

# Recent Advances in the Treatment of Asthma

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Professor of Pediatrics and Medicine

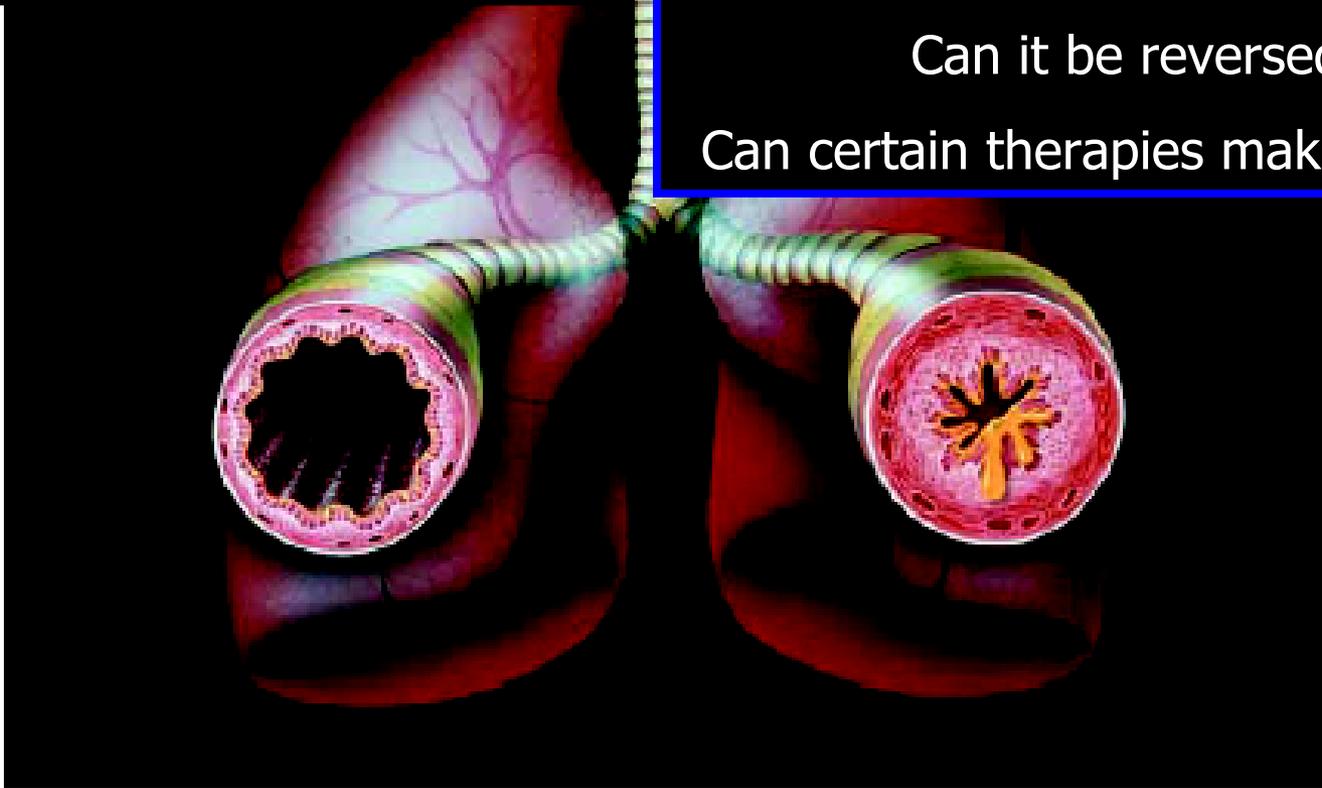
University of Wisconsin School of Medicine and Public Health  
Madison, WI



Madison, WI

# Asthma is Inflammation

Mild to moderate asthma



When does it start?

Can it be prevented?

Can it be reversed?

Can certain therapies make it worse?

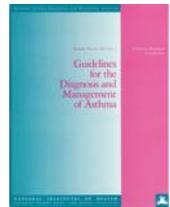
# NHLBI Asthma Guidelines

## National Asthma Education and Prevention Program: Expert Panel Report #3



1991

Asthma is an inflammatory disease



1997

Early recognition and treatment



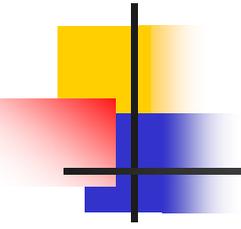
2002

Update on selected topics



2007

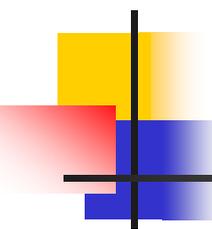
***EPR-3***



# New Concepts

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- Recommendations are now made using 3 age ranges, not 2 (0-4, 5-11,  $\geq 12$  yrs)
- Concept of severity and control
- Evaluation of both severity and control using two domains:
  - Impairment
  - Risk



# Severity, Control and Responsiveness

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## Severity

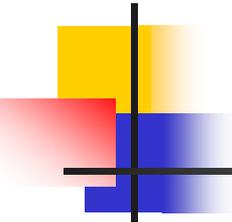
- Intrinsic intensity of the disease process
- Severity is most easily and directly measured in patients not receiving long-term therapy
- *Guides clinical decisions during the initial evaluation and prior to start of controller therapy*

## Control

- Degree to which asthma-related symptoms, functional impairment, and risk of untoward events are minimized and the goals of therapy are met
- *Guides clinical decisions to either maintain or adjust therapy once therapy is initiated*

## Responsiveness

- Ease with which asthma control is achieved by therapy
- Responsiveness to asthma treatment is highly variable



# Current Impairment and Future Risk

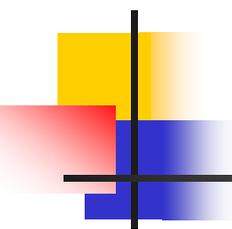
**Both severity and control include the domains of current impairment and future risk**

## **Impairment (cross-sectional)**

- Frequency and intensity of symptoms and functional limitations (pulmonary function, quality of life) the patient is currently experiencing or has recently experienced

## **Risk (longitudinal)**

- Likelihood of asthma exacerbations, progressive decline in lung function, or risk of adverse effects from medications



# Primary Goal of Therapy: Achieving and Maintaining Asthma Control

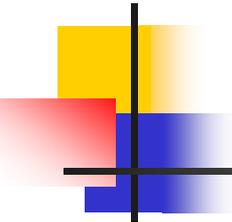
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- Primary goal of asthma therapy is to enable a patient to achieve and maintain control over their asthma
  - Eliminate impairments including symptoms, functional limitations, poor quality of life, and other manifestations of asthma
  - Reduce risk of exacerbations, ED use, and hospitalizations
- Treatment goals are identical for all levels of asthma severity

Asthma Clinical Research Network  
(ACRN)

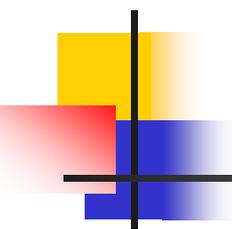
Childhood Asthma Research  
and Education Network  
(CARE)

Funded by the National Heart Lung and Blood Institute



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# Short acting beta agonists (SABAs)

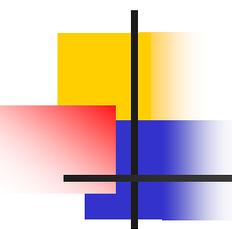


# Safety and Efficacy of Therapies Used to Treat Mild to Moderate Asthma: *Beta Agonists*

## BAGS (Beta Agonist Study) Trial

- Question: Is treatment with regularly scheduled albuterol safe?
- Answer: Not harmful; not beneficial

