TPAC (Thai Pharmacist Practitioner Group in Asthma and COPD )
Association of Hospital Pharmacy (Thailand)

# "Novel Pharmacotherapy in Asthma and COPD"


Suthan Chanthawong

B. Pharm, Grad Dip in Pharmacotherapy

Specialized Residency in Internal Medicine

Faculty of Pharmaceutical Sciences, Khon Kaen University

# Scope of Presentation

- INDACATEROL: COPD
- ROFLUMILAST: COPD
- OMALIZUMAB: ASTHMA

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# "Ultra-LABAs: Indacaterol"


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# Indacaterol

- Powder capsule administered by a
  - Breezhaler (Onbrez ®) or
  - Neohaler (Acapta®)

- Mechanism of Action
  - § Ultra Long-acting beta-2 agonist (LABA)

# Clinical Application

- Indications:
  - The long-term maintenance treatment of airflow obstruction in patients with COPD
- Place in therapy:
  - Once daily alternative to salmeterol (bid), formoterol (bid), or tiotropium (od) in the treatment of *moderate to severe COPD*

# Clinical Application

- Contraindications:
  - Asthma (without use of a long-term asthma control medication)
- Warnings/Precautions:
  - Asthma-related death
  - Acutely deteriorating COPD
  - Relief of acute symptoms
  - Excessive use (CV effects)
  - Paradoxical bronchospasm

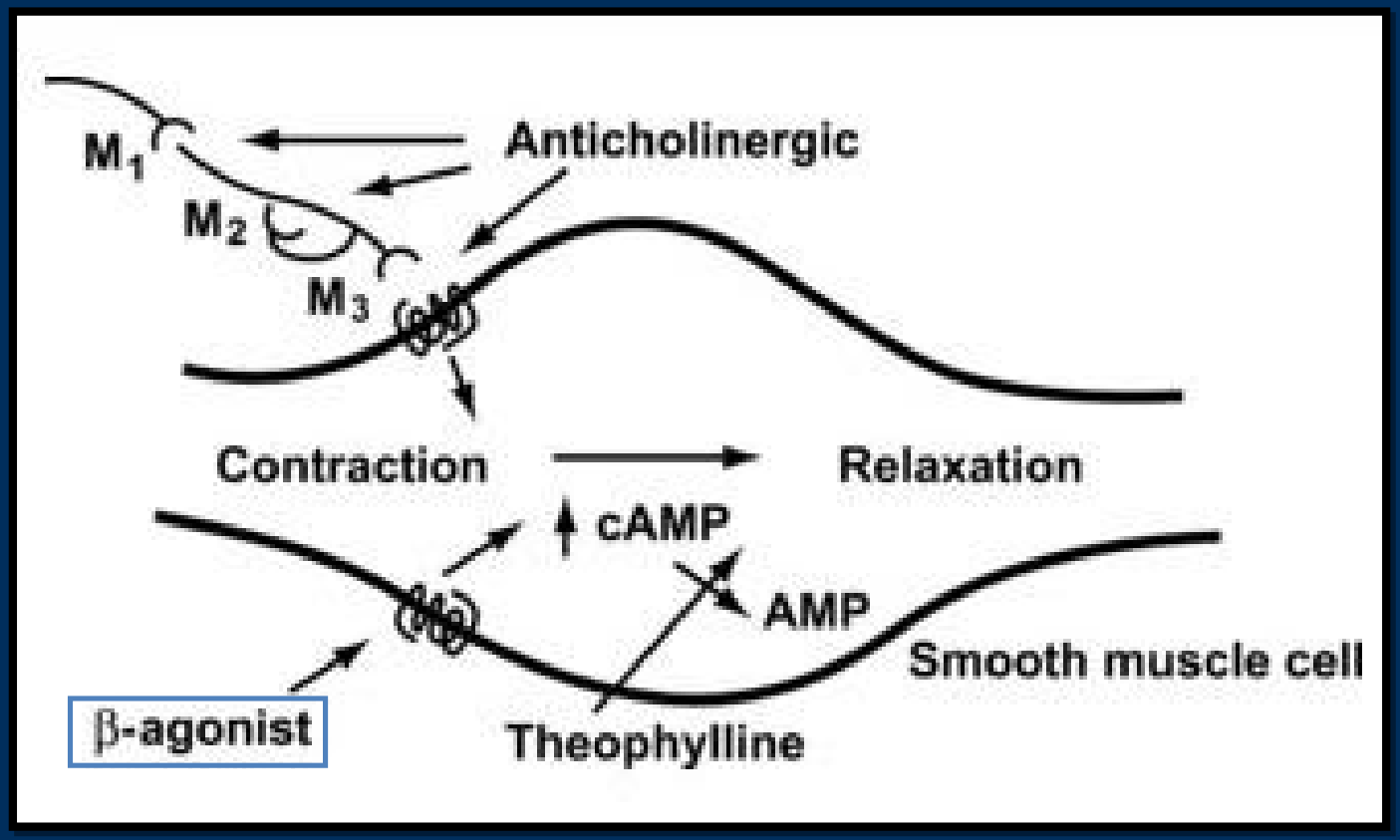
# Clinical Application

- Pregnancy:
  - Category C
- Lactation:
  - Use with caution
  - Unknown if excreted in breast milk

# Drug Facts

- Pharmacology:
  - Long-acting beta$_2$-adrenergic agonist
  - Inhalation powder acts locally in lungs as bronchodilator
  - Stimulates intracellular adenyl cyclase to catalyze the conversion of ATP to cAMP
  - Increased cAMP causes bronchial smooth muscle relaxation

# $B_2$ agonist: Mechanism of Action



# Pharmacokinetics

| Parameter | Information |
|---|---|
| Absorption | Bioavailability ~45%;<br>$T_{max}$ ~15 min |
| Distribution | Vd ~2,500 L;<br>~95% protein-bound |
| Metabolism | Hydroxylation by CYP3A4 (Major) |
| Elimination | Feces (54% unchanged, 23% hydroxylated metabolite)<br>Urine (< 2% unchanged)<br>$T_{1/2}$ ~40-56 hours |

# Drug Interactions

- Drug Interactions – Object Drugs:
  - § No known significant interactions at the systemic exposure levels achieved in clinical practice.

# Drug Interactions

- Drug Interactions – Precipitant Drugs:
  - Adrenergic drugs (↑ sympathetic effects)
  - Xanthine derivatives, steroids, or diuretics (↑ hypokalemic effects)
  - MAOIs, TCAs, QTc prolonging drugs (↑ cardiovascular effects)
  - Beta blockers (↓ bronchodilation, ↑ risk of severe bronchospasm)

# Adverse Effects

| | Indacaterol (499) | Placebo (445) |
|---|---|---|
| | N (%) | N (%) |
| Respiratory, thoracic and mediastinal disorders | | |
| Cough | 29 (6.5) | 20 (4.5) |
| Oropharyngeal pain | 10 (2.2) | 3 (0.7) |
| Infections | | |
| Nasopharyngitis | 24 (5.3) | 12 (2.7) |
| Nervous system disorders | | |
| Headache | 23 (5.1) | 11 (2.5) |
| Gastrointestinal disorders | | |
| Nausea | 11 (2.4) | 4 (0.9) |

# Monitoring Parameters

- Efficacy Monitoring:
  - $FEV_1$
  - $PaO_2$
  - Symptomatic improvement
    - Cough, sputum production, exercise tolerance, use of rescue inhaler, etc.
- Toxicity Monitoring:
  - BP, HR, $K^+$

# Prescription Information

- Dosing / Cost:
  - 75 mcg once daily (USFDA 2011)
  - 150-300 mcg once daily (EMEA 2009)
  - Geriatric dosing: no
  - Renal dosing: no
  - Hepatic dosing: no
  - Dry powder capsule for inhalation with use of Neohaler™ device only

www.drugstore.com accessed 9/02/12

# 2011 FDA consideration

- In an article in the December 15, NEJM 2011 regulators from:
  - FDA's Center for Drug Evaluation & Research (CDER),
  - Badhul Chowdhury (director of Division of Pulmonary, Allergy, and Rheumatology Products)
- Detail *decision making process that led to approval of a single 75 µg dose of Novartis's Arcapta Neohaler indacaterol DPI for the treatment of COPD*.

Chowdhury BA, et al. N Engl J Med 2011: 365;24

# 2011 FDA consideration

- "Since the European Medicines Agency (EMA) had approved indacaterol at doses of **150 µg and 300 µg in 2009**,"

- "One might question why the FDA selected a 75 µg dose."

