Alair® System

Asthmatx, Inc.

FDA Advisory Panel Meeting
October 28, 2009

Agenda

Introduction	Debera Brown
Background - Severe Asthma - The Problem - Alair System - Therapeutic Concept - Pre-clinical Experience - Clinical Experience (prior to Pivotal)	Gerard Cox, MB
AIR2 Trial (Pivotal IDE Study) - Statistical Design - Study Design and Results	 Donald Berry, PhD Mario Castro, MD, MPH
Maximizing Safety Post Approval	Debera Brown
Putting AIR2 into Context	Michael Wechsler, MD, MMSc

Intended Use

The Alair System is indicated for the treatment of severe persistent asthma in patients 18 years and older

Introduction

- Sponsor is required to provide
  - *"reasonable assurance that the device is safe and effective for its conditions of use."*

- Alair System - a new device for the treatment of asthma
  - Unmet medical need – severe persistent asthma
  - In development for more than 10 years
  - 5 clinical studies
  - Long-term follow-up in humans (~500 patient years)

Rigorous Scientific Approach

- Worked with thought leaders in the field of asthma
- Collaborated with FDA on the design of pre-clinical and clinical studies
- Conducted 5 clinical trials
  - 3 were multi-center RCTs
- Executed double-blind, sham-controlled pivotal trial
  - Over the past 5 years FDA has approved 159 original PMAs with evaluable summaries. Only 2 (1.3%) have been supported by a double-blind, sham-controlled pivotal trial[1]

[1] FDA PMA Database – www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm (SSEDs for original PMA approvals from 9/1/04 – 9/18/09 containing term "sham" in clinical study discussion)

Gerard Cox, MB, FRCPC, FRCPI

Professor of Medicine

Director of Division of Respirology

McMaster University, St. Joseph's Healthcare

Hamilton, Ontario, Canada

- Past President of the Canadian Thoracic Society
- Investigator in all five Alair clinical trials
- Long-term experience with Alair-treated patients

Disclosure

- Investigator in a number of studies with standard reimbursement to my institution
- No stock or financial interest in Asthmatx
- Consultant to Asthmatx, though all compensation goes to my institution
- Travel and lodging reimbursed by Asthmatx

Severe Persistent Asthma

The Problem

Asthma Is Prevalent

Significant Morbidity and Mortality

National Center for Health Statistics, CDC, 2005

Control is the Goal

*" The goal of asthma therapy is to **control** asthma so that patients can live full, active lives while minimizing their risk of asthma exacerbations and other problems."*

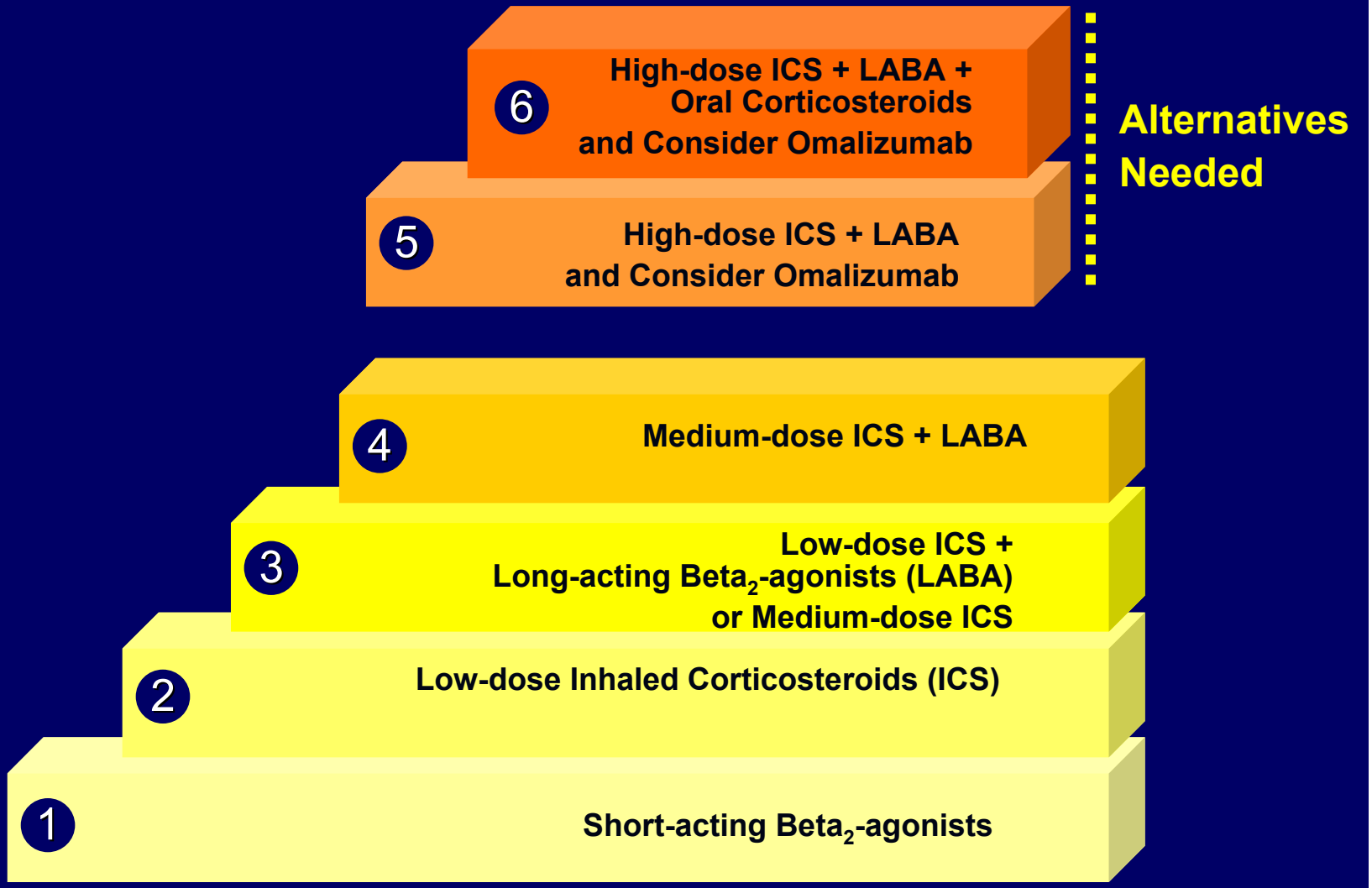
William Busse, MD
Professor of Medicine
University of Wisconsin

Chairman, Expert Panel
National Asthma Education and Prevention Program
NHLBI/NIH

The first comprehensive update of asthma guidelines in more than a decade.