NEJM 335:841, 1996



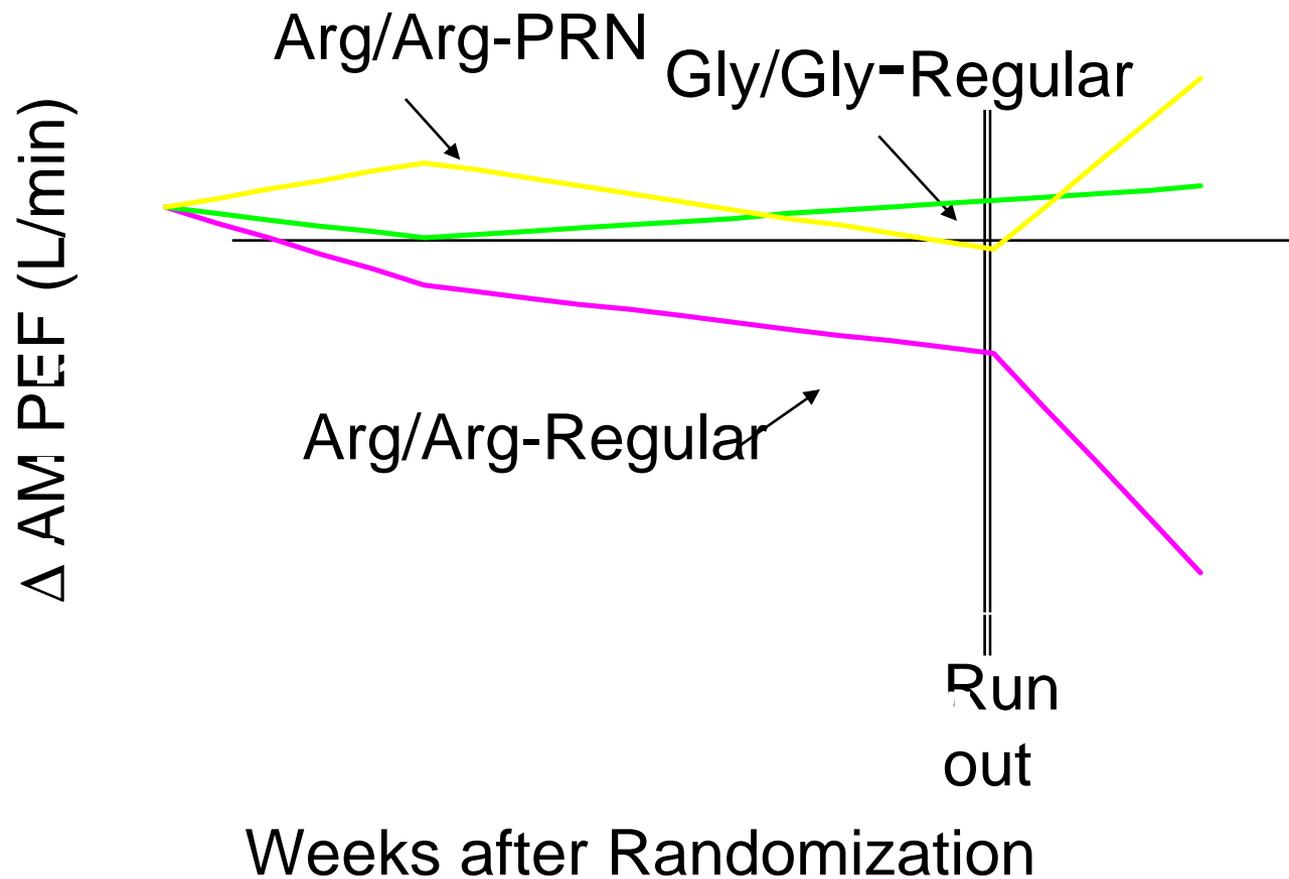
# Safety and Efficacy of Therapies Used to Treat Mild to Moderate Asthma: *Beta Agonists*

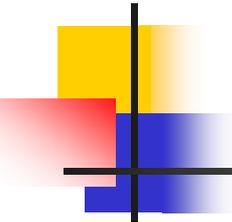
## BAGS Retrospective Ancillary Study

- Question: Do beta receptor polymorphisms influence response to chronic treatment with beta agonists?
- Answer: Yes. Patients with the Arg/Arg genotype at codon 16 may be at increased risk of loss of asthma control

AJRCCM 162:75, 2000

# BAGS Genetic Analysis

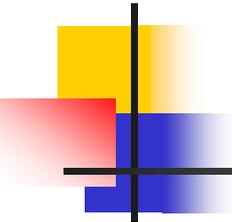




## Safety and Efficacy of Therapies Used to Treat Mild to Moderate Asthma: *Beta Agonists*

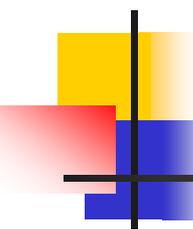
### BARGE (Beta Adrenergic Response by Genotype) Trial

- Question: Does the B16 loci influence asthma outcome measures other than PEF?  
*First asthma clinical trial in which patients were randomized by genotype*
- Answer: Yes. Subjects with the Arg/Arg genotype have better control when regularly scheduled albuterol is stopped. Subjects with the Gly/Gly genotype have improved control with regular use.



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# Long acting beta agonists (LABAs)

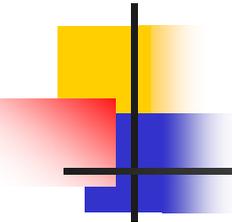


# Safety and Efficacy of Therapies Used to Treat Mild to Moderate Asthma: *Beta Agonists*

## SOCS (Salmeterol OFF Corticosteroids)

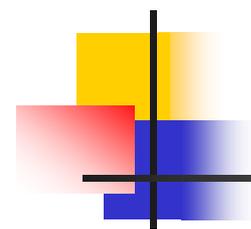
- Question: In patients with mild persistent asthma, well controlled on ICS, can salmeterol replace the ICS and be used as monotherapy?
- Answer: No. Salmeterol monotherapy increases the risk of loss of asthma control.

JAMA 285:2583, 2001



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# Combination Therapy

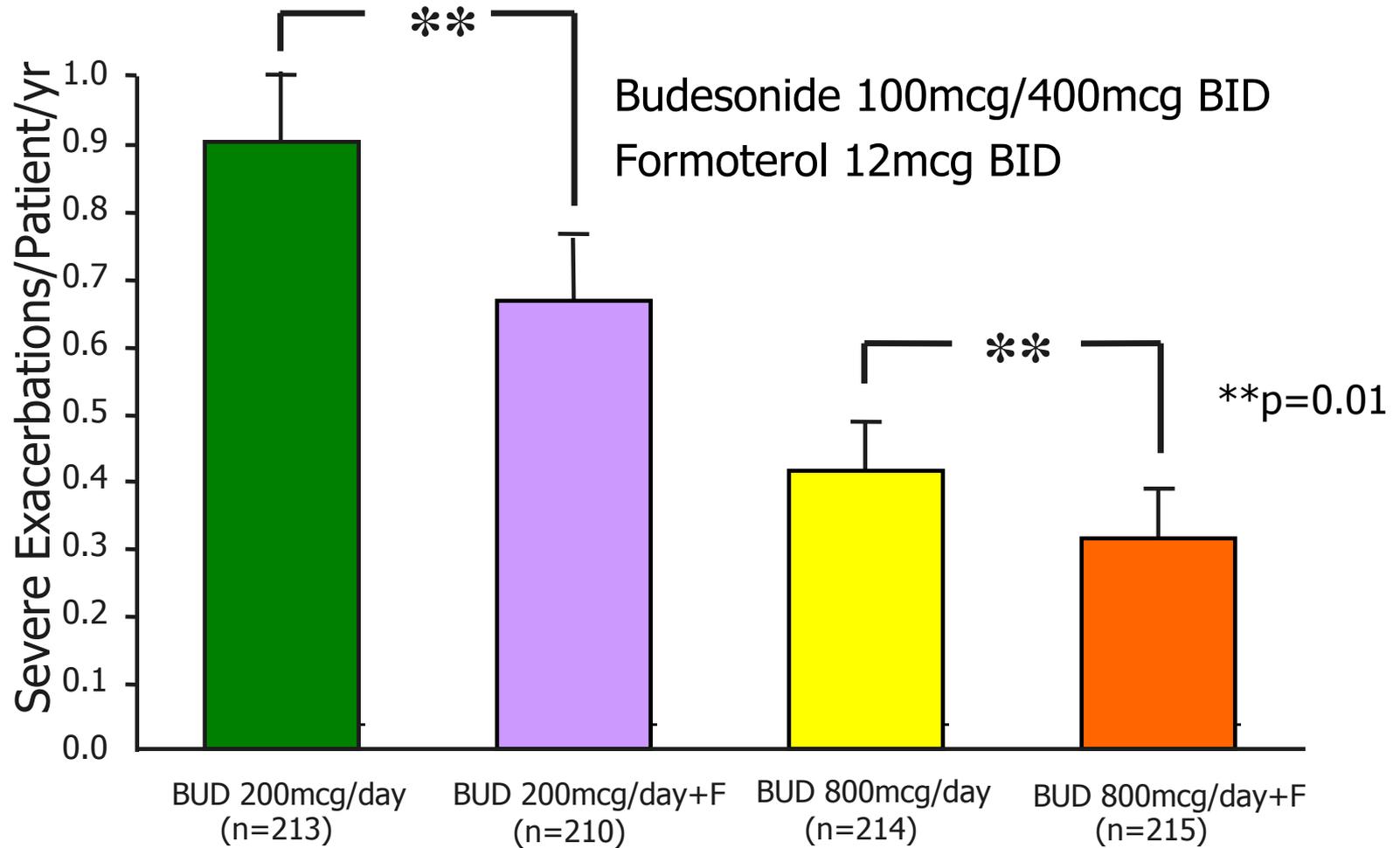


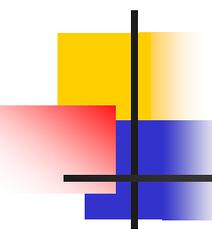
# More ICS or add a LABA?

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- **Greening, A.** et al. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. *Lancet* 344 (8917):219-224, 1994.
  - Improved impairment; no difference in risk domain
- **Woolcock, A** et al. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *AJRCCM* 153 (5):1481-1488, 1996.
  - Improved impairment; no difference in risk domain

# FACET Study: Formoterol and Budesonide in Moderate Asthma





# Safety and Efficacy of Therapies Used to Treat Mild to Moderate Asthma: *Beta Agonists*

## SLIC (Salmeterol ± Inhaled Corticosteroids)

- Question:

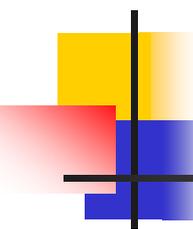
ICS (uncontrolled) →

add salmeterol (improved control) →

can ICS dose be reduced and/or eliminated?