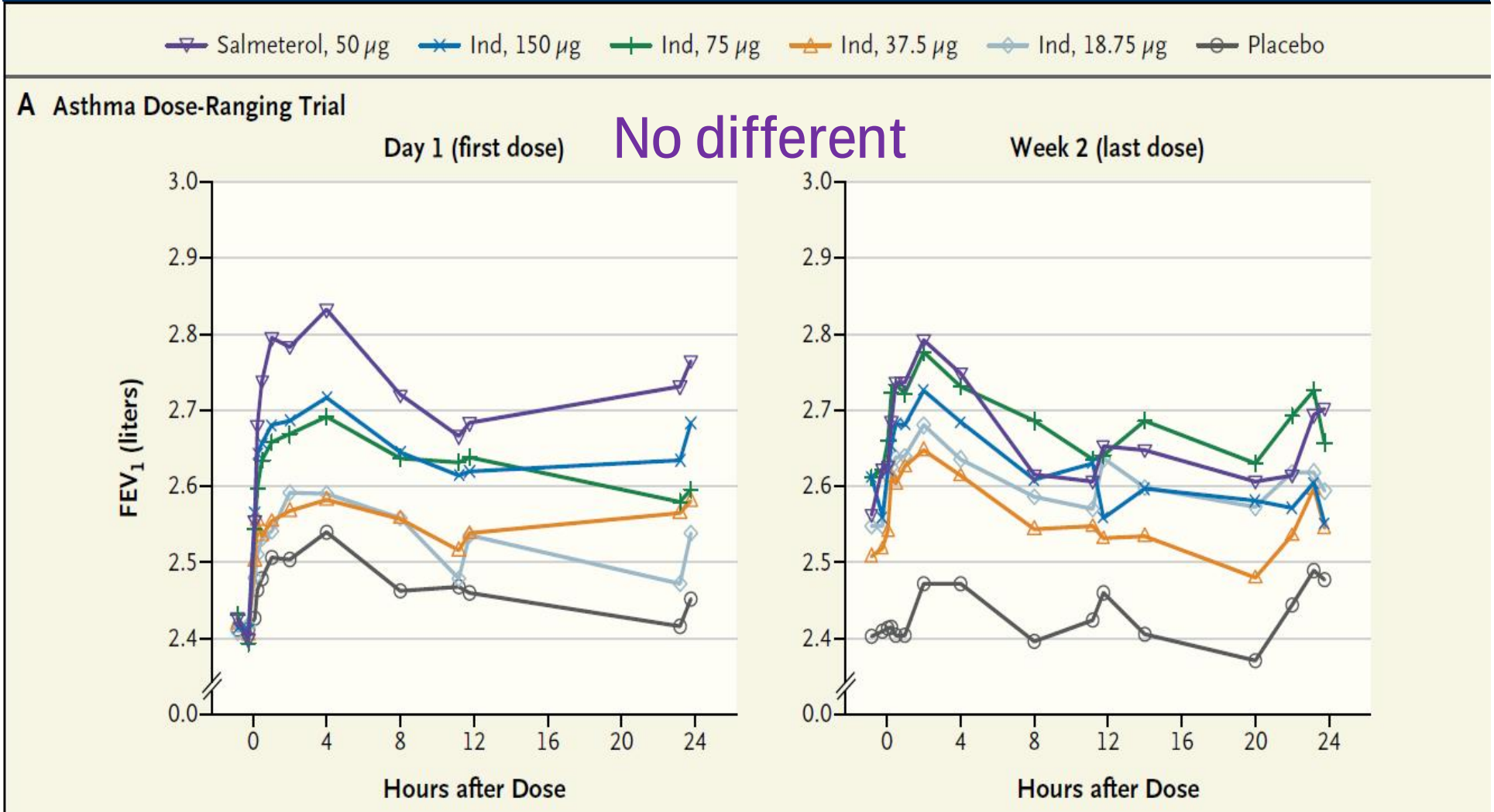
Chowdhury BA, et al. N Engl J Med 2011: 365;24

# FDA consideration

- The rejection of the original NDA (submitted in 2009)
  - Resulted from safety concerns, including "a small numerical increase in serious asthma exacerbations and respiratory-related deaths" in asthma patients receiving doses of 300 μg and 600 μg in a dose ranging trial.
  - At the same time: no significant difference in efficacy between the 75 μg dose and higher doses, suggesting that higher doses were unnecessary.

Chowdhury BA, et al. N Engl J Med 2011: 365;24

# Asthma and COPD Dose-Ranging Trials

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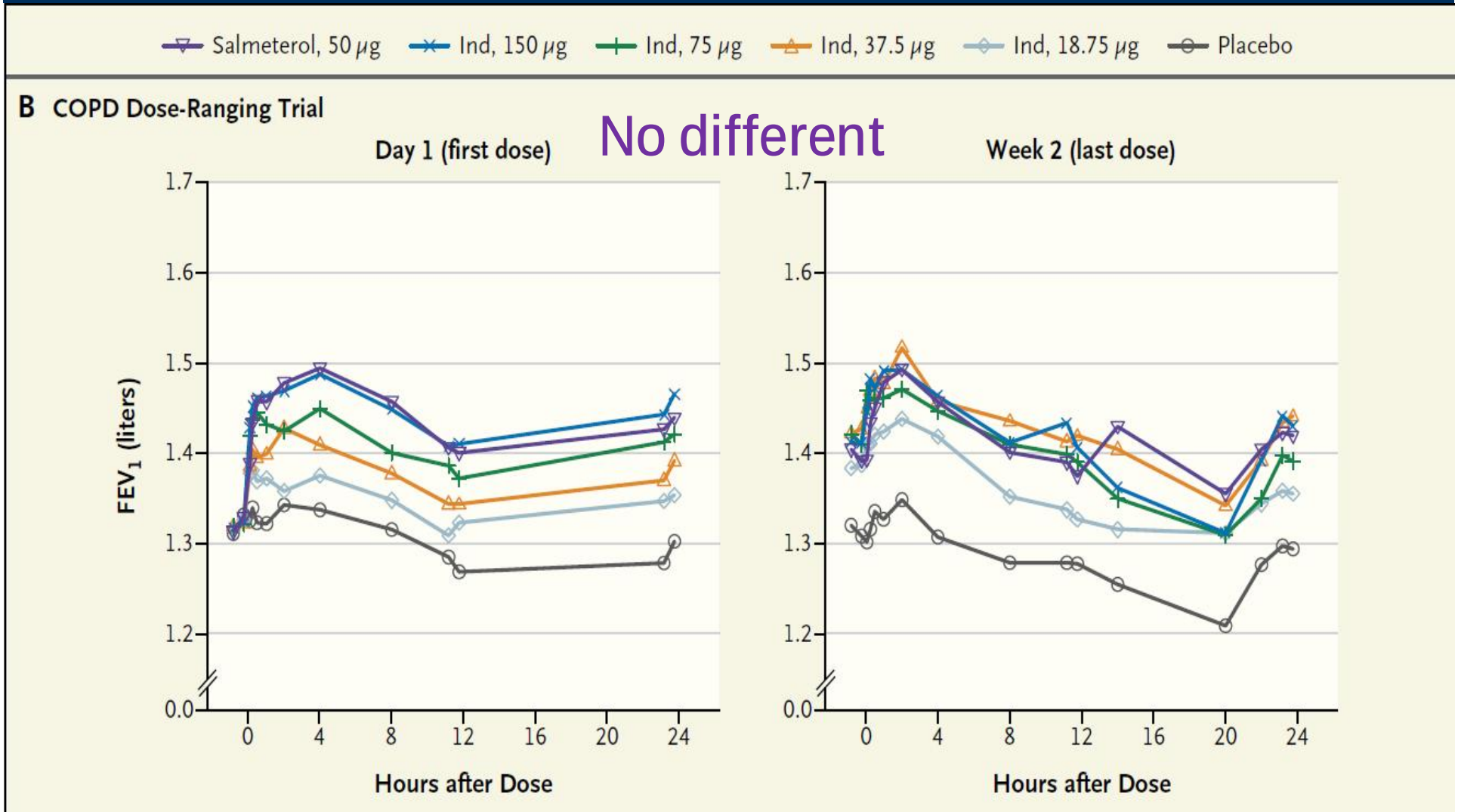
# Asthma and COPD Dose-Ranging Trials




Chowdhury BA, et al. N Engl J Med 2011: 365;24

# FDA consideration

- With no data to show superiority of the 150 μg dose over the 75 μg dose
  - *"The FDA emphasized dose selection and safety to ensure that the marketed dose would provide maximal benefit without posing unnecessary safety risks."*

# Literature Review

- Safety:

§ Slightly more AEs in the indacaterol group than in the placebo group (44.7% vs. 40.9%)

§ Frequency of cough was 3x higher in indacaterol group (9.4% vs. 3.1%)

§ No significant difference in serious AEs

Novartis. NDA 022-383, March 2011.