Source: NIH Press Release, August 29, 2007

Stepwise Approach for Managing Asthma



Adapted from National Asthma Education and Prevention Program (NAEPP) Guidelines. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute, NIH Publication No. 07-4051, Revised August 2007

Severe Persistent Asthma

Symptomatic despite use of high-dose inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA)

Severe/Difficult to Control Asthma

The TENOR Study[1]

- Prospective, observational, multi-center, 3-year study
- 4,756 patients; severe or difficult to control asthma
  - 56% on three medications, 35% on two medications
- During past 3 months:
  - 60% required an oral steroid burst
  - 20% had a emergency department visit
  - 10% had to be hospitalized
- Severe asthma patients consume disproportionate healthcare resources

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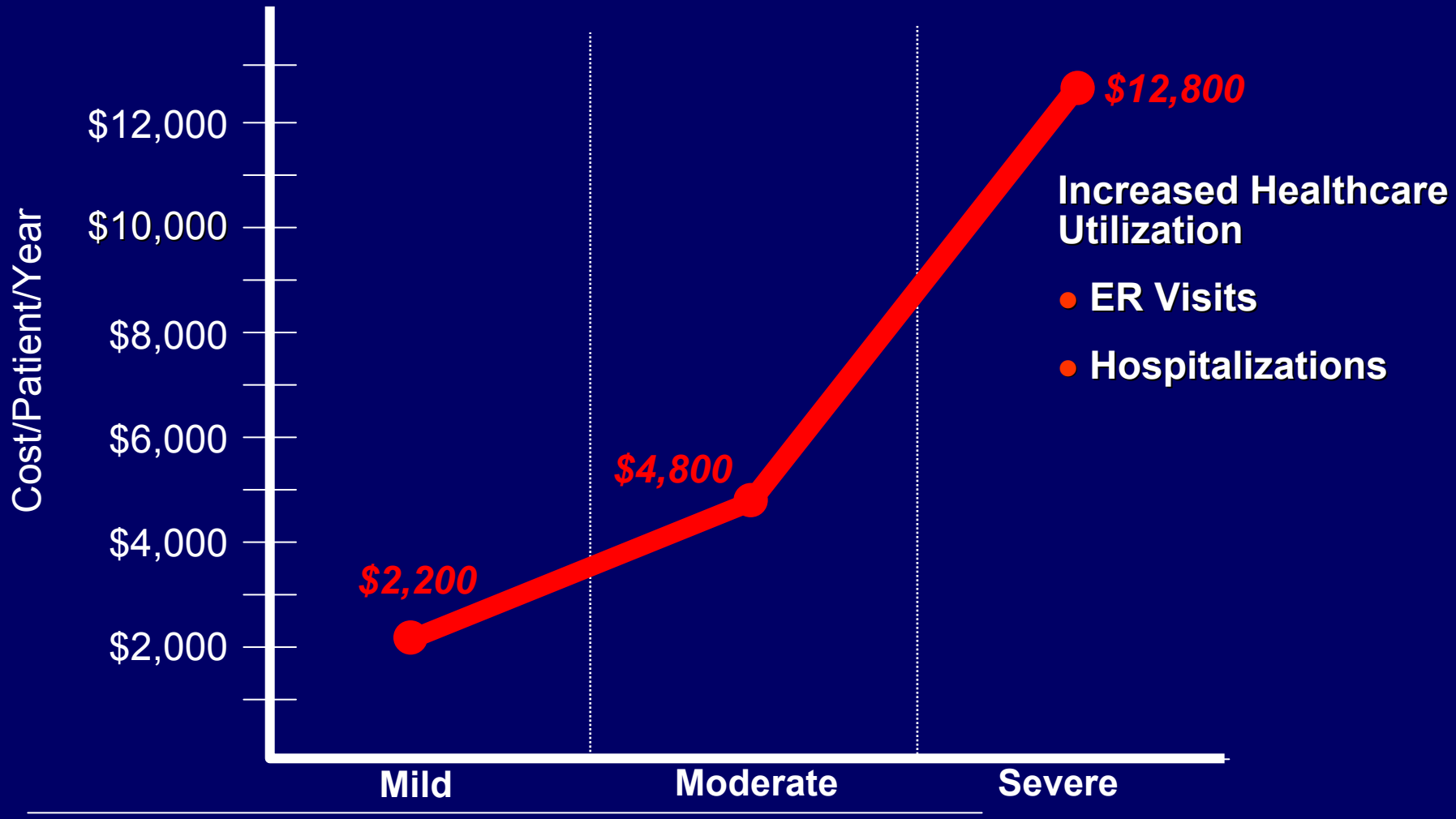
[1] **Dolan et al. *Ann Allergy Asthma Immunol* 2004; 92: 32-39**

Annual Cost by Asthma Severity[1]



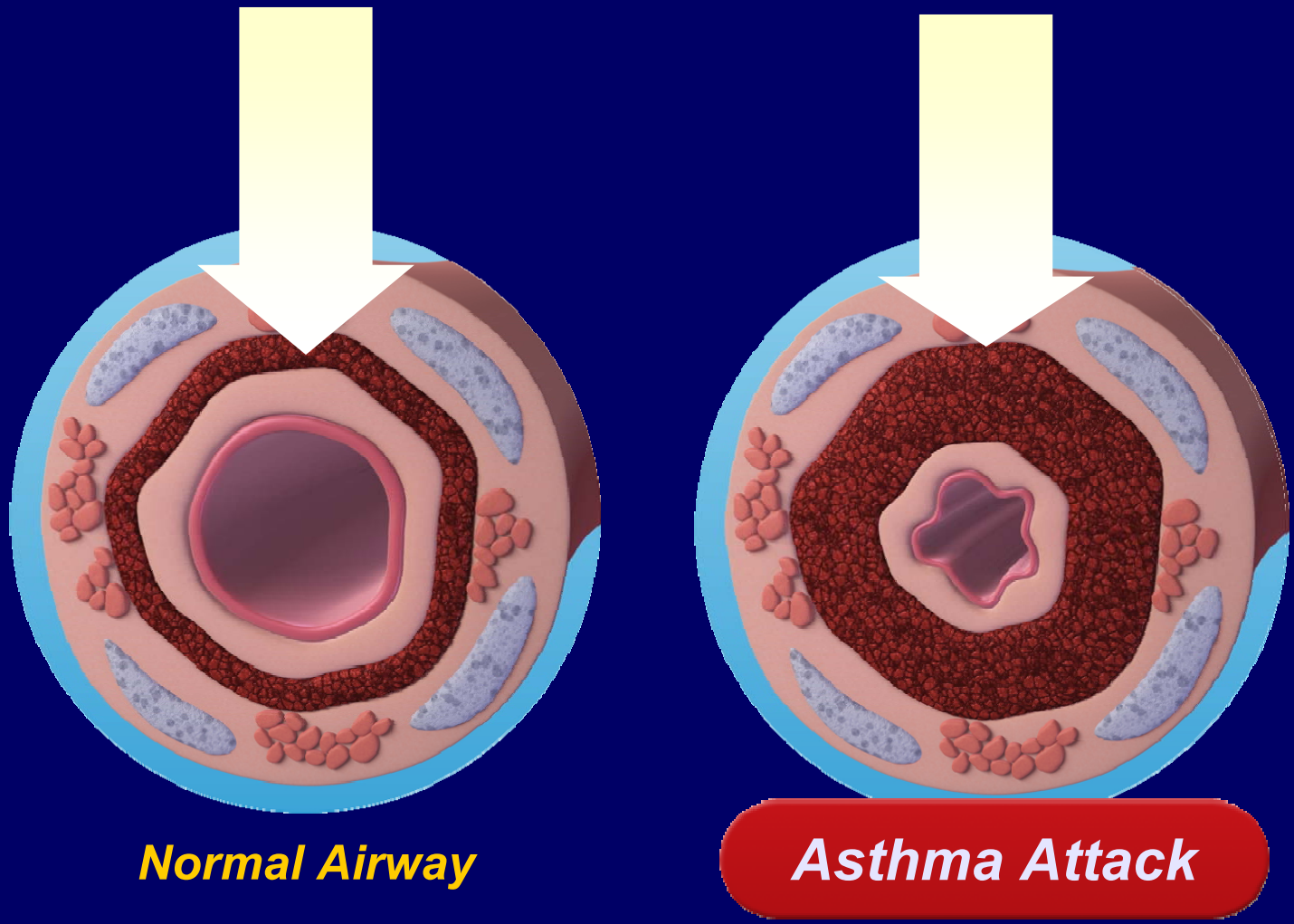
[1] Cisternas M, et al., A comprehensive study of the direct and indirect costs of an adult with asthma. *J Allergy Clin Immunol* 2003; 111(6): 1212-1218