- Answer: Reduction, yes. Elimination, no.

JAMA 285:2594, 2001



# Safety and Efficacy of Therapies Used to Treat Mild to Moderate Asthma: *Beta Agonists*

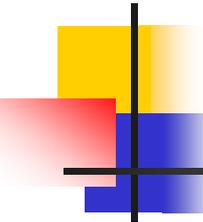
## SOCS/SLIC Retrospective Genotype Analysis

### ■ Questions:

- Are the adverse effects of chronic albuterol treatment in patients with the Arg/Arg genotype at B16 also demonstrable with the LABA salmeterol?
- If so, does concomitant treatment with ICS alter these effects?

### ■ Answers:

- Similar adverse effects are seen with salmeterol in Arg/Arg patients.
- The effect is not prevented by ICS treatment.

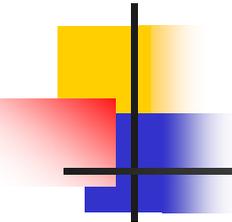


# Safety and Efficacy of Therapies Used to Treat Mild to Moderate Asthma: *Long Acting Beta Agonists*

## LARGE (Long Acting Beta Agonist Response by Genotype) Trial

- **Question:** Are there genotype attributable adverse effects on control due to beta receptor polymorphisms in patients receiving LABAs in combination with ICS?
- **Answer:** NO. Addition of salmeterol to ICS for 18 weeks produced similar improvements in airway caliber in both Arg/Arg and Gly/Gly genotype groups. Exacerbation rates were also similar.

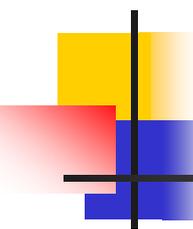
Manuscript in preparation



# LABA and Beta-Adrenergic Genotype

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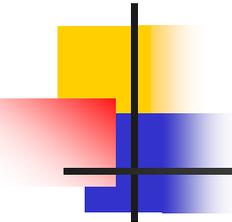
- Design: Subjects (n = 183) currently receiving short-acting beta<sub>2</sub>-agonists were randomized to twice-daily therapy with salmeterol, 50 µg, administered with fluticasone propionate, 100 µg, in a single inhaler or daily therapy with montelukast for 12 weeks, followed by a 2- to 4-day run-out period.
- Results: Response to therapy NOT dependent on B16 genotype or haplotype
- Conclusion: Response to salmeterol does not vary between beta adrenergic genotypes after chronic dosing with an inhaled corticosteroid



# Why were no differences observed?

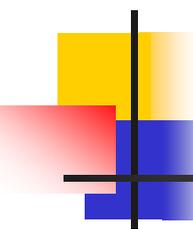
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- Genotype-specific differences only occur with short-acting beta-agonists but not with long-acting beta-agonists when used with inhaled corticosteroids
- Higher doses of ICS blunt a genotype-specific effect of salmeterol
- Higher doses of ICS delay a genotype-specific effect of salmeterol
- Genotype-specific effects may be more prominent in sub-populations underrepresented in the study



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# Combination Therapy in Children

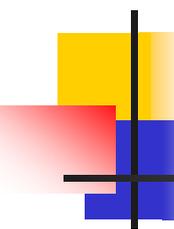


# Salmeterol Powder for Pediatric Asthma

## Patient Criteria

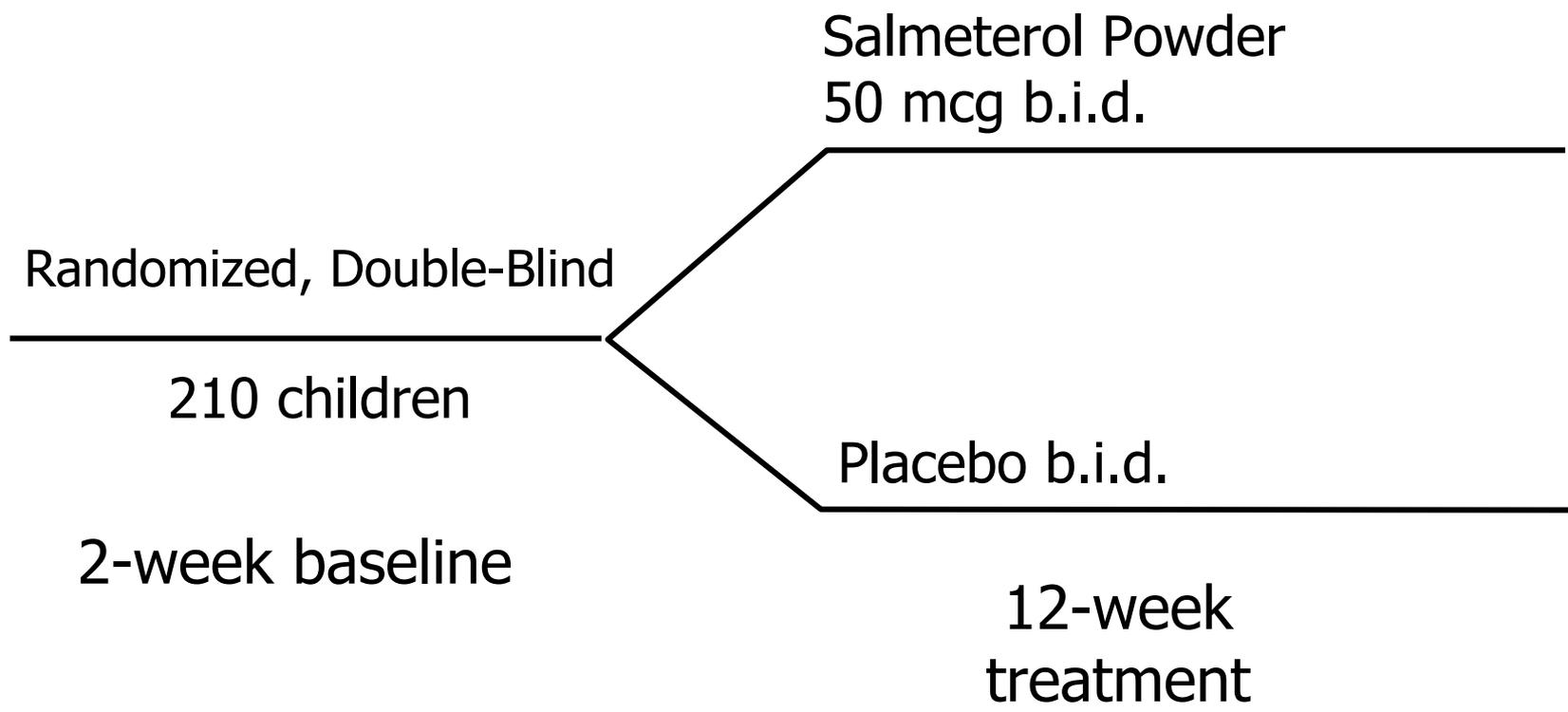
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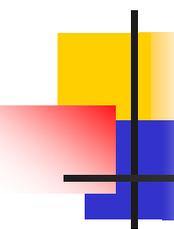
- 4 to 16 years of age
- Currently taking inhaled corticosteroids  $\geq 400$  mcg/day
  - beclomethasone or budesonide
- PEFr % predicted  $\leq 90\%$
- Diurnal variation in PEFr  $\geq 15\%$