# Literature Review

- Conclusion:

§ Indacaterol produced a superior response in trough $FEV_1$ when compared to placebo after 12 weeks

§ Indacaterol increased the percentage of days with no rescue use, but failed to improve Transitional Dyspnoea Index (TDI) focal scores and health-related QOL

Novartis. NDA 022-383, March 2011.

# GOLD 2011 Update
# Stable COPD: Pharmacologic Therapy

| Group | 1st line | 2nd line | Alternative |
|---|---|---|---|
| A | SAAC prn or<br>SABA prn | LAAC or<br>LABA or<br>SABA + SAAC | Theophylline |
| B | LAAC or<br>LABA | LAAC + LABA | SABA and/or SAAC<br>Theophylline |
| C | ICS +<br>LABA or LAAC | LAAC + LABA | PDE4<br>SABA and/or SAAC<br>Theophylline |
| D | ICS +<br>LABA or LAAC | ICS + LAAC or<br>ICS + LABA + LAAC<br>ICS + LABA + PDE4 | Carbocysteine<br>SABA and/or SAAC<br>Theophylline |

# Where does Indacaterol fit?

- Alternative to salmeterol, formoterol, tiotropium
  - Once daily like tiotropium
  - Not in combination products
  - No data to reduce exacerbations like tiotropium

- Indacaterol in elderly patients
  - Easy to use
  - May increase adherence compared to salmeterol and formoterol

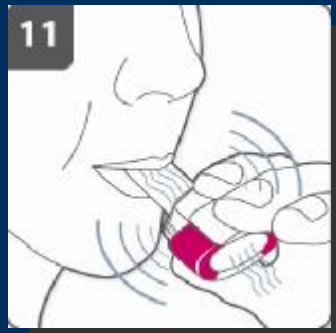
# How to use breezhaler/neohaler



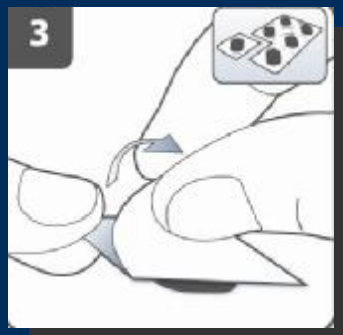















# Summary

- Indacaterol, is a new once daily alternative for the maintenance treatment of moderate to severe COPD
- Indacaterol improves trough $FEV_1$ and reduces percentage of days requiring rescue use after 12 wks of tx with only a minimal increase in adverse effects (cough)
- Indacaterol is not indicated for the treatment of asthma, and like other LABAs, carries a BBW for asthma-related death
- More studies are needed to compare the efficacy of indacaterol to other currently available agents

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# "PDE4 Inhibitors: Roflumilast"


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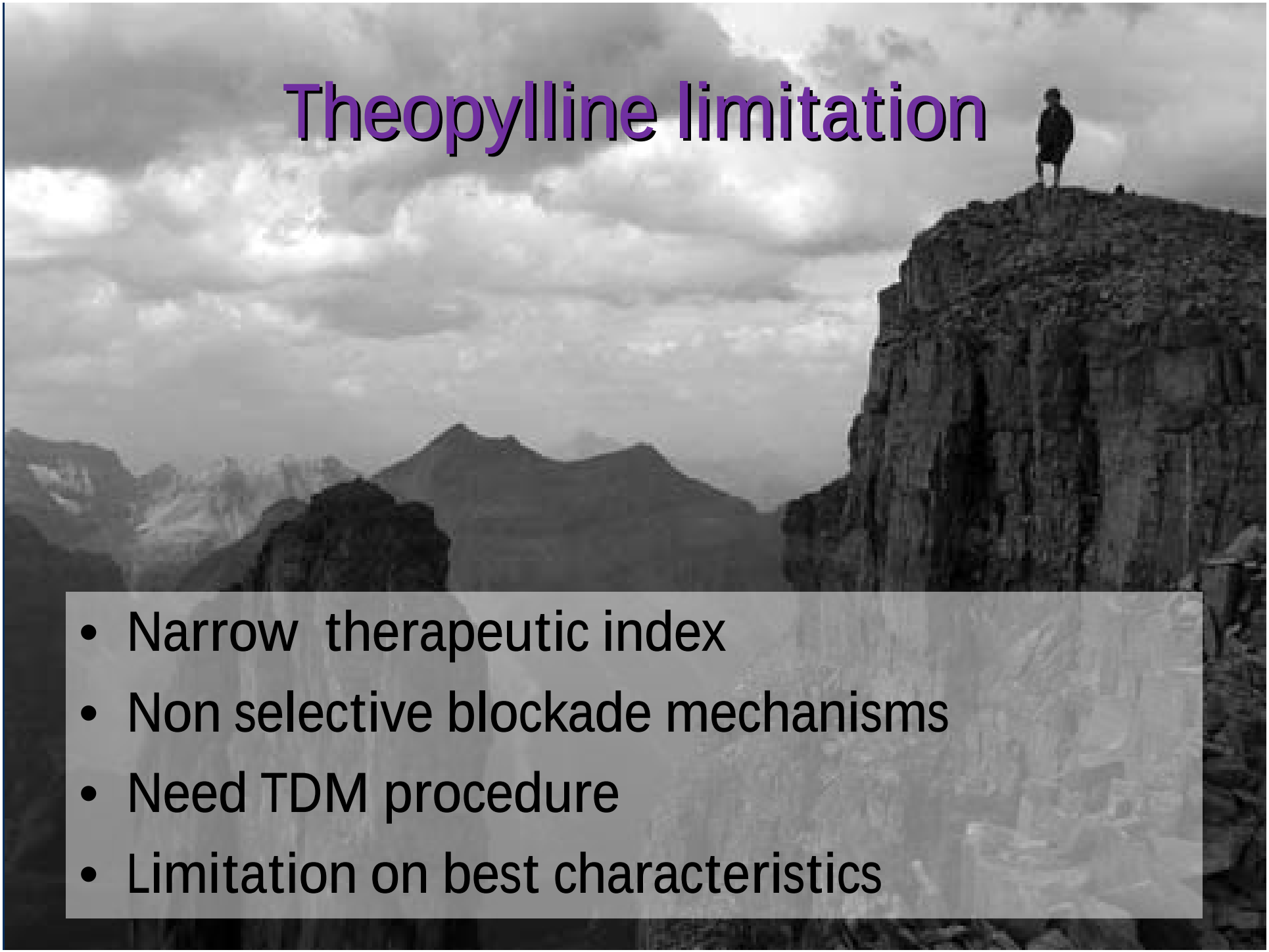


# Theopylline limitation

- Narrow  therapeutic index
- Non selective blockade mechanisms
- Need TDM procedure
- Limitation on best characteristics

# PDE enzyme function

| PDE Family | Function(s) |
|---|---|
| PDE1 | PDE1A probably serves to regulate vascular smooth muscle contraction and may play a role in sperm function; PDE1B is involved in dopaminergic signaling as well as immune cell activation and survival; PDE1C is required for vascular smooth muscle cell proliferation and may also regulate sperm function and neuronal signaling |
| PDE2 | PDE2 frequently mediates cross-talk between cGMP and cAMP pathways; it regulates aldosterone secretion from the adrenal gland, cAMP and PKA phosphorylation of $Ca^{+2}$ channels in the heart, cGMP in neurons, long-term memory, and barrier function of endothelial cells under inflammatory conditions |
| PDE3 | PDE3A regulates cardiac contractility, platelet aggregation, vascular smooth muscle contraction, oocyte maturation, and regulation of renin release; PDE3B mediates insulin signaling, especially its antilipolytic effects; PDE3B also regulates cell cycle/proliferation and mediates the inhibitory effects of leptin and other signals on insulin secretion and renin release |
| PDE4 | At least one form is expressed in most cells, and PDE4s play roles in a wide array of processes, including brain function, monocyte and macrophage activation, neutrophil infiltration, vascular smooth muscle proliferation, fertility, vasodilation, and cardiac contractility |
| PDE5 | PDE5 is a well-documented regulator of vascular smooth muscle contraction, especially in penis and lung; it is involved in NO-cGMP signaling in platelets to control aggregation and may also play a role in regulation of cGMP signaling in the brain |
| PDE6 | PDE6 is involved in signal transduction of the photoresponse in the eye; it may also regulate melatonin release from the pineal gland |
| PDE7 | PDE7 is implicated to play a role in T-cell activation and activation of other inflammatory cells |
| PDE8 | PDE8 may play a role in T cell activation, sperm, or leydig cell function |
| PDE9 | The function of PDE9 is currently unknown, but it has been postulated to regulate NO-cGMP signaling in the brain |
| PDE10 | PDE10A is thought to be a regulator of cGMP in the brain and may play a role in learning and memory |
| PDE11 | PDE11 possibly has a role in sperm development and function |