Unmet Need in Severe Persistent Asthma

- Prevalence of severe asthma 5-20% (NAEPP/NHLBI)
- Many patients remain symptomatic despite standard of care medications
- Treatments are limited, require adherence, and may have serious side effects
- New options are needed

Therapeutic Concept and Method for Bronchial Thermoplasty with The Alair System

Role of Airway Smooth Muscle in Asthma



Normal Airway

Asthma Attack

Alair Therapy Rationale

Bronchial Thermoplasty with the Alair System

↓

Long-Term Reduction of Excessive Airway Smooth Muscle (ASM)

↓

Reduced Ability for Muscle-Mediated Bronchoconstriction

↓

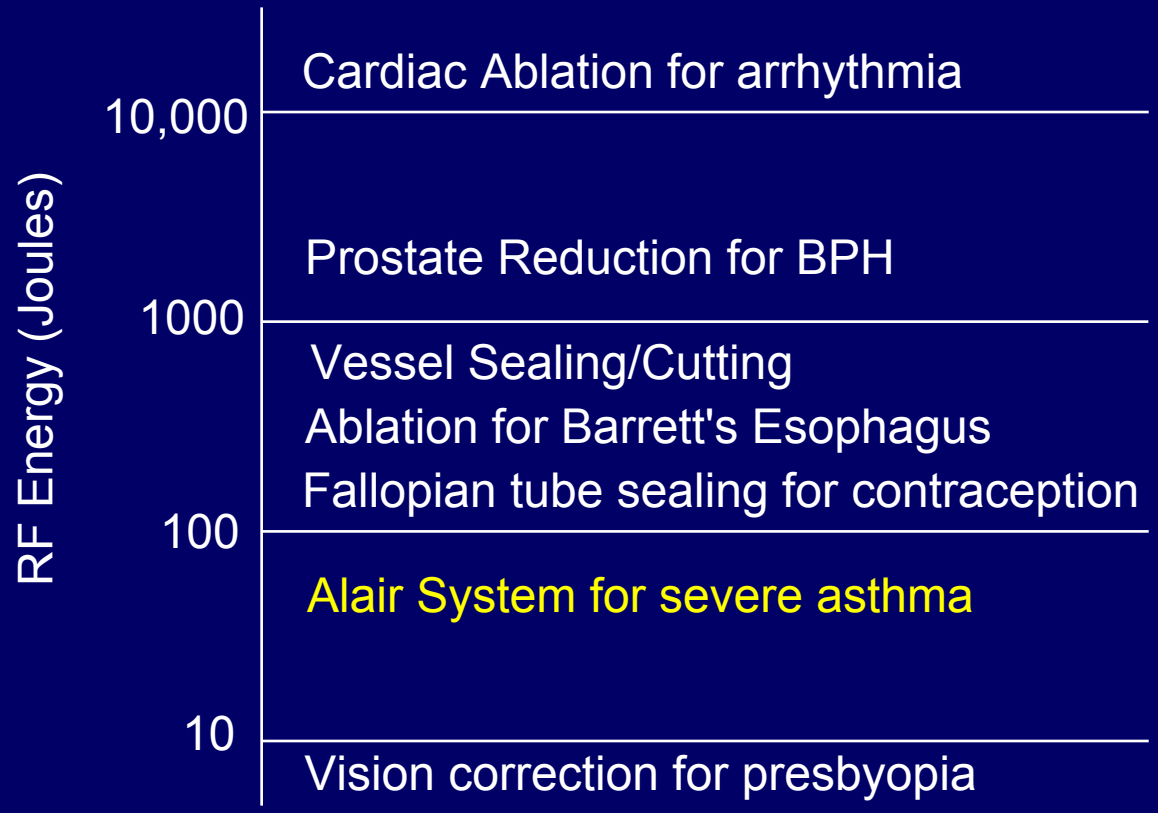
Reduced Asthma Symptoms and Exacerbations

↓

Improved Asthma Control and Quality of Life

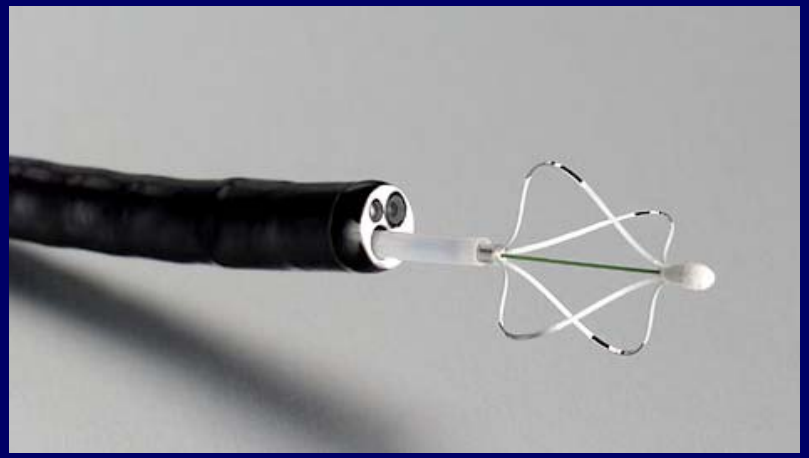
Safe Use of Radiofrequency (RF) Energy

- History of safe use in medical procedures
- Alair System uses lower energy than many other approved/cleared devices