# Salmeterol Powder for Pediatric Asthma

## Moderate-to-Severe Asthma





# Salmeterol Powder for Moderate-to-Severe Pediatric Asthma

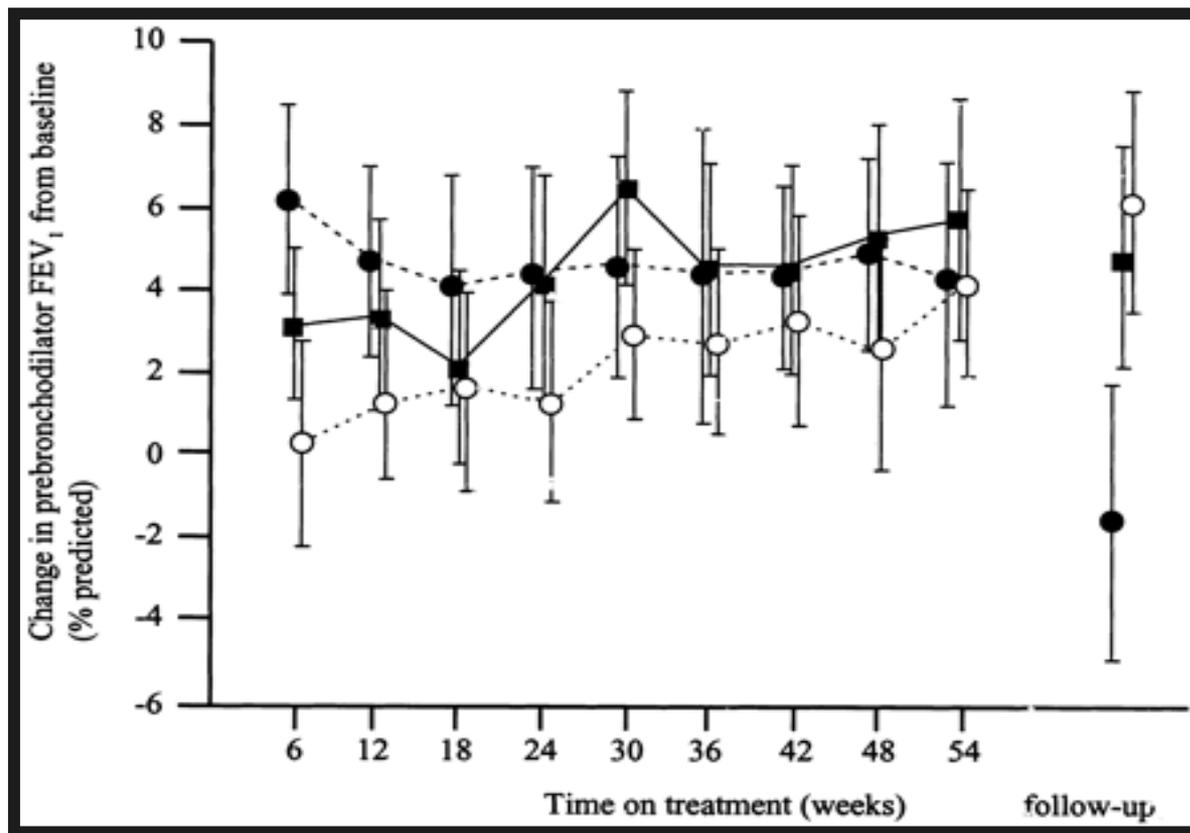
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- Addition of salmeterol powder (50 mcg b.i.d.) to  $\geq 400$  mcg/day of BDP or BUD therapy significantly:
  - Improved morning PEFR
  - Reduced asthma symptoms
  - Reduced daytime rescue albuterol use
- Evening PEFR, nighttime asthma symptoms, and nighttime rescue albuterol use followed a similar pattern, but were not significant after the first 4 weeks
- The overall incidence of adverse events was similar in both groups; however, headaches were more common in the salmeterol group

# Addition of Salmeterol vs Doubling the Dose of Beclomethasone in Children with Asthma

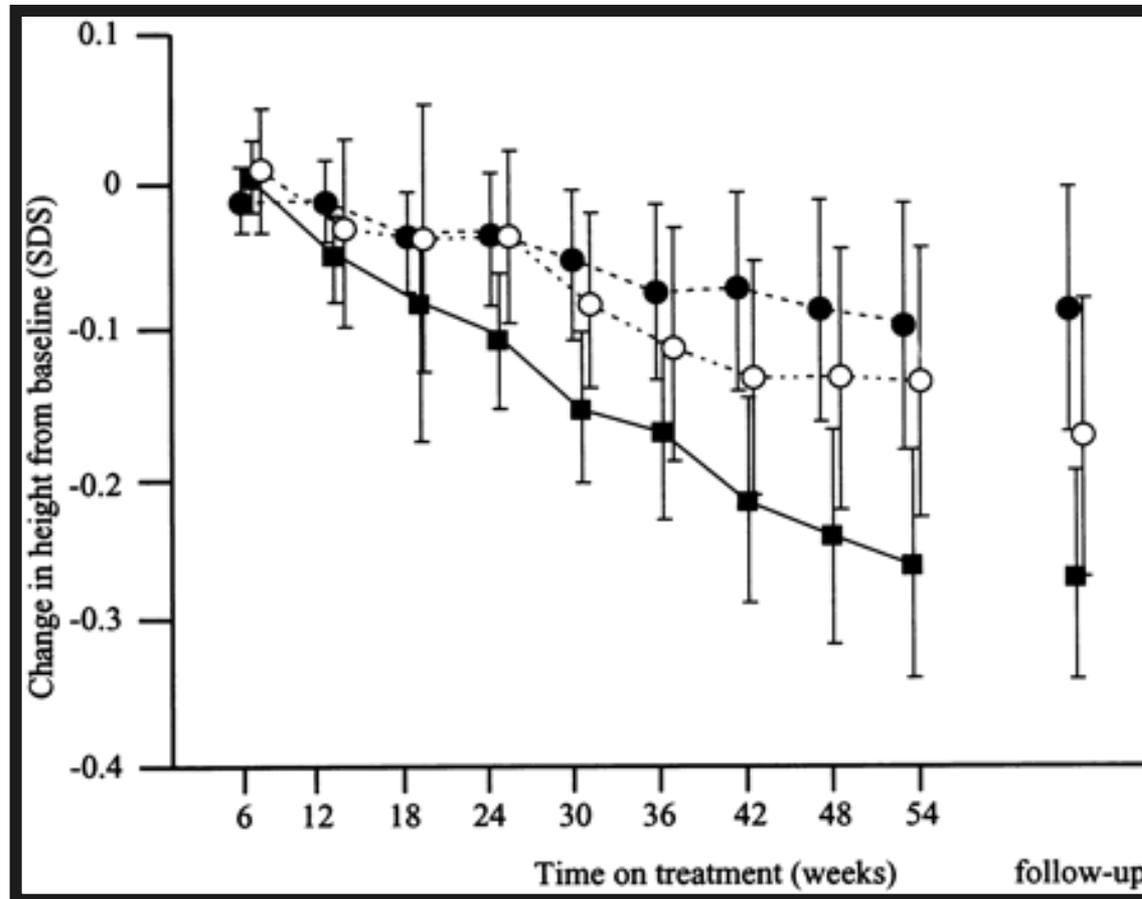
- 177 children (6-16 yrs) with mild-moderate asthma (ATS) with FEV<sub>1</sub> 55-90% predicted and using 200-800 mcg of ICS for at least 3 months
- Demonstration of reversibility ( $\geq 10\%$ ) and methacholine hyperresponsiveness  $\geq 2$  SD below mean of healthy children
- 6 week run-in on beclomethasone (BDP) 200  $\mu\text{g}$  BID monotherapy, then treated for 54 weeks with: (Rotadisks<sup>®</sup> in combination with a Diskhaler<sup>®</sup>)
  - Placebo (BDP 200  $\mu\text{g}$  BID)
  - BDP 200  $\mu\text{g}$  BID (BDP 400  $\mu\text{g}$  BID)
  - Salmeterol 50  $\mu\text{g}$  BID + placebo (BDP 200  $\mu\text{g}$  BID)

# Combination Salmeterol + Beclomethasone in Childhood Asthma: Effect on Prebronchodilator FEV<sub>1</sub>



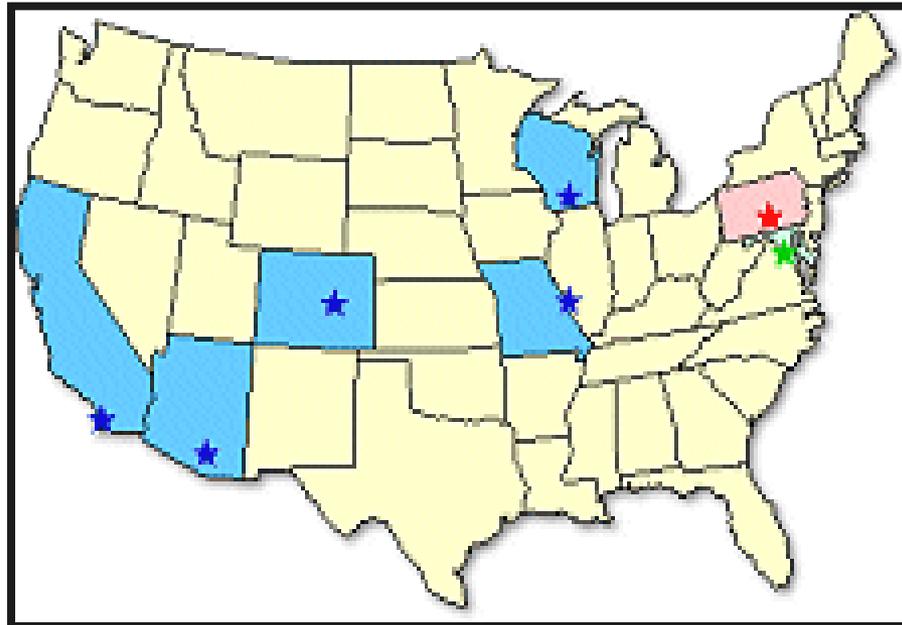
● = B (400 µg) + S  
○ = B (400 µg)  
■ = B (800 µg)

# Combination Salmeterol + Beclomethasone in Childhood Asthma: Effect on Growth



- = B (400 µg) + S
- = B (400 µg)
- = B (800 µg)

# Childhood Asthma Research and Education Network (CARE)



## Clinical Centers

Denver: National Jewish Medical & Research Center

Madison: University of Wisconsin

San Diego: University of California  
Kaiser Permanente California

St. Louis: Washington University

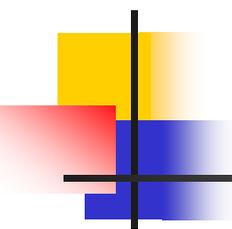
Tucson: University of Arizona

## Data Coordinating Center

Hershey: Penn State University

## NIH Funding Agency

Bethesda, MD: NHLBI



# PACT (Pediatric Asthma Controller Trial)

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- What is the best choice of therapy for the treatment of mild persistent asthma in children?
  - ICS monotherapy
  - Combination therapy (ICS + LABA)
  - Monotherapy with montelukast?