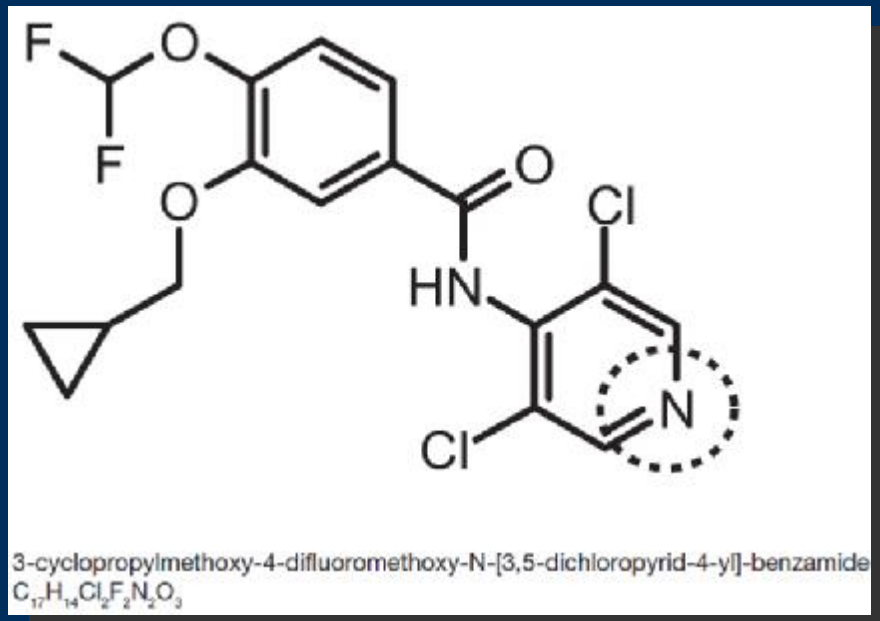
Bender AT, Beavo JA. *Pharmacol Rev 58:488–520, 2006*

# Roflumilast

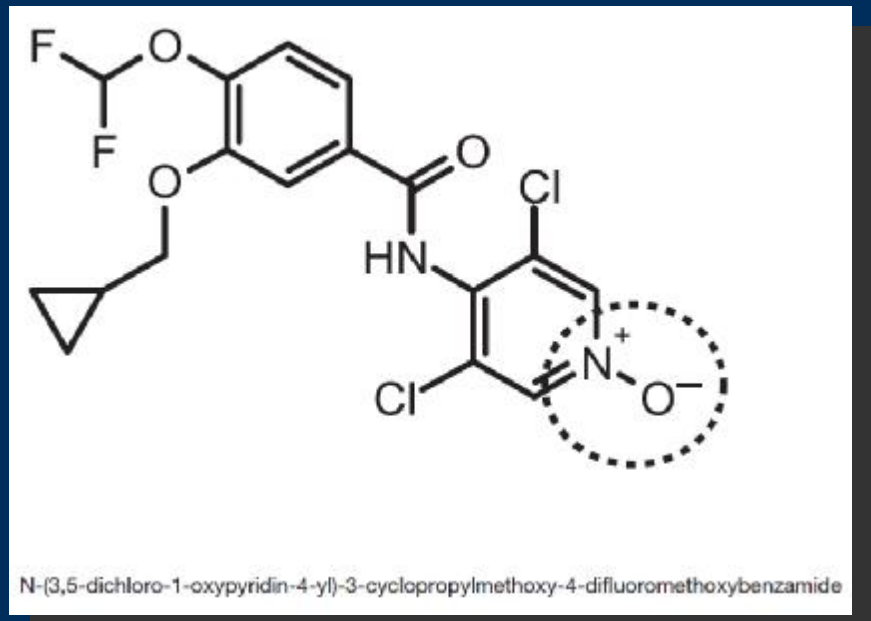
- FDA-approved (February 28, 2011) to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations

- Manufacturer
  - Forest Pharmaceuticals

# Chemical structure of roflumilast and roflumilast N-oxide




Roflumilast




Roflumilast N-oxide

# Roflumilast

- Dosage and Administration
  - 500 mcg tablet daily
  - With or without food
- Contraindications
  - Moderate to severe liver impairment
    - Child-Pugh B/C

# Roflumilast

- Warnings and Precautions
  - Psychiatric events (insomnia, depression, anxiety)
  - 3 suicide events in roflumilast vs. 1 suicide event with placebo
  - Weight loss (5-10% of body weight)
    - 20% vs. 7%

# Roflumilast

- Metabolism
  - CYP 3A4 and CYP1A2
    - To the active metabolite roflumilast N-oxide
  - Active metabolite contributes 90% to PDE-4 inhibition

# Roflumilast

- Drug interactions
  - Inducers reduce exposure: CBZ, PHB, PHT
  - Inhibitors increase exposure:
    - Erythromycin, fluvoxamine
  - Should not be given with Theophylline
    - PK study showed no effect on theophylline
    - Methlyxanthines may also be non-selective PDE inhibitors

# Roflumilast

- Geriatric use
  - 4500 subjects exposed for up to 12 months
    - 2022 were > 65 years; 471 were > 75 years
  - No differences in safety/efficacy; no adjustment

- No dose adjustment in renal impairment
- Cost: $215 monthly

# Roflumilast

- Adverse Effects
  - § Diarrhea, nausea, vomiting, weight loss, decreased appetite, abdominal pain, dyspepsia
  - § Headache, dizziness, insomnia, anxiety, depression
  - § Back pain, muscle spasm
  - § Tremor

# Roflumilast

- Gold Guidelines 2011:
  - *"Roflumilast may be useful to reduce exacerbations in patients with $FEV_1$ < 50% predicted, chronic bronchitis, and frequent exacerbations"*
  - Recommended as 2nd and alternative choice in Stage C and Stage D patients (both high risk for exacerbation) combined with a long-acting bronchodilator

- There are no comparison or add-on studies of roflumilast and inhaled corticosteroids