The Alair® System

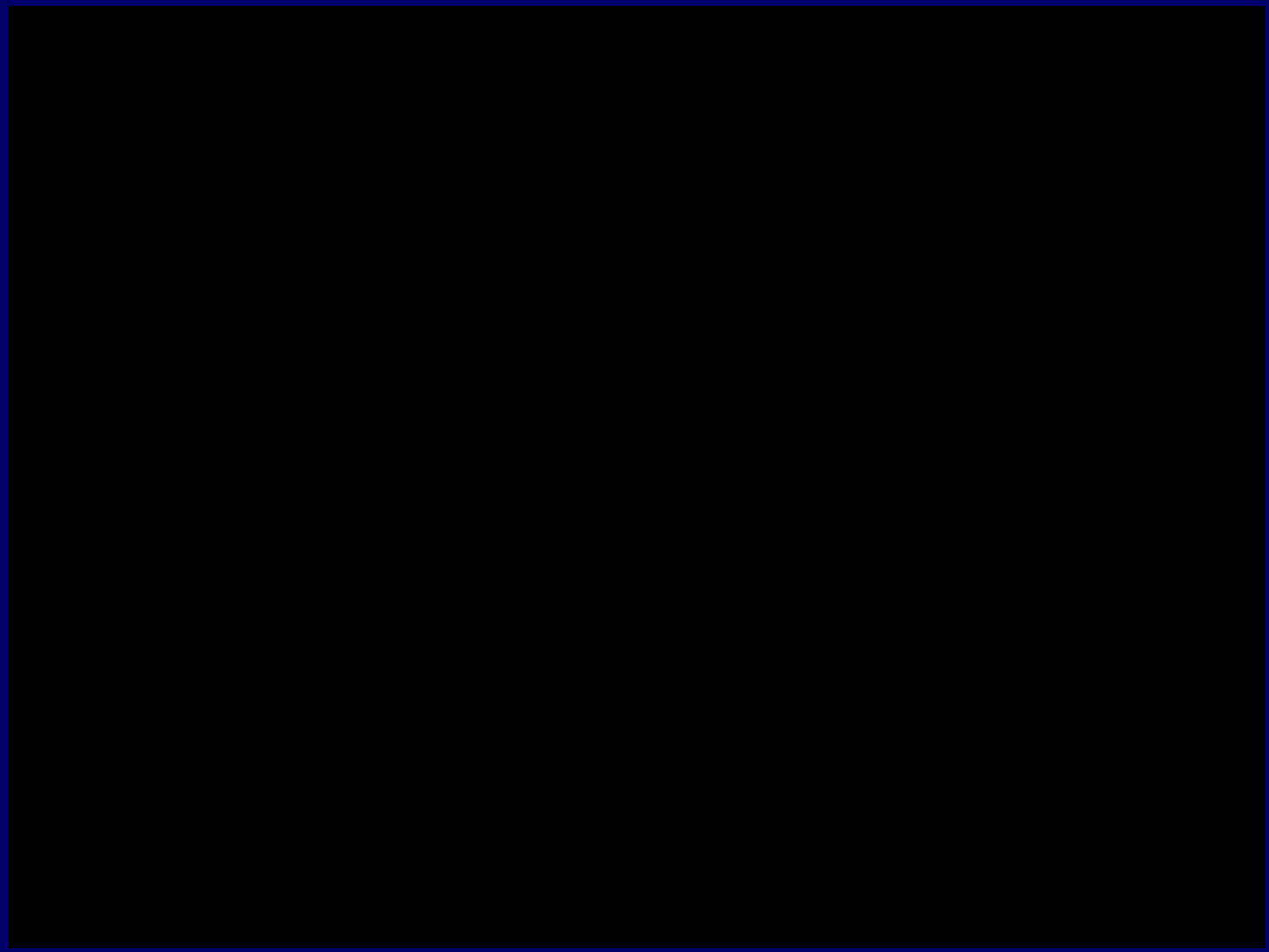
- **The *Alair* Catheter is a flexible tube with an expandable wire array at the tip**



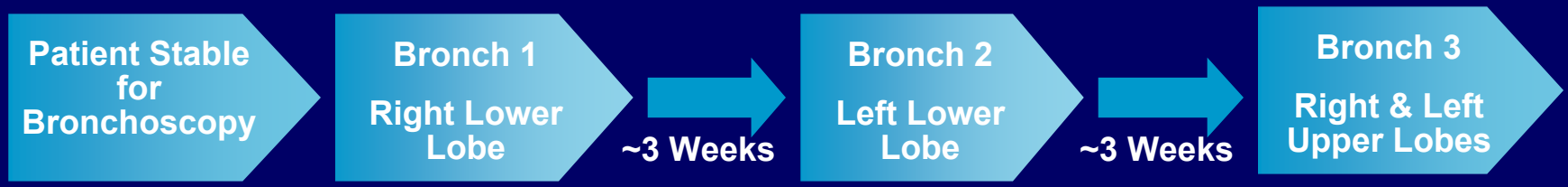
- **The *Alair* Radiofrequency Controller supplies energy that is converted to heat in the airway wall**

- Monopolar radiofrequency (RF) energy
  - Temperature controlled: 65 °C
  - 10 seconds
- Multiple safety algorithms to ensure controlled energy delivery

Treatment Method



Procedure Details



- Procedures performed in Bronchoscopy Suite
- Prophylactic medication: Prednisone
  - 50 mg/day for 5 days (3 days prior, Day of, and Day after procedure)
- Standard sedation and monitoring techniques
- Post-procedure monitoring (O_2 saturation, FEV_1)

Safety of Bronchoscopy Established

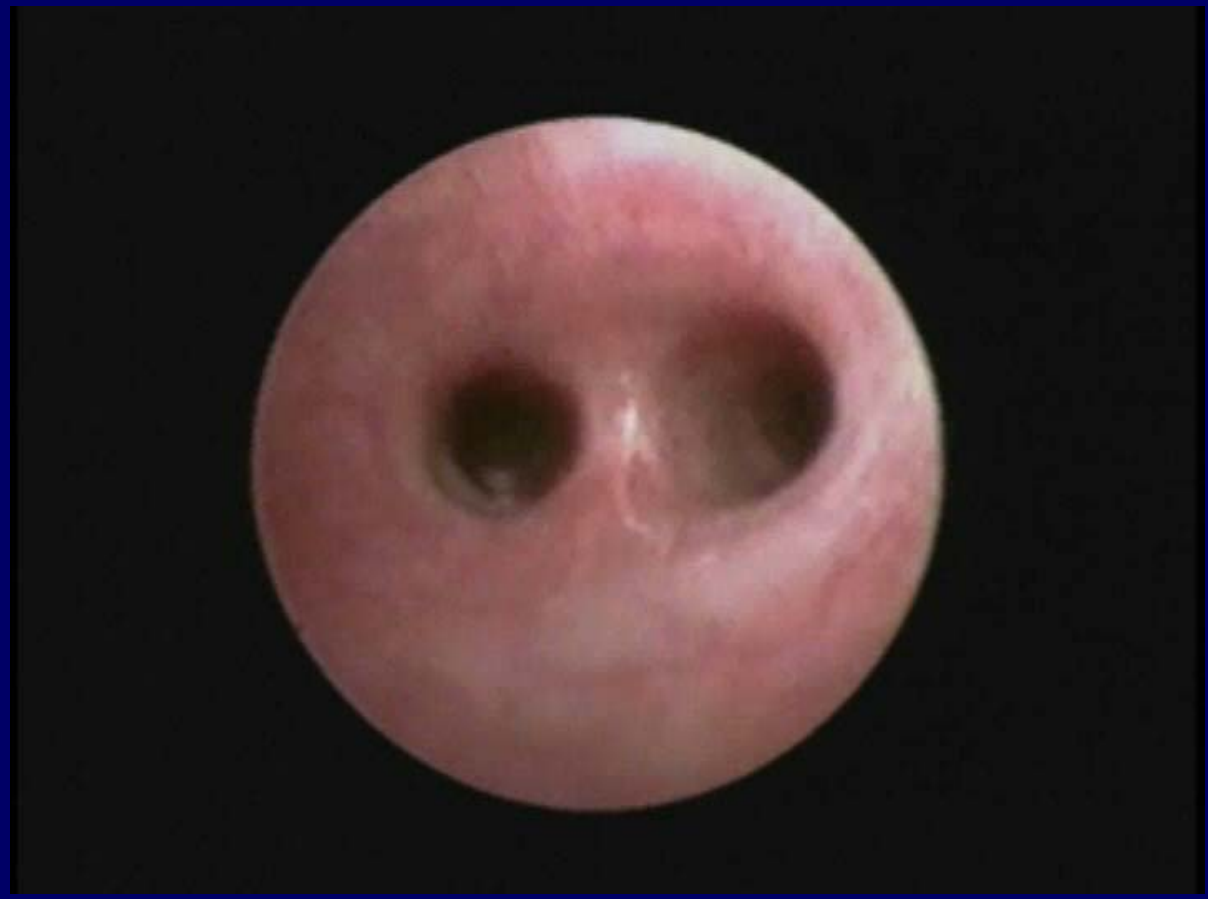
- Routine procedure in pulmonology
  (Diagnostic & therapeutic applications)
- ~ 500,000 performed per year
- Guidelines for bronchoscopy published by American College of Chest Physicians
- Performed in patients with severe asthma
- Safety of bronchoscopy in severe asthma patients understood (SARP)