# PACT: Study Schematic

2-week run-in

48-week treatment period

Randomization

2 clinic visits

All participants receive

Albuterol prn

placebo diskus in the morning and evening

placebo capsule in the evening



8 study encounters (5 clinic and 3 telephone) at 6-week intervals

Morning Diskus

Evening Diskus

Evening Capsule

ICS

fluticasone

fluticasone

placebo

ICS 50% + LABA

fluticasone/salmeterol

salmeterol

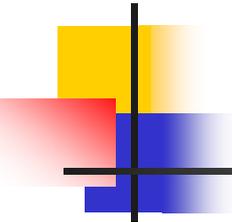
placebo

LTRA

placebo

placebo

montelukast



# Primary Outcome

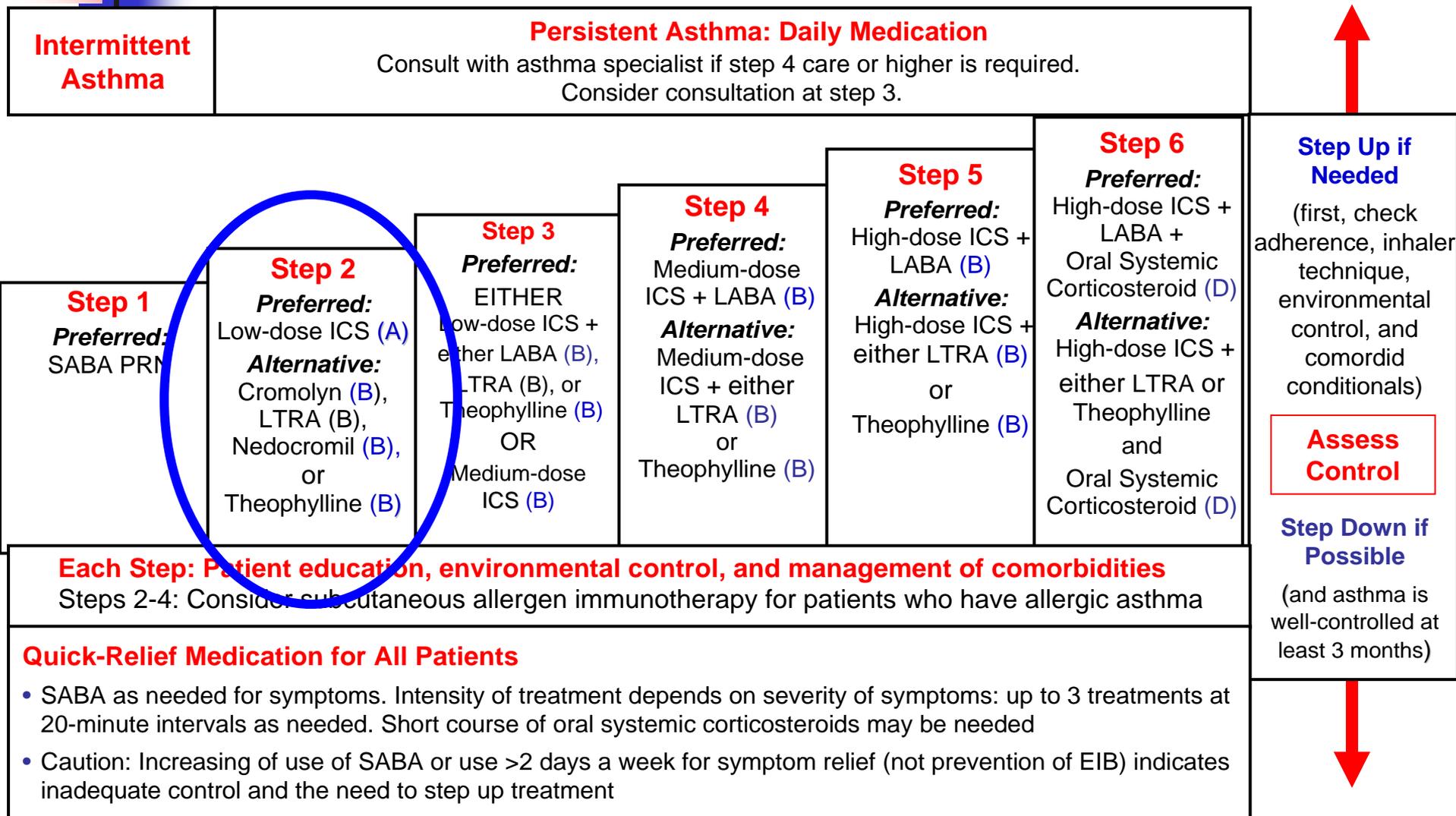
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- Percent of *Asthma Control Days (ACD)* during the 12-month treatment period
- Using self-reported daily diary data, an *ACD* was defined as a day without:
  - Albuterol use (permitted pre-exercise)
  - Use of non-study asthma medications
  - Daytime or nighttime asthma symptoms
  - Unscheduled health care provider visits for asthma
  - School absenteeism for asthma

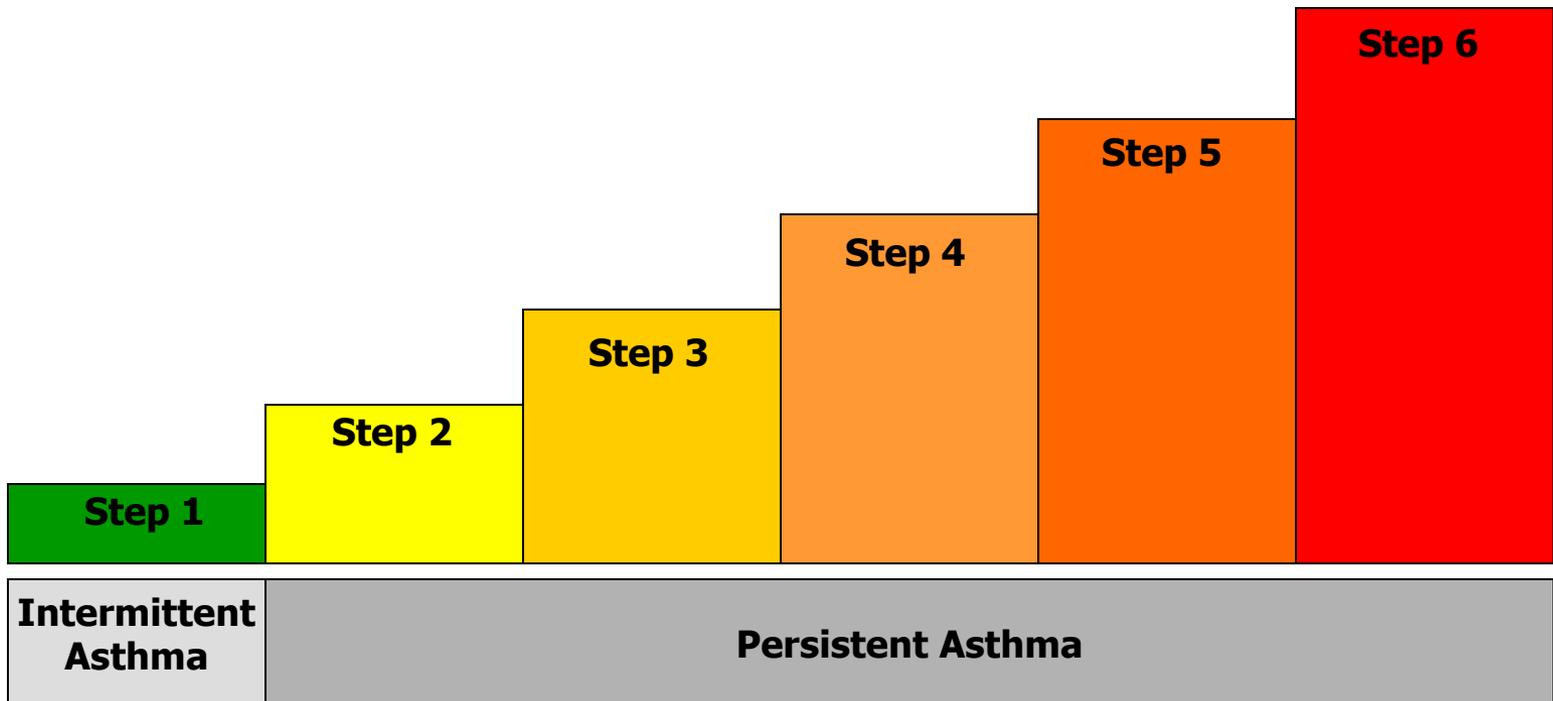
# Comparison of PACT Therapies

		Favors fluticasone over montelukast	Favors fluticasone over combination	Favors combination over montelukast
Asthma Burden	ACD over 12 months	●		●
	ACQ	●		
Asthma Treatment	Time to prednisone burst	●		
	Time to treatment failure	●		
	Number of treatment failures	●		
Pulmonary Function	AM and PM PEF	●		●
	FEV <sub>1</sub> and FEV <sub>1</sub> /FVC	●	●	●
	eNO	●	●	●
	PC <sub>20</sub>	●	●	●
	Max BD response	●	●	