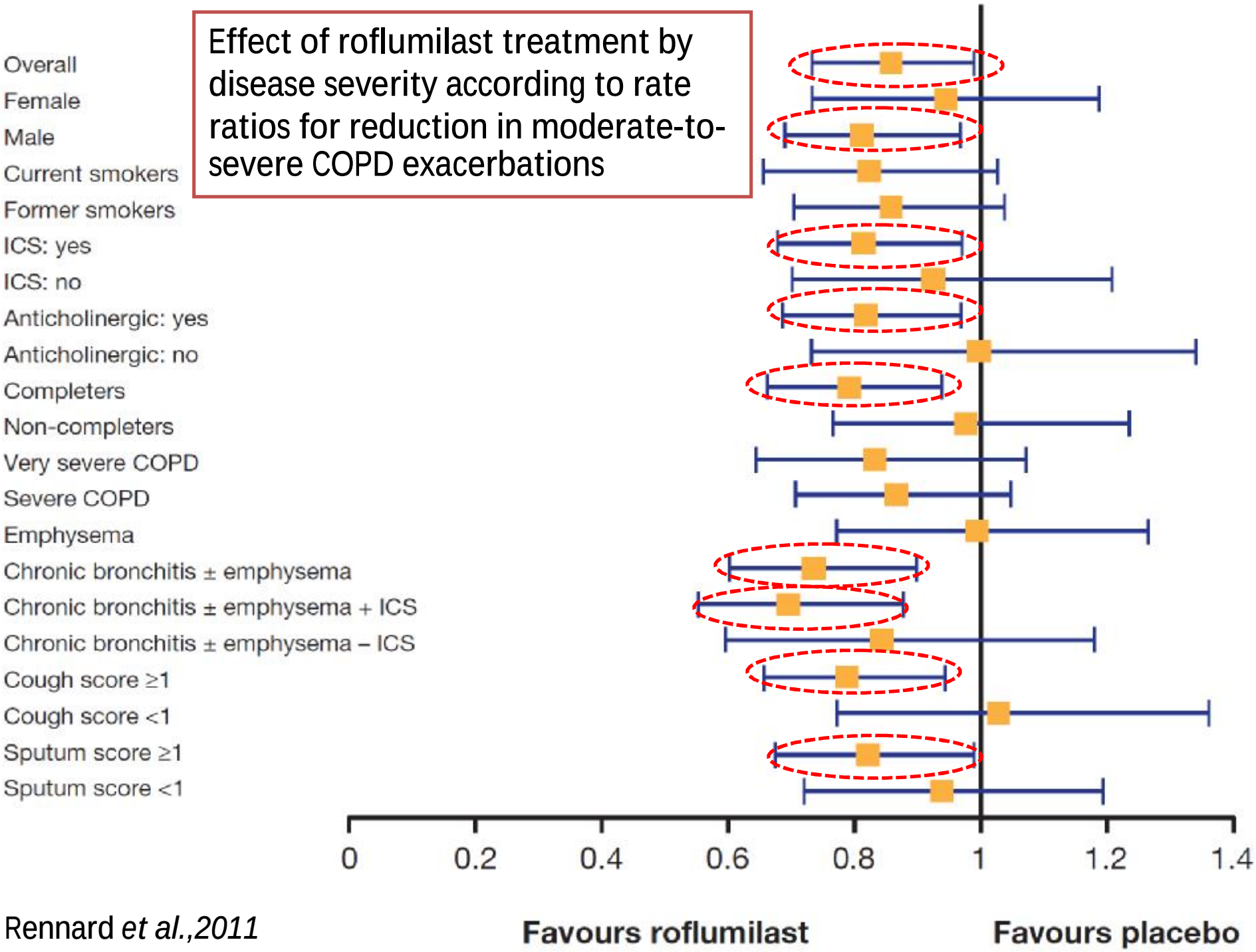
# Roflumilast: Clinical data

| Outcome (Exacerbations) | Roflumilast (n = 1537) | | Placebo (n = 1554) | | Hazard ratio (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | Events (n) | Event rate* | Events (n) | Event rate* | | |
| Primary (mod + severe) | 717 | 1.14 | 821 | 1.37 | 0.83 (0.75-0.92) | 0.0003 |
| Severe | 157 | 0.12 | 198 | 0.15 | 0.82 (0.63-1.06) | 0.1334 |
| Moderate | 624 | 0.99 | 723 | 1.19 | 0.83 (0.75-0.92) | 0.0007 |
| Systemic steroids and/or Antibiotics | 700 | 1.13 | 798 | 1.35 | 0.84 (0.76-0.92) | 0.0003 |

- Absolute risk reduction (ARR):
  - Risk pla – Risk Roflu = 821/1554 – 717/1537 = 0.528 – 0.466 = 6.2%
- Number needed to treat = 1 / ARR = 1 / 0.062 = 16
- * Mean rate, per patient per year

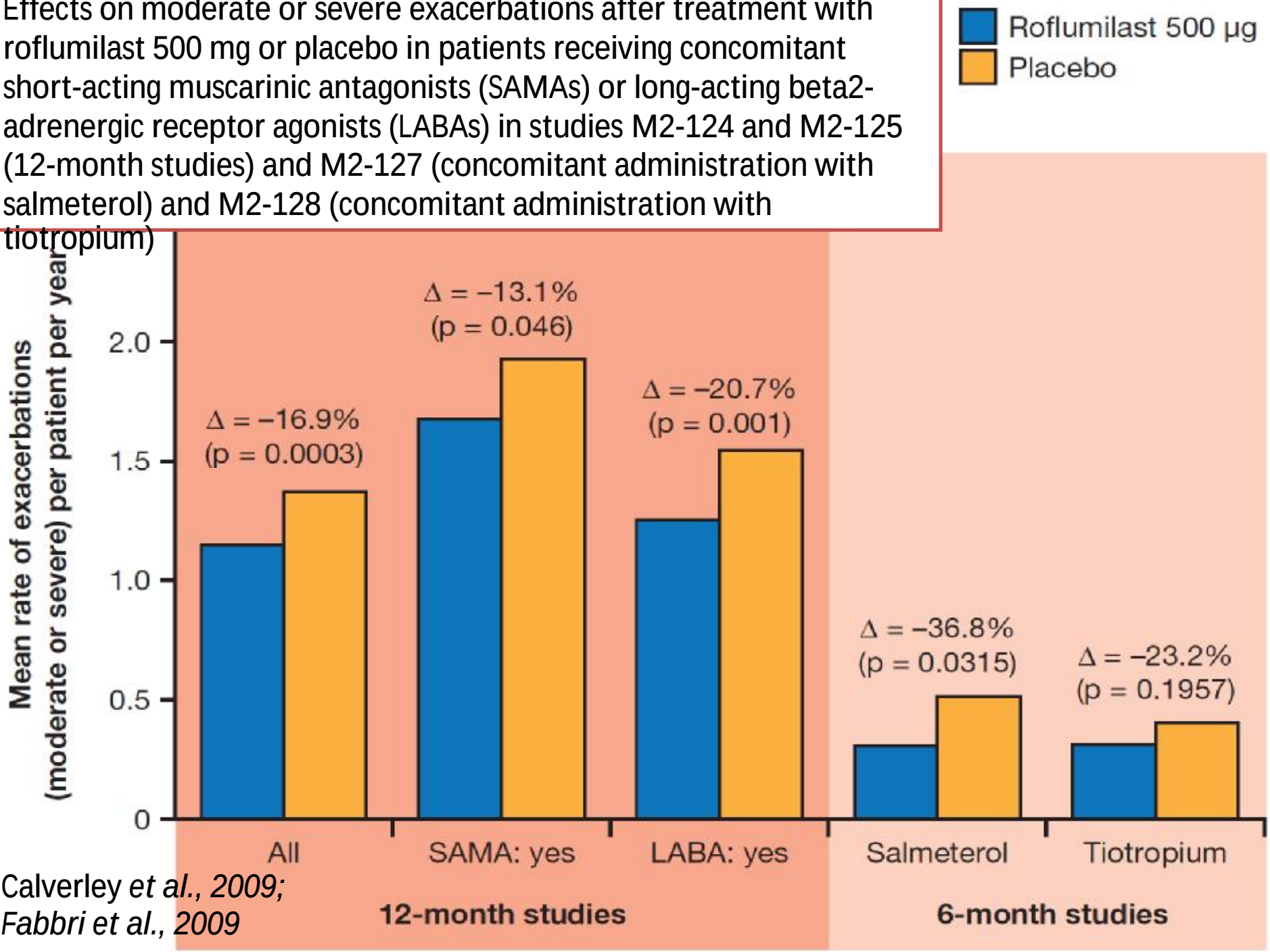
Lancet. 2009; 374: 685-94

Effect of roflumilast treatment by disease severity according to rate ratios for reduction in moderate-to-severe COPD exacerbations