Pre-Clinical Experience

Preclinical Development Program

- Four pre-clinical studies
  - One randomized and sham-controlled
  - 50 dogs (35 Alair treated)
  - Up to 3 years of follow-up

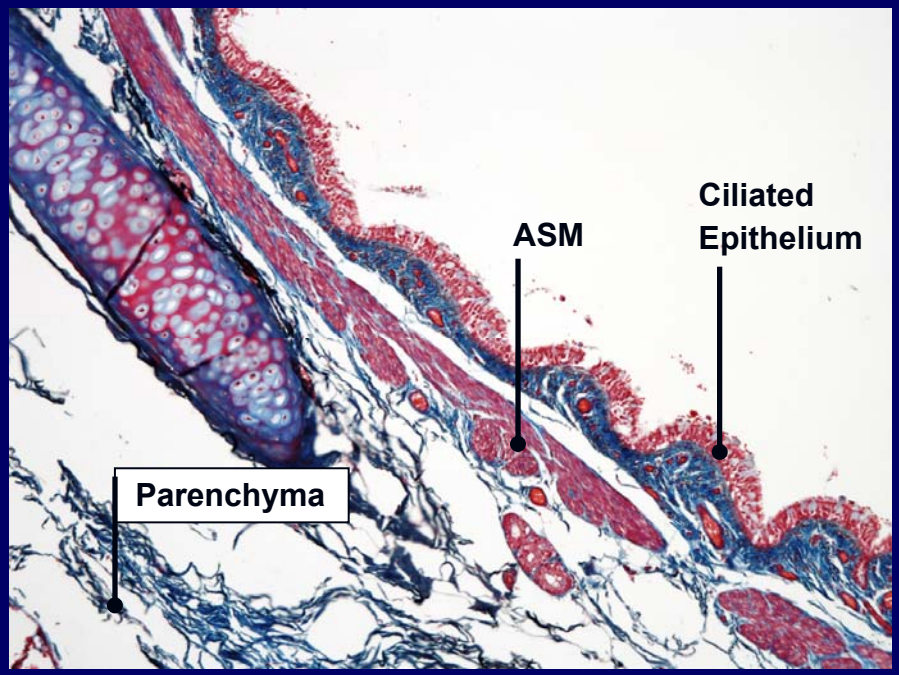
Local Bronchoprovocation of Alair-Treated Airway (Canine)



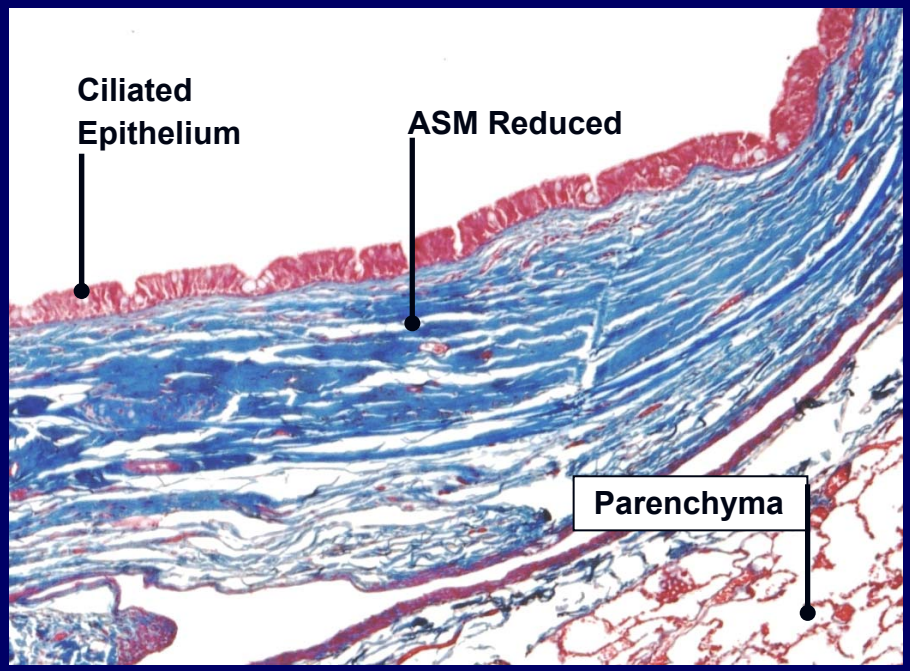
Alair-treated airway on left

Cox et al. *Eur Respir Journal.* 2004; 24: 659-663

Reduced Airway Smooth Muscle
3 Years Post-Treatment (Canine Model)



UNTREATED



TREATED

Masson's Trichrome stain

Preclinical Development Program

- Key Findings
  - Defined treatment parameters (Temp. / Time)
  - Long-term reduction of ASM via histology
  - Significant correlation between ASM reduction and decreased bronchoconstriction

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Danek et al. *J Appl Physiol* 2004; 97(5): 1946-1953

Cox et al. *Eur Respir J* 2004; 24(4): 659-663

Alair Clinical Program

Clinical Studies

- Lobectomy (n=8)
  - Safety
  - Cancer patients scheduled to undergo resection
  - Procedure done 1-3 weeks prior to lobectomy
  - Human histology showed reduced ASM consistent with pre-clinical histology