# Stepwise Approach for Managing Asthma in Children 5-11 Years of Age



# Asthma Treatment



# CARE Trial in Progress



**ACRN**

**CARE**

**BADGER**

**Step 6**

**Step 5**

**Step 4**

**Step 3**

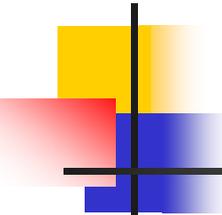
**Step 2**

**Step 1**

**Intermittent  
Asthma**

**Persistent Asthma**





# Research Question: Children

## **BADGER**

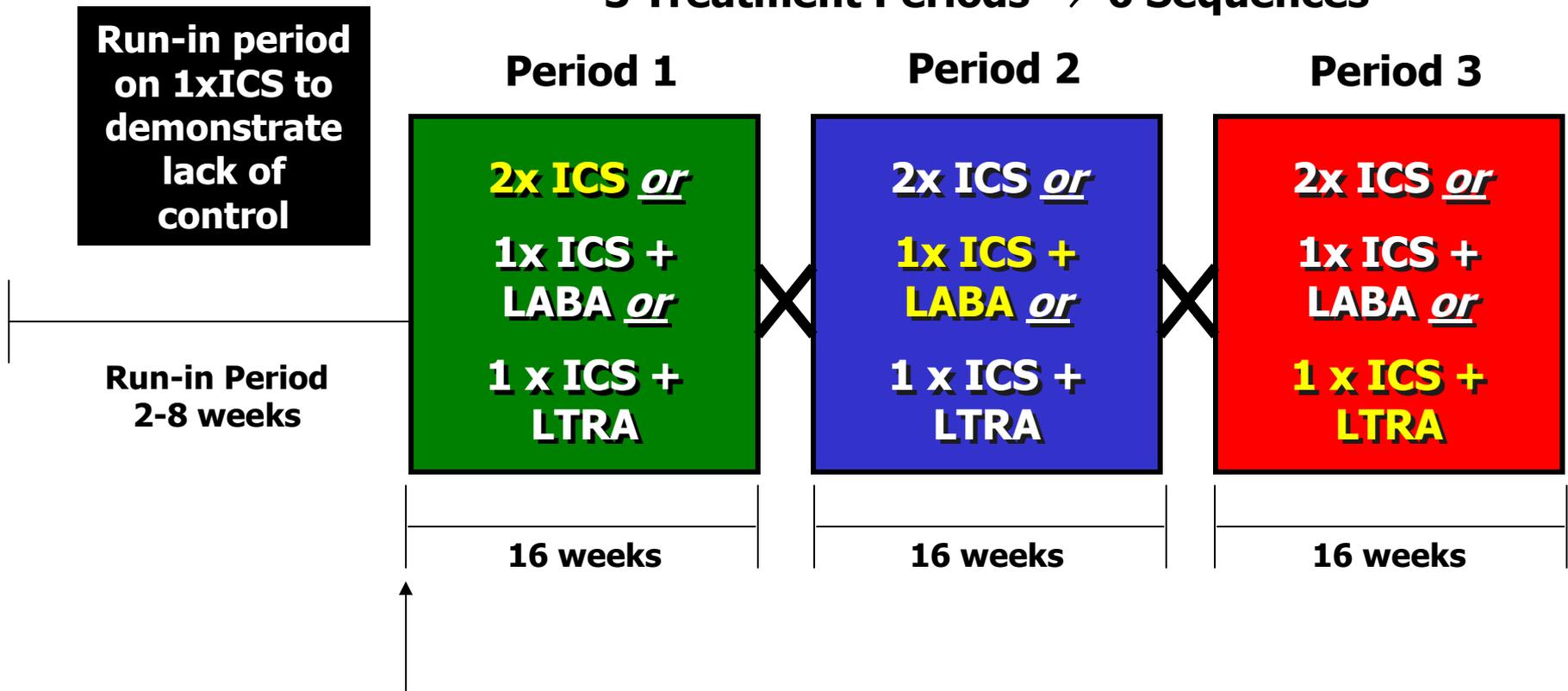
**B**est **A**dd-on Therapy **G**iving  
**E**ffective **R**esponses

- In patients receiving daily low dose ICS treatment who are not well controlled, what are the next best treatment options?

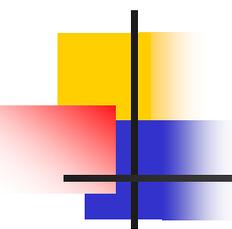
# BADGER Protocol: Overview

Double blind 3 way cross-over

3 Treatment Periods → 6 Sequences

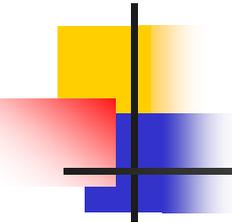


*Randomization*



# BADGER: Outcome measures to determine differential response

- 3 outcome measures defined a priori:
  - Exacerbations:
    - occurs when the total amount of prednisone prescribed to control asthma symptoms is at least 180 milligrams less on one treatment than on either of the other two treatments
  - FEV<sub>1</sub>:
    - occurs when the FEV1 change is at least 5.0% higher on one treatment than on either of the other two treatments
  - Asthma Control Days:
    - occurs when the number of annualized ACD (AACD) achieved is at least 31 days more on one treatment than on either of the other two treatments



# BADGER: Outcome Evaluation

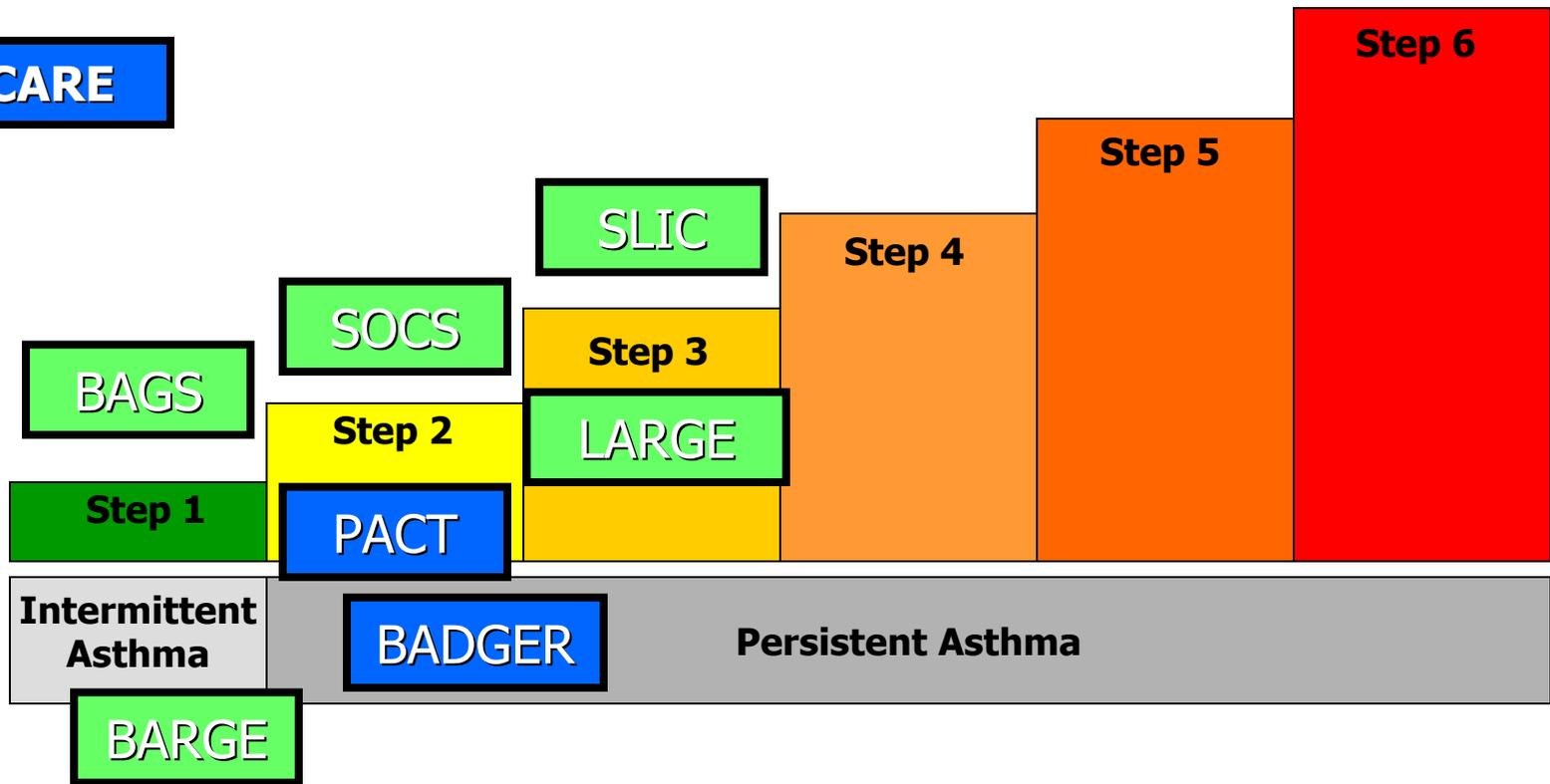
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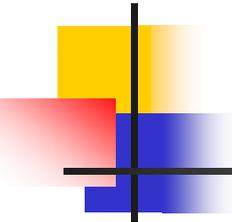
- If children demonstrate a preferential response to one treatment, they will then be evaluated using secondary outcomes to determine if there are phenotypic and/or genotypic characteristics that are associated with this positive response.