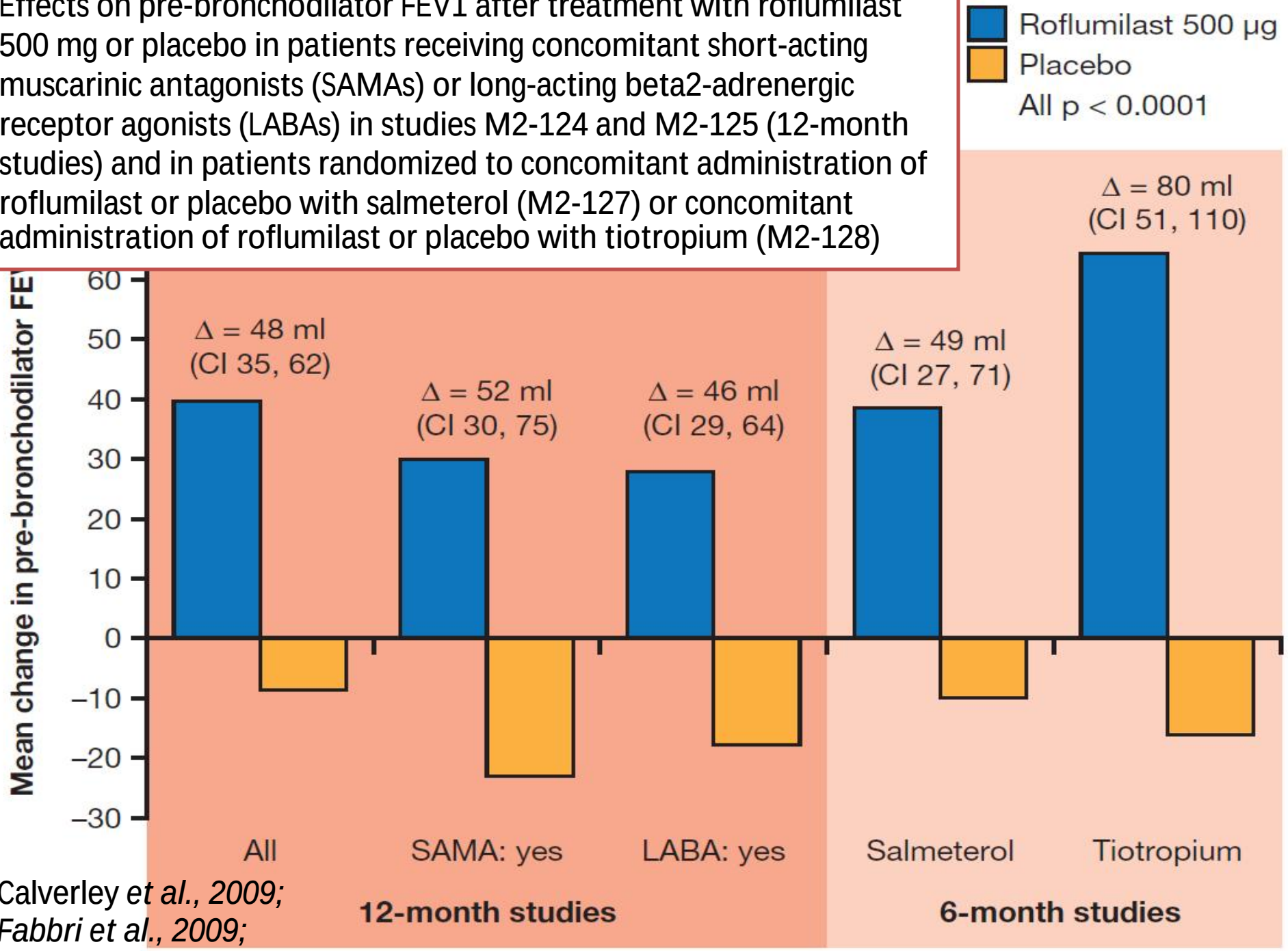

Rennard *et al.,2011*

Effects on moderate or severe exacerbations after treatment with roflumilast 500 mg or placebo in patients receiving concomitant short-acting muscarinic antagonists (SAMAs) or long-acting beta2-adrenergic receptor agonists (LABAs) in studies M2-124 and M2-125 (12-month studies) and M2-127 (concomitant administration with salmeterol) and M2-128 (concomitant administration with tiotropium)




Calverley *et al., 2009; Fabbri et al., 2009*

Effects on pre-bronchodilator FEV1 after treatment with roflumilast 500 mg or placebo in patients receiving concomitant short-acting muscarinic antagonists (SAMAs) or long-acting beta2-adrenergic receptor agonists (LABAs) in studies M2-124 and M2-125 (12-month studies) and in patients randomized to concomitant administration of roflumilast or placebo with salmeterol (M2-127) or concomitant administration of roflumilast or placebo with tiotropium (M2-128)




Calverley *et al., 2009;*
*Fabbri et al., 2009;*

# GOLD 2011 Update
# Stable COPD: Pharmacologic Therapy

| Group | 1st line | 2nd line | Alternative |
|---|---|---|---|
| A | SAAC prn or<br>SABA prn | LAAC or<br>LABA or<br>SABA + SAAC | Theophylline |
| B | LAAC or<br>LABA | LAAC + LABA | SABA and/or SAAC<br>Theophylline |
| C | ICS +<br>LABA or LAAC | LAAC + LABA | **PDE4**<br>SABA and/or SAAC<br>Theophylline |
| D | ICS +<br>LABA or LAAC | ICS + LAAC or<br>ICS + LABA + LAAC<br>ICS + LABA + **PDE4** | Carbocysteine<br>SABA and/or SAAC<br>Theophylline |

# True or False?

## Summary

- PDE4 inhibitor: anti-inflammatory effects
- Increases $FEV_1$ and FVC
- Reduces exacerbations requiring steroids in patients with severe COPD
- No change in QOL or mortality
- Side effects mainly GI (N/V/D) and weight loss

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# "Anti-IgE: Omalizumab"


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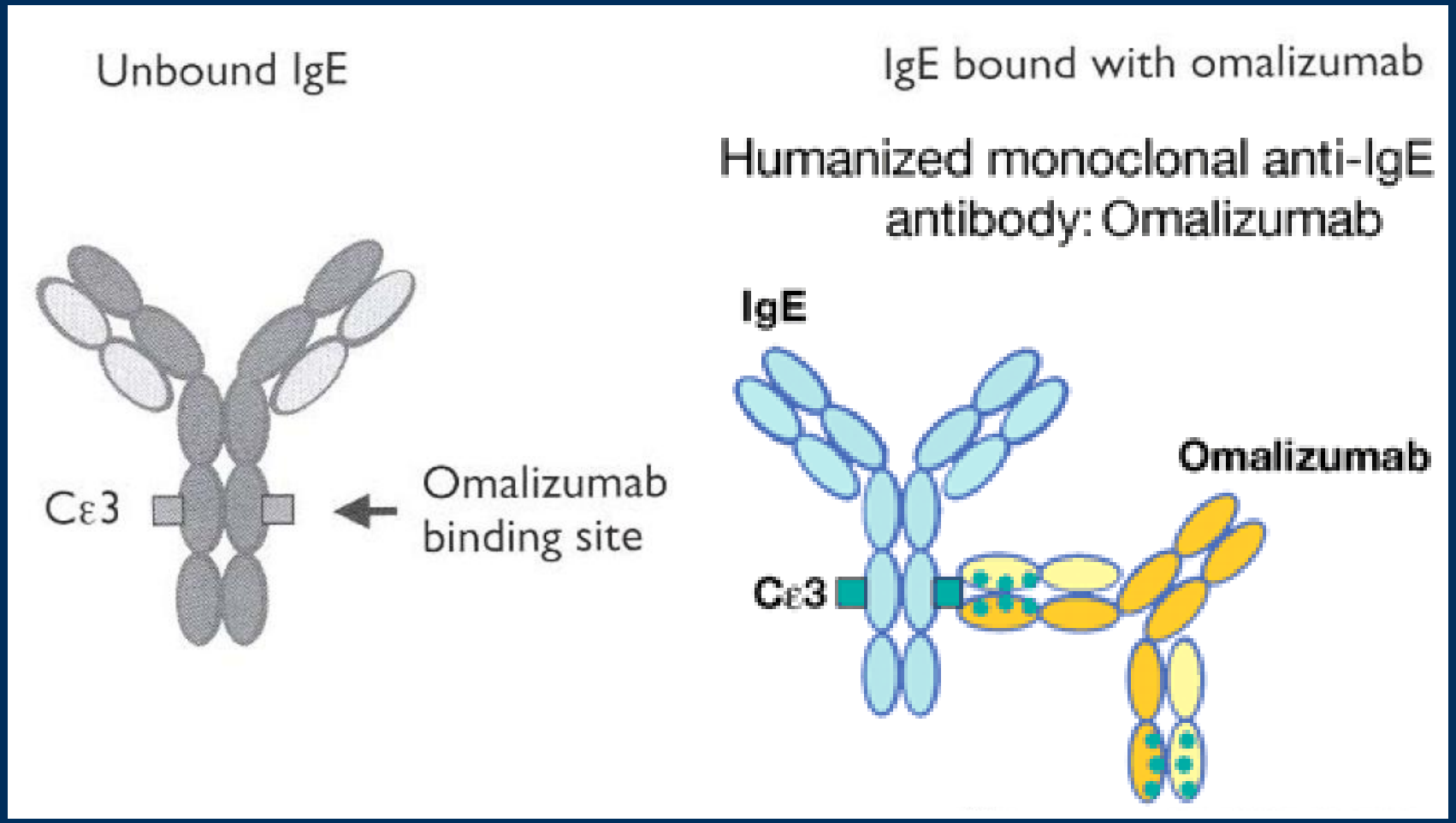
# IgE Blocker Therapy
# Omalizumab (XolairTM)