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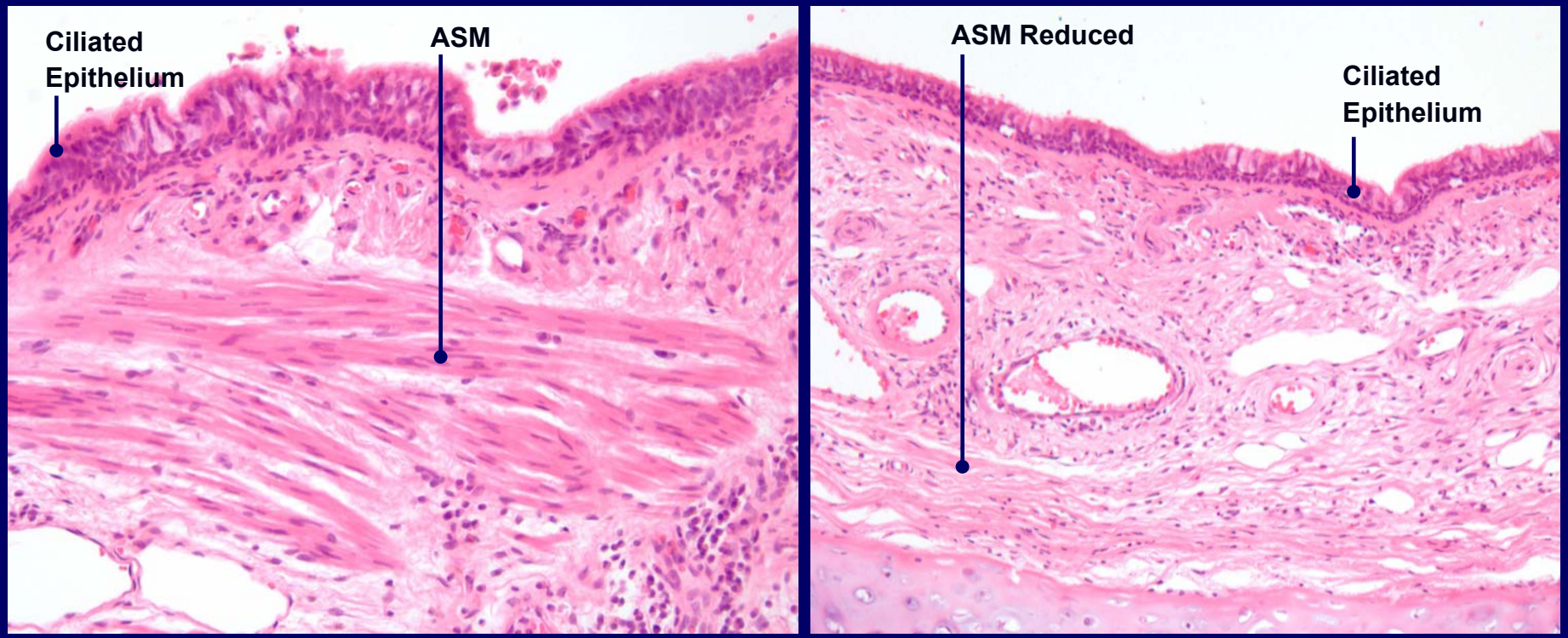
Miller et al. *CHEST* 2005; 127(6): 1999-2006

Reduced Airway Smooth Muscle

12 Days Post-Treatment (Lobectomy Study)



UNTREATED TREATED

H&E stain

Miller et al. *CHEST* 2005; 127(6): 1999-2006

Studies in Asthma Patients

Alair® Clinical Studies in Asthma

* Asthma Intervention Research Trial

** Research in Severe Asthma Trial

Baseline Demographics
Alair Treated Subjects

Parameter	Feasibility	AIR Trial	RISA Trial
Number of Subjects	16	55	15
Age (years)	39.0 ± 8.6	39.4 ± 11.2	39.1 ± 13.0
Gender	F 10 (63%)	F 31 (56%)	F 9 (60%)
Pre-BD FEV_1 (% Pred)	82.2 ± 14.1	72.65 ± 10.41	62.9 ± 12.2
ICS Dose (µg/day) Beclomethasone or Equiv.	900 ± 424	1351 ± 963	2333 ± 817
OCS Dose (mg/day)	0	0	14.4 ± 6.2 (N=8)
% Symptom Free Days	50 ± 33	34 ± 34	5 ± 14

Multiple Studies Support Effectiveness

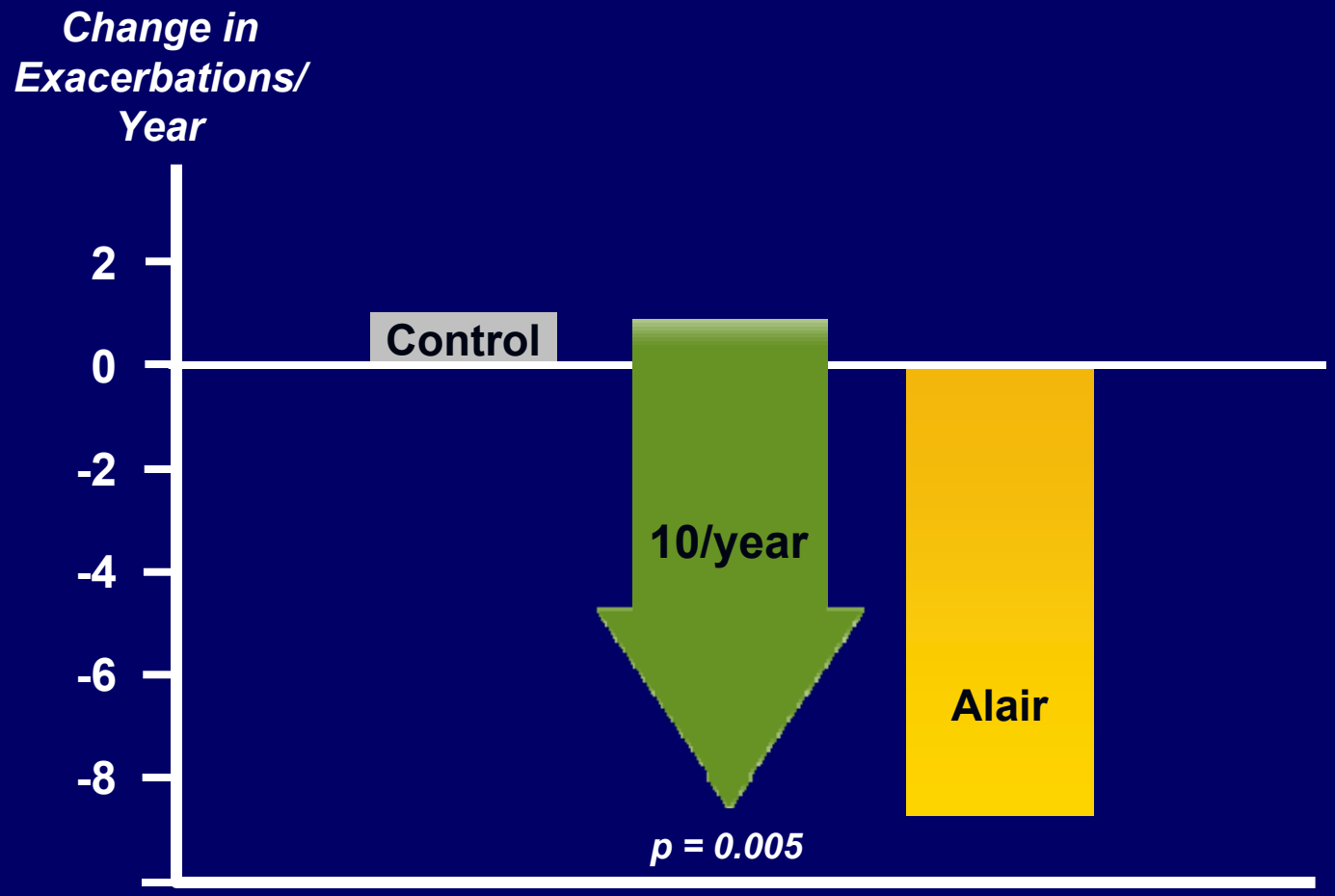
	Feasibility (n = 16)	AIR (n = 109)	RISA (n = 32)
AQLQ Score	--	✓	✓
ACQ Score	--	✓	✓
Exacerbations	--	✓	--
Symptom-Free Days	✓	✓	NS
Rescue Med	--	✓	✓
Lung Function	✓ PEF	✓ PEF	✓ FEV_1
Meth. PC_{20}	✓	NS	NS
Reduced OCS	--	--	(p=0.12)
	AJRCCM, v173, May 2006	*NEJM*, v356, Mar 2007	*AJRCCM*, v176, Sep 2007