# ACRN and CARE Trials Summary

**ACRN**

**CARE**



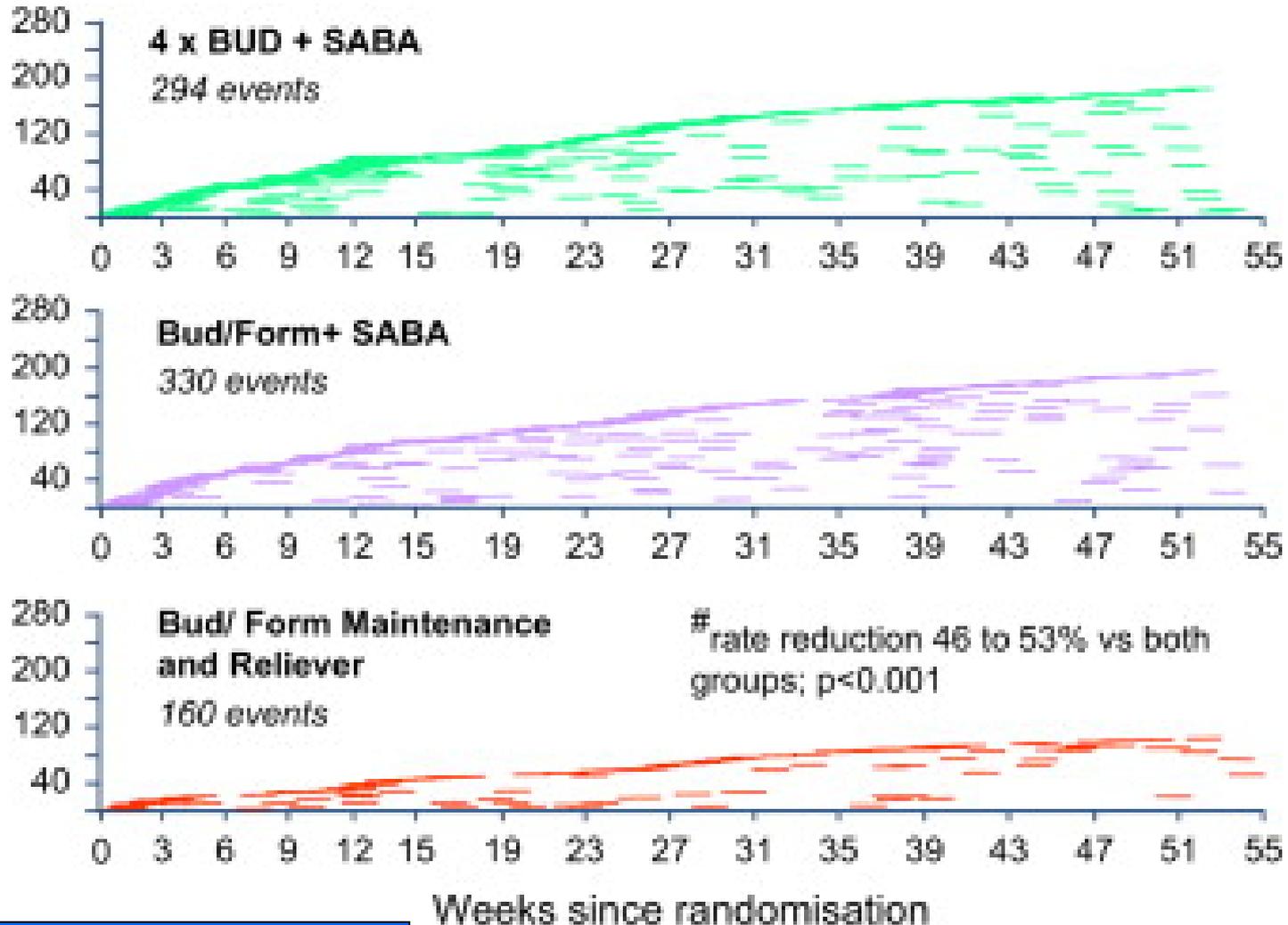


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**Beta Agonists + ICS:  
Maintenance  
and  
Reliever Therapy?**

# Combination Therapy: STAY Study

Severe Asthma Exacerbations



# Is a Long Acting Beta Agonist Necessary for Control?

- Mild asthma subjects (n=455)
- Six months treatment
- Primary outcome: AM PEF

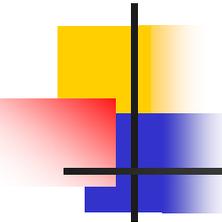
Treatment Group	Scheduled	As needed
A	Placebo	BDP 250 mcg + Albuterol 100 mcg
B	Placebo	Albuterol 100 mcg
C	BDP 250 mcg	Albuterol 100 mcg
D	BDP 250 mcg + Albuterol 100 mcg	Albuterol 100 mcg

## Results:

- AM PEF and Exacerbations:

Group A = C = D > B

- Cumulative dose of ICS lower in Group A compared to C and D



# Research Question: Children

## TREXA

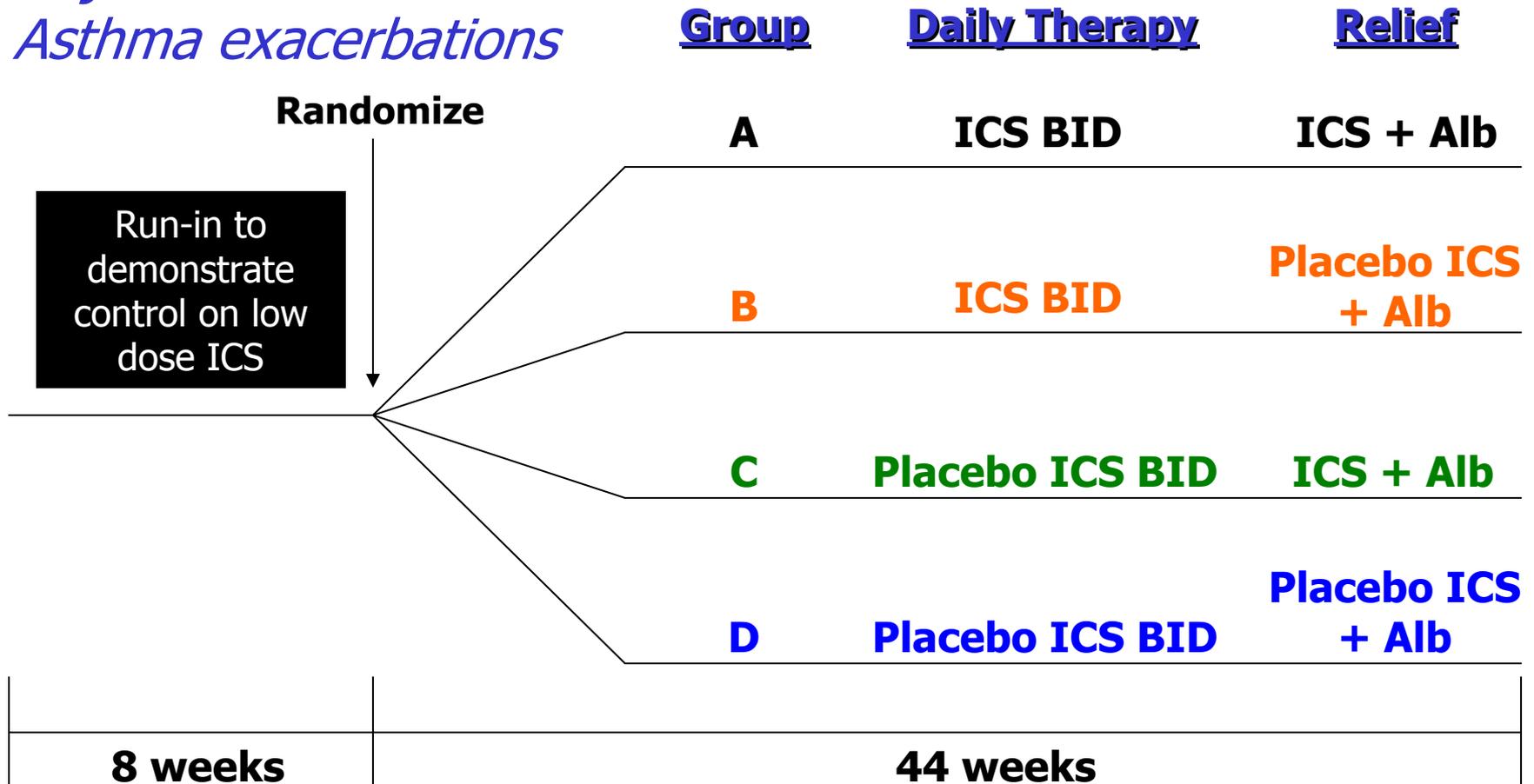
**T**reating Children to Prevent  
**EX**acerbations of **A**sthma

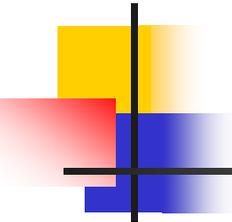
- In patients receiving daily low dose ICS treatment who are well controlled, can ICS doses be reduced and, if possible, what is the best strategy for doing so?