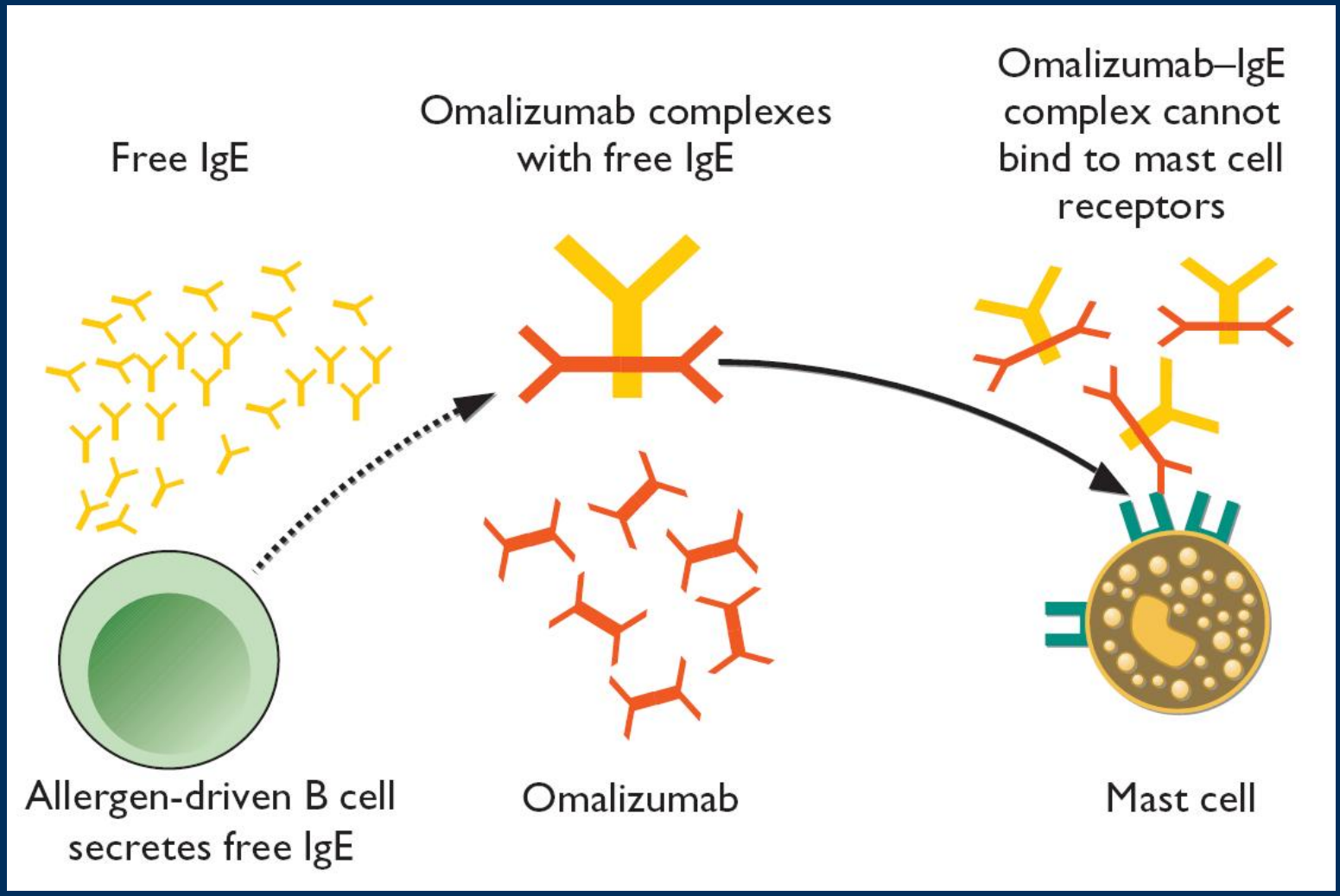
- Approved June 20, 2003
- Humanized mAb against IgE (95% human)
- Binds circulating IgE regardless of specificity
- Forms biologically inert omalizumab-IgE complexes
- 150 to 375 mg, s.c., q. 2 or 4 weeks

# BINDING OF OMALIZUMAB TO IgE



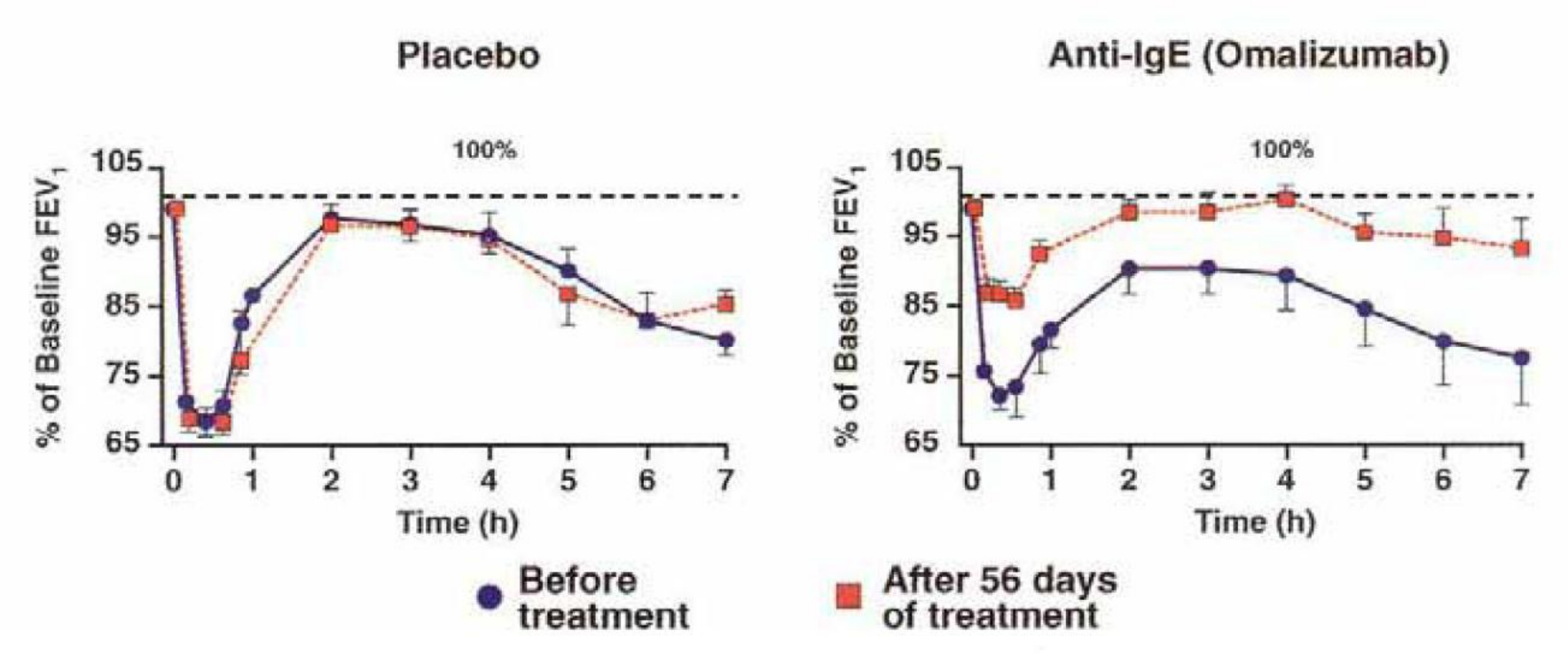

(Based on Rosenwasser & Nash, *Pharmacy & Therapeutics 2003;28:400-10.)*

# BINDING OF OMALIZUMAB TO IgE




(Based on Rosenwasser & Nash, *Pharmacy & Therapeutics 2003;28:400-10.)*

# Effect of Allergen Challenge on $FEV_1$

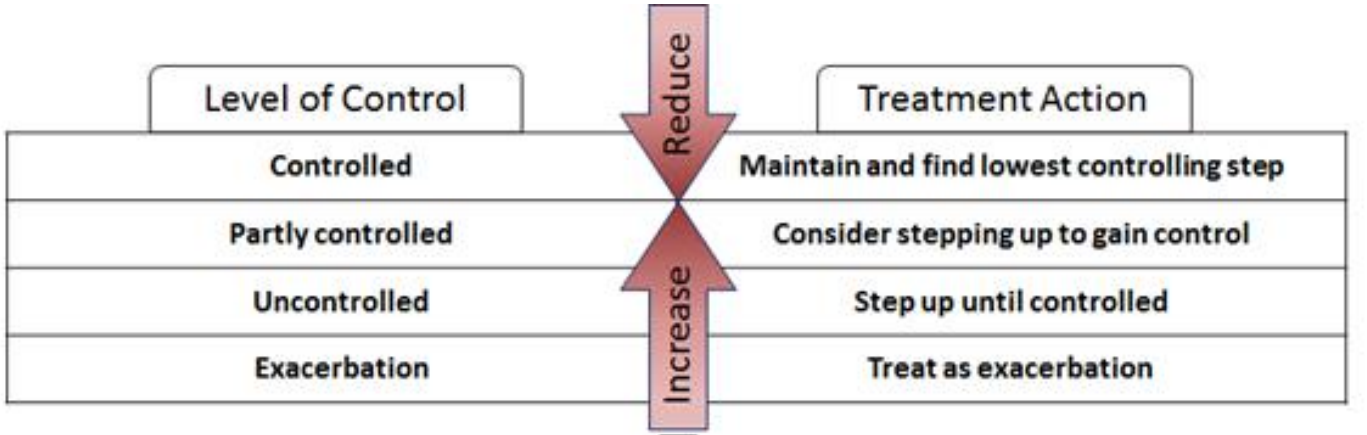



Boushey HA Jr. J Allergy Clin Immunol 2001;108:S77-S83

# Who fit to omalizumab therapy?

# Omalizumab

- Moderate to severe persistent asthma (step 5)
- 12 years, or older
- IgE level 30-700 IU/ml
- Positive skin test, or in vitro reactivity perennial aero-allergen
- Inadequate control with inhaled CS