✓ = $p < 0.05$

"—" = not evaluated

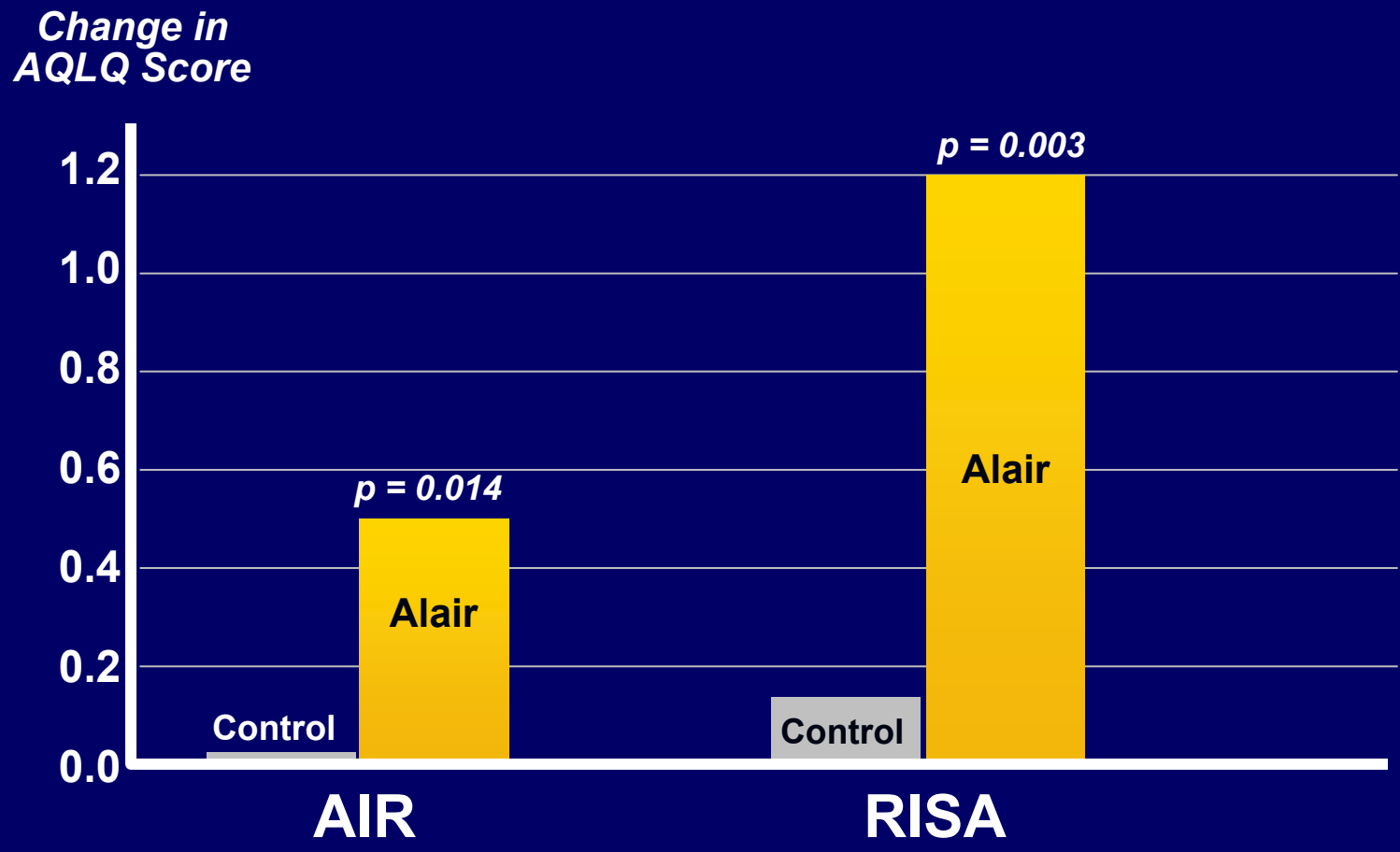
NS = not significant

Reduction in Exacerbations (AIR Trial)



Cox et al. Asthma control during one year after bronchial thermoplasty, *NEJM* 2007; 356(13): 1327-1337

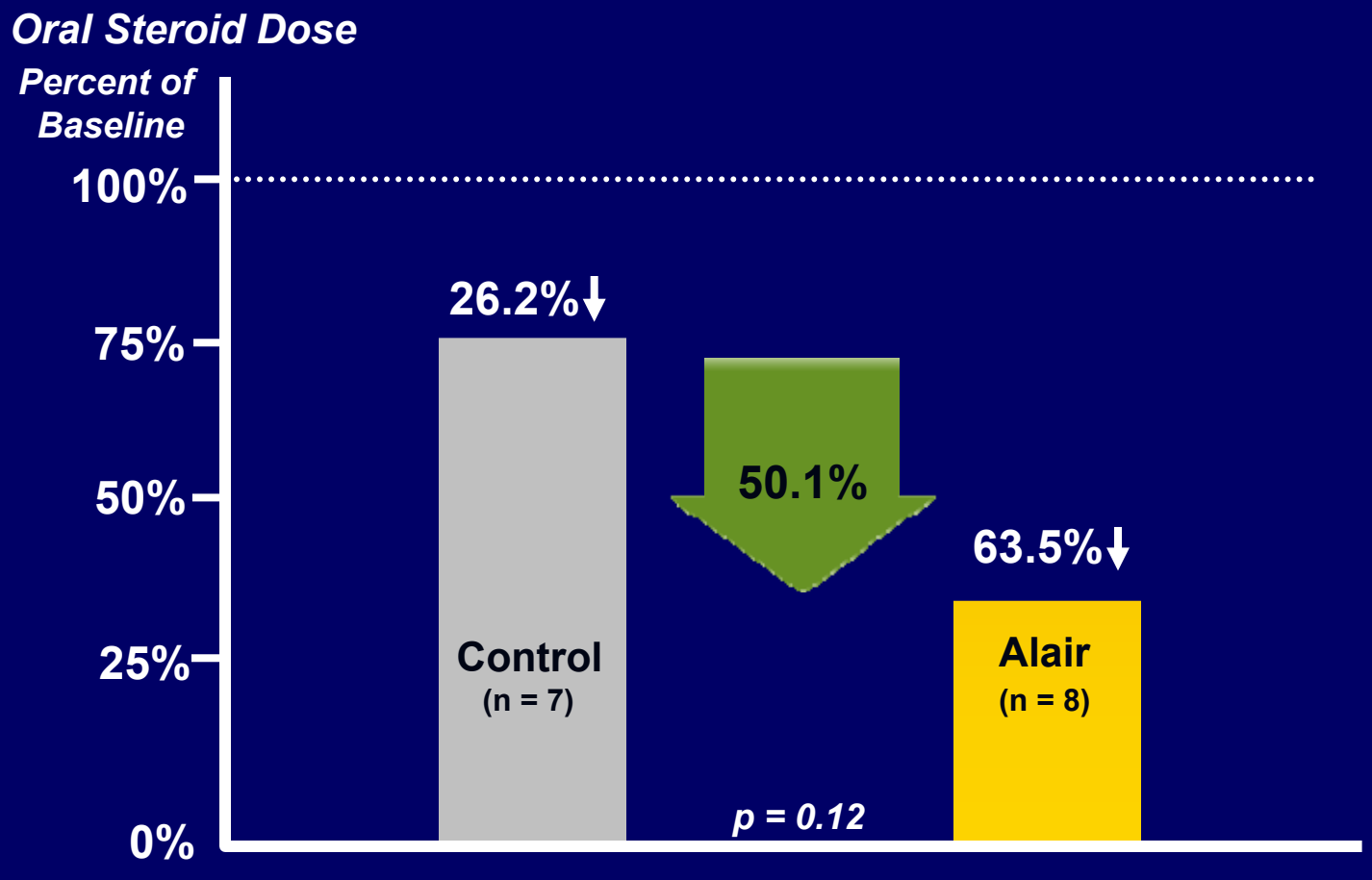
Change in Asthma Quality of Life (AQLQ) Score (AIR & RISA Trials)



