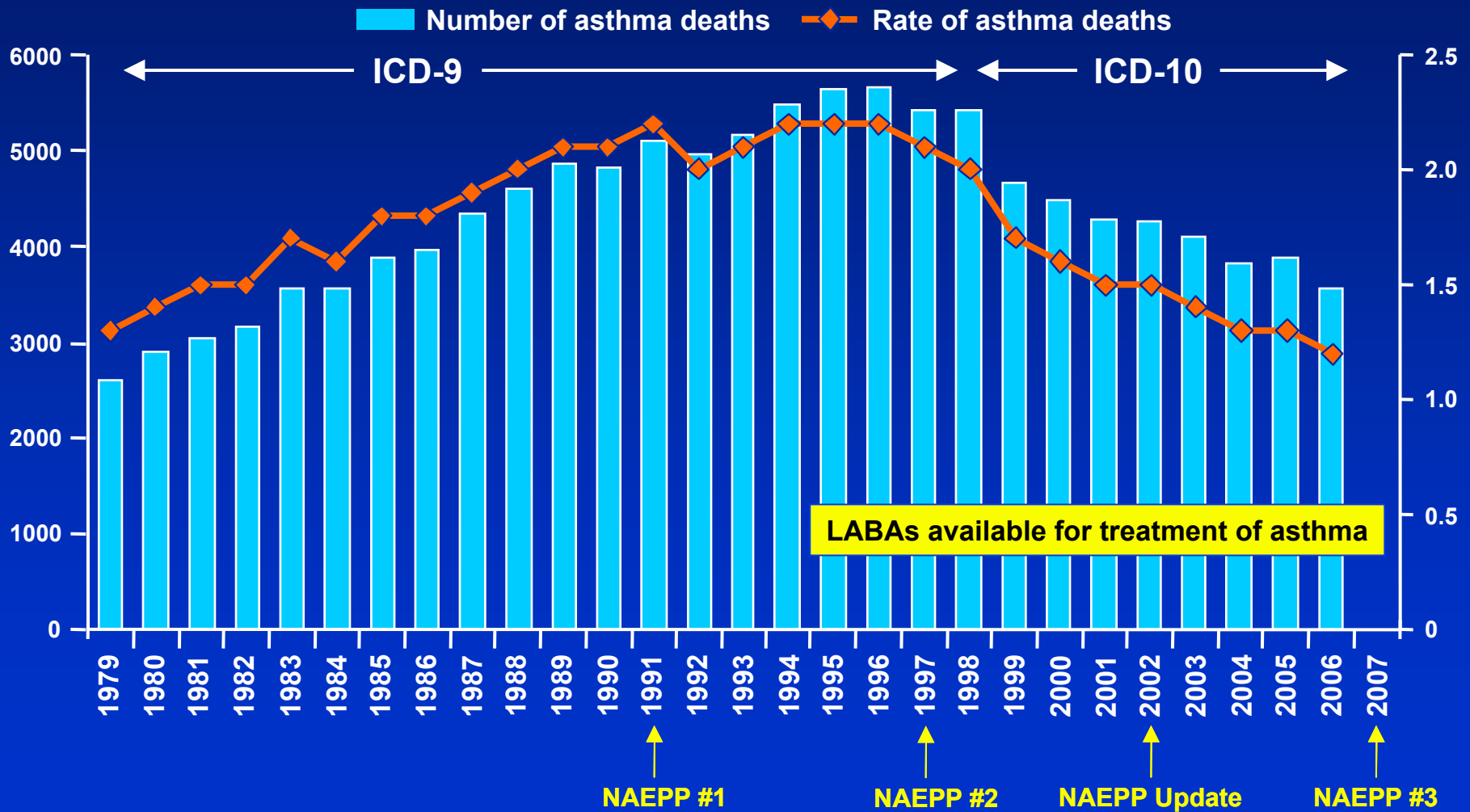


# Asthma-Related Hospitalizations

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