**Asthma education – Environmental control**

| Step 1 | Step 2 | Step 3 | Step 4 | Step 5 |
|---|---|---|---|---|
| As needed rapid-acting $\beta_2$-agonist | As needed rapid-acting $\beta_2$-agonist | | | |
| Controller options** | Select one | Select one | To Step 3 treatment, select one or more | To Step 4 treatment, add either |
| | Low-dose ICS* | Low-dose ICS plus long-acting $\beta_2$-agonist | Medium- or high-dose ICS plus long-acting $\beta_2$-agonist | Oral glucocorticosteroid (lowest dose) |
| | Leukotriene modifier** | Medium- or high-dose ICS | Leukotriene modifier | Anti-IgE treatment |
| | | Low-dose ICS plus leukotriene modifier | Sustained release theophylline | |
| | | Low-dose ICS plus sustained release theophylline | | |

* ICS = inhaled glucocorticosteroid

** Receptor antagonist or synthesis inhibitors

** Preferred controller options in shaded boxes

*Alternative reliever treatments include inhaled anticholinergics, short-acting oral* $\beta_2$-agonists, some long-acting $\beta_2$-agonists, and short-acting theophylline. Regular dosing with short and long-acting $\beta_2$-agonists is not advised unless accompanied by regular use of an inhaled glucocorticosteroid.

# Omalizumab: ADVERSE REACTIONS

- MOST COMMON ADVERSE REACTIONS
  - Injection site reaction (45%) – bruising, erythema
  - Viral infections (23%)
  - URI (20%)
  - Sinusitis (16%)
  - Headache (15%)
  - Pharyngitis (11%)
- MOST SERIOUS
  - malignancy (0.5%)
  - anaphylaxis (rare)

# Omalizumab dosing

| Baseline IgE (IU/mL) | Total dose (mg) per 28 days<br>Body weight (kg)<br>>20–25 | >25–30 | >30–40 | >40–50 | >50–60 | >60–70 | >70–80 | >80–90 | >90–125 | >125–150 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥30–100 | 75 | 75 | 75 | 150 | 150 | 150 | 150 | 150 | 300 | 300 | Q4 wks |
| >100–200 | 150 | 150 | 150 | 300 | 300 | 300 | 300 | 300 | 450 | 600 | Q2 wks |
| >200–300 | 150 | 150 | 225 | 300 | 300 | 450 | 450 | 450 | 600 | 750 | |
| >300–400 | 225 | 225 | 300 | 450 | 450 | 450 | 600 | 600 | | | |
| >400–500 | 225 | 300 | 450 | 450 | 600 | 600 | 750 | 750 | | | |
| >500–600 | 300 | 300 | 450 | 600 | 600 | 750 | | | | | |
| >600–700 | 300 | 450 | 450 | 600 | 750 | | | | | | |

Do not dose

# Omalizumab clinical study

| Study | Number of patients | Treatment duration | Efficacy endpoint |
|---|---|---|---|
| INNOVATE study[1] | 419 | 28 weeks | Asthma exacerbation rate |
| ETOPA study[2] | 312 | 52 weeks | Asthma exacerbation rate |
| SOLAR study[3] | 405 | 28 weeks | Asthma exacerbation incidence |
| Busse study[4] | 525 | 52 weeks | Asthma exacerbation rate |
| Solèr study[5] | 546 | 52 weeks | Asthma exacerbation rate |
| Holgate study[6] | 341 | 32 weeks | Reduction in ICS use |
| ALTO safety study | 1,899 | 24 weeks | Asthma exacerbation rate |

*93% of patients met GINA 2002 criteria for severe persistent asthma*

*1. Humbert M, et al. Allergy 2005; 2. Ayres JG, et al. Allergy 2004; 3. Vignola AM, et al. Allergy 2004, 4. Busse W, et al. J Allergy Clin Immunol 2001; 5. Soler M, et al. Eur Respir J 2001, 6. Holgate ST, et al. Clin Exp Allergy 2004*

# Omalizumab clinical study

| | Annual exacerbation rate treatment difference | Percent reduction | p-value |
|---|---|---|---|
| INNOVATE study[1] | 0.49 | 26.6% | 0.039 |
| ETOPA study[2] | 1.49 | 60.4% | <0.001 |
| SOLAR study[3] | 0.29 | 37.5% | 0.027 |
| Busse study[4] | 0.40 | 40.3% | <0.001 |
| Solèr study[5] | 0.70 | 57.6% | <0.001 |
| Holgate study[6] | 0.42 | 26.5% | 0.165 |
| ALTO study | 0.18 | 15.3% | 0.077 |
| Pooled[7] | 0.56 | 38.3% | <0.0001 |

*1. Humbert M, et al. Allergy 2005; 2. Ayres JG, et al. Allergy 2004; 3. Vignola AM, et al. Allergy 2004, 4. Busse W, et al. J Allergy Clin Immunol 2001; 5. Soler M, et al. Eur Respir J 2001, 6. Holgate ST, et al. Clin Exp Allergy 2004; 7. Bousquet J, et al. Allergy 2005*

# Omalizumab clinical study

- *Add-on therapy to improve asthma control in patients (≥6 years) with*
  - *severe persistent allergic asthma*
  - *positive skin test or in-vitro reactivity to a perennial*
  - *multiple documented severe asthma exacerbations despite daily high-dose ICS, plus a LABA*
  - *in patients ≥12 years: reduced lung function ($FEV_1$ <80%)*
- *Omalizumab treatment should only be considered for patients with convincing IgE-mediated asthma*

**In EU, Omalizumab is indicated for severe persistent allergic (IgE-mediated) asthma**

*FEV1 = forced expiratory volume in 1 second*
*ICS = inhaled corticosteroid; LABA = long-acting β2-agonist*

*EU SmPC (omalizumab) 2009*

# Omalizumab EU label stipulates 16-week response assessment

- *At 16 weeks after commencing omalizumab therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered*

- *The decision to continue omalizumab should be based on whether or not a marked improvement in overall asthma control is seen*

EU SmPC (omalizumab) 2009

# The safety of omalizumab

- Clinical trial safety database of >7,500 patients
  - >5,000 treated with omalizumab
  - majority with allergic asthma
- Frequencies of AEs were similar between omalizumab and control groups, even in severe patients
- No pattern or cluster of Aes
- Majority of AEs were mild-to-moderate and of short duration
- In studies where the local symptoms and signs of injection site reactions were evaluated prospectively after each dose, the overall frequency of injection site reactions was similar
  - omalizumab: 45%; placebo: 43%

Corren J, et al. Clin Exp Allergy 2009

# Current omalizumab dosing table includes patients with total IgE ≤700 IU/mL* and body weight ≤150 kg

| Baseline IgE (IU/mL) | Body weight (kg) >20–25 | >25–30 | >30–40 | >40–50 | >50–60 | >60–70 | >70–80 | >80–90 | >90–125 | >125–150 |
|---|---|---|---|---|---|---|---|---|---|---|
| ≥30–100 | 75 | 75 | 75 | 150 | 150 | 150 | 150 | 150 | 300 | 300 |
| >100–200 | 150 | 150 | 150 | 300 | 300 | 300 | 300 | 300 | 225 | 300 |
| >200–300 | 150 | 150 | 225 | 300 | 300 | 225 | 225 | 225 | 300 | 375 |
| >300–400 | 225 | 225 | 300 | 225 | 225 | 225 | 300 | 300 | | |
| >400–500 | 225 | 300 | 225 | 225 | 300 | 300 | 375 | 375 | | |
| >500–600 | 300 | 300 | 225 | 300 | 300 | 375 | DO NOT ADMINISTER | | | |
| >600–700 | 300 | 225 | 225 | 300 | 375 | Data are unavailable for dose recommendation | | | | |

Dose (mg) to be administered every 4 weeks

Dose (mg) to be administered every 2 weeks

*Pretreatment

EU SmPC (omalizumab)

# Thank you for your attention