Cox et al. *NEJM* 2007; 356(13): 1327-1337

Pavord et al. *Am J Respir Crit Care Med*, 2007; 176: 1185-1191

Ability to Wean Patients Off Oral Steroids (RISA Trial)



Pavord et al. *Am J Respir Crit Care Med*, 2007; 176: 1185-1191

Limitations of Findings

- FEV_1 improved only in RISA Trial
  - Changes in FEV_1 not expected based on mechanism of action
  - Small sample size in RISA (n=32)
- Methacholine reactivity (PC_{20}) improved significantly in Feasibility Study only
  - Baseline airflow obstruction
  - Heterogeneity across multiple centers
  - Dependence on maintenance medications

Safety

Treatment Period Adverse Events

- No unanticipated device-related adverse events
- Adverse events were transient
- Typical symptoms of worsening asthma
  - Cough
  - Wheeze
  - Increased sputum production
  - Dyspnea
  - Chest pain
- Median time to onset was 1 day (2 days in Feasibility Study)
- Median time to resolution was less than 7 days

Treatment Period Respiratory-Related Hospitalizations

	AIR Trial		RISA Trial	
	Alair (n=55)	Control (n=54)	Alair (n=15)	Control (n=17)
No. Hospitalizations (No. of Subjects)	6 (4)	2 (2)	7 (4)	0 (0)
No. of Bronchs	161	-	45	-
Events/Bronch (%)	3.7%	-	15.6%	-

Control = Standard of care medications

Respiratory-Related Hospitalizations

AIR Trial

Alair (n=55) 6 Events in 4 Subjects		Control (n=54) 2 Events in 2 Subjects	
Asthma Aggravated	2	Chest Pain	1
Dyspnea / Wheeze	1	Dyspnea / Chest Pain	1
Dyspnea	1		
Pleurisy	1		
Atelectasis	1		

RISA Trial

Alair (n=15) 7 Events in 4 Subjects		Control (n=17) 0 Events
Dyspnea / Cough	1	
Dyspnea / Wheeze	2	
Dyspnea	1	
Chest Tightness	1	
Atelectasis	2	

Multiple Studies Support Long-Term Safety

- ≥ 3 year follow-up in 3 different studies (Feasibility, AIR, and RISA Trials)
  - Stable pulmonary function based on spirometry
  - Absence of clinical complications related to the device
- Annual HRCT scans for 5 years (Feasibility Study)
  - No radiographic evidence of structural changes
- Alair treatment has a consistent and excellent safety profile over the long-term
- Safety experience from AIR and RISA Trials informed AIR2 patient selection

Pivotal IDE Study

Asthma Intervention Research 2 (AIR2) Trial

Statistical Design	Donald Berry, PhD
Study Design and Results	Mario Castro, MD, MPH

Donald Berry, PhD

Chairman, Dept of Biostatistics
Head, Division of Quantitative Sciences
Frank T. McGraw Memorial Chair of Cancer Research
Univ of Texas MD Anderson Cancer Center
Houston, TX

Senior Statistical Scientist
Berry Consultants, LLC, Specializing in
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Mario Castro, MD, MPH

Professor of Medicine and Pediatrics
Director, The Asthma & Airway Translational Research Unit
Washington Univ. School of Medicine, St. Louis, MO

Adjunct Associate Professor of Community Health
St. Louis University School of Public Health

- Principal Investigator in AIR2 Trial
- Severe Asthma Research Program (SARP-NIH)
- Asthma Clinical Research Network (ACRN-NIH)
- Asthma Clinical Research Center (ACRC-ALA)

AIR2 Trial

Statistical Design

Donald Berry, PhD

Disclosure

- No stock or financial interest in Asthmatx
- Consultant to Asthmatx
- Travel and lodging reimbursed by Asthmatx

1997 FDAMA

- "The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."
- First Bayesian approval in 1998
- Draft Bayesian guidance in 2006

Current Use of Bayesian Adaptive Designs

- MD Anderson Cancer Center
  (> 300 trials)
- Many device companies
  (> 20 PMAs, many 510(k)s)
- All top drug companies; many Biotechs

Why Bayesian Approach?

- Probabilities of hypotheses, such as treatment superiority
- Updating during trial on basis of accumulating data
- Modeling missing and future data
- Tool for developing efficient designs having good frequentist properties
  - Type I error rate controlled
  - Achieve power with least sample size

Relation to Standard Analysis of Final Data

Assuming non-informative prior:

- Posterior probability of superiority
  ≈ 1 - p-value
- 95% probability interval
  ≈ 95% confidence interval

Same scientific rigor

AIR2 Pivotal Trial

- Designed using Adaptive Bayesian statistics to:
  - Minimize sample size, if possible
  - Stop study early, if possible
- In agreement and in concert with FDA

Design of AIR2 Trial

- Prospectively randomized: 2 (Alair) : 1 (Sham)
- Original SAP: Max. sample size 600 (with 7 interim analyses starting at 225 accrued)
- Revised SAP: Fixed sample size at 300 (with 2 interim analyses)
  - Due to rapid enrollment
  - SAP revised prior to any analyses
- Objective: 95% probability of superiority
- Design cut point to control Type 1 error accounting for interim analyses: 96.4% (primary endpoint only)
- Trial continued to maximum follow-up to 12 Months

AIR2 Statistical Considerations

Bayesian statistical analysis of:

- Primary