# TREXA Protocol: Overview

*Major outcome measure:  
Asthma exacerbations*

## Treatment Groups





# Beta Agonists: Conclusions

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- LABAs should not be used as monotherapy
- Combination therapy significantly improves asthma control in both the current impairment and future risk domains
- Are responses to therapy based on beta adrenergic receptor genotype different with SABAs than with LABAs?
- Do children respond differently to LABAs (not adversely but therapeutically)?
- Concept of maintenance and reliever with ICS + beta agonist needs further study



Volcán Osorno, Chile

**Thank you**

# Classifying Severity in Patients 5-11 Years of Age Not Currently Taking Long-Term Controllers

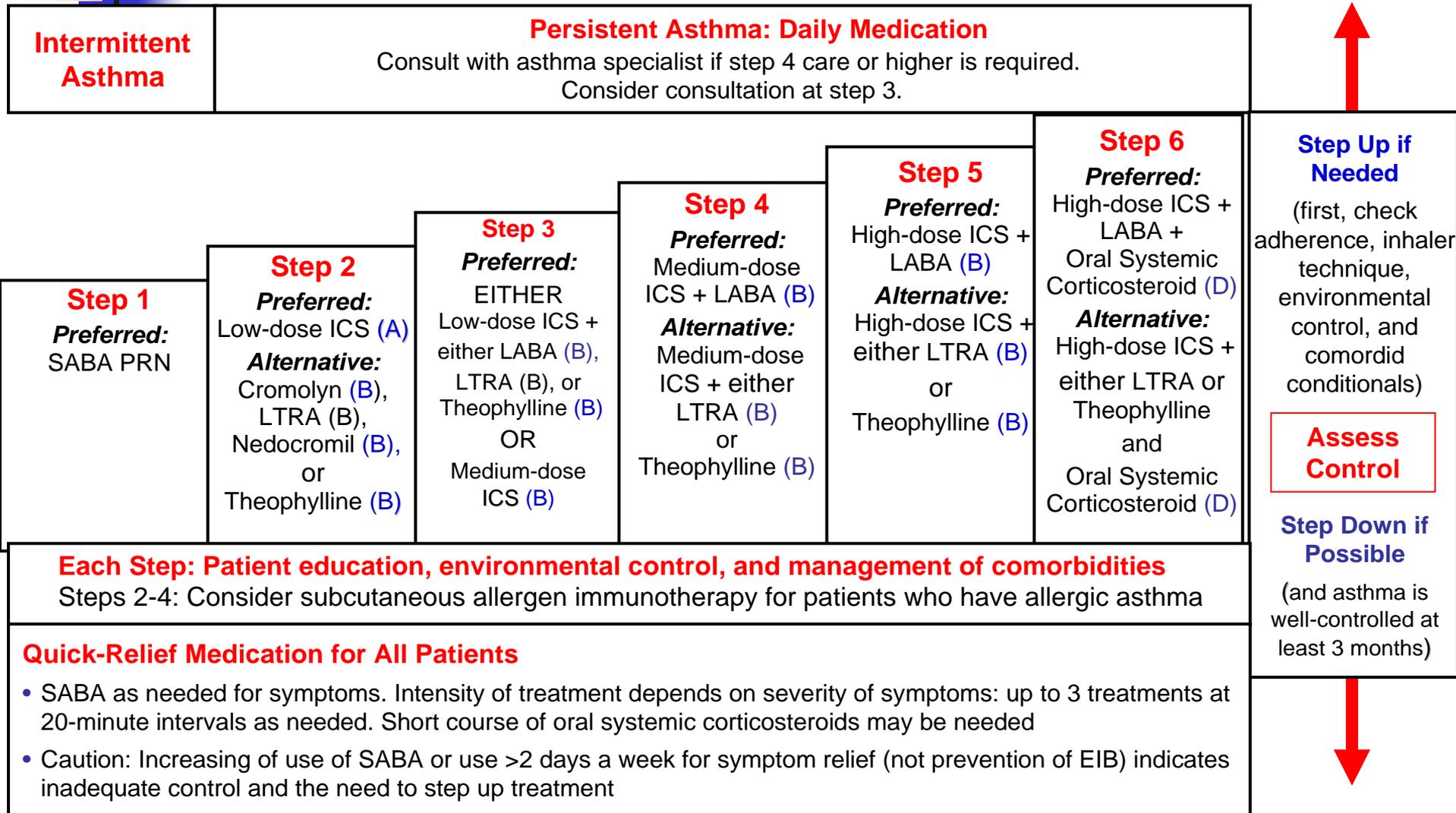
Components of Severity		Intermittent	Persistent		
			Mild	Moderate	Severe
<b>Impairment</b>	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3-4x/month	>1x/week but not nightly	Often 7x/week
	SABA use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung Function	<ul style="list-style-type: none"> <li>■ Normal FEV<sub>1</sub> between exacerbations</li> <li>■ FEV<sub>1</sub> &gt;80% predicted</li> <li>■ FEV<sub>1</sub>/FVC &gt;85%</li> </ul>	<ul style="list-style-type: none"> <li>■ FEV<sub>1</sub> ≥80% predicted</li> <li>■ FEV<sub>1</sub>/FVC &gt;80%</li> </ul>	<ul style="list-style-type: none"> <li>■ FEV<sub>1</sub> = 60%-80% predicted</li> <li>■ FEV<sub>1</sub>/FVC = 75%-80%</li> </ul>	<ul style="list-style-type: none"> <li>■ FEV<sub>1</sub> &lt;60% predicted</li> <li>■ FEV<sub>1</sub>/FVC &lt;75%</li> </ul>
<b>Risk</b>	<b>Exacerbations requiring oral systemic corticosteroids</b>	0-1/year	≥2/year Consider severity and interval since last exacerbation Frequency and severity may fluctuate over time for patients in any severity category		
		Relative annual risk of exacerbations may be related to FEV <sub>1</sub>			
<b>Recommended Step for Initiating Treatment</b>		<b>Step 1</b>	<b>Step 2</b>	<b>Step 3, medium-dose ICS option and consider short course of oral systemic corticosteroids</b>	<b>Step 3, medium-dose ICS option, or Step 4</b>
		In 2 to 6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly			

FVC = forced vital capacity.

# Assessing Asthma Control in Patients 5-11 Years of Age

Components of Control		Well Controlled	Not Well Controlled	Very Poorly Controlled
<b>Impairment</b>	Symptoms	≤2 days/week but not > than 1x on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	≥2x/month	≥2x/week
	Interference with nl activity	None	Some limitation	Extremely limited
	SABA use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function <ul style="list-style-type: none"> <li>■ FEV<sub>1</sub> or peak flow</li> <li>■ FEV<sub>1</sub>/FVC</li> </ul>	>80% predicted/ personal best >80%	60%-80% predicted/ personal best 75%-80%	<60% predicted/ personal best <75%
<b>Risk</b>	<b>Exacerbations requiring oral systemic corticosteroids</b>	<b>0-1/year</b>	<b>≥2/year</b>	
		<b>Consider severity and interval since last exacerbation</b>		
	Reduction in lung growth	Evaluation requires long-term follow-up		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk		
<b>Recommended Action for Treatment</b>		<ul style="list-style-type: none"> <li>■ Maintain current step</li> <li>■ Regular follow-up every 1 to 6 months</li> <li>■ Consider step down if well controlled for at least 3 months</li> </ul>	<ul style="list-style-type: none"> <li>■ Step up at least 1 step and</li> <li>■ Reevaluate in 2 to 6 weeks</li> <li>■ For side effects, consider alternative rx options</li> </ul>	<ul style="list-style-type: none"> <li>■ Consider short course of oral systemic corticosteroids</li> <li>■ Step up 1 or 2 steps, and</li> <li>■ Reevaluate in 2 weeks</li> <li>■ For side effects, consider alternative rx options</li> </ul>

# Stepwise Approach for Managing Asthma in Children 5-11 Years of Age



## Baseline Characteristics at the Start of the Run-in Period and at Randomization by Treatment Group

Characteristic	BDP 400 + Salm	BDP 800	BDP 400
<b>Start of run-in</b>			
Prebronch FEV <sub>1</sub> (% pred)	87.2 (13)	85.3 (13.8)	86.5 (13.2)
Postbronch FEV <sub>1</sub> (% pred)	103.2 (14.1)	100.9 (12.3)	102.2 (12.0)
Meth PD <sub>20</sub> (μg)	24.5 (11-47.5)	22.5 (7.5-42.5)	26 (12-38)
<b>At randomization</b>			
Prebronch FEV <sub>1</sub> (% pred)	89.7 (11.8)	87.4 (12.3)	89.2 (13.4)
Postbronch FEV <sub>1</sub> (% pred)	103.5 (14.1)	102.3 (11.4)	103.0 (13.6)
Meth PD <sub>20</sub> (μg)	29 (9-59)	20 (6-56)	27 (16.5-44)
Days in 2 wks with symptoms	6 (3-11)	5 (1.5-10)	4 (1-9)
Nights in 2 wks with symptoms	6 (3-10)	4.5 (1-11)	5 (1-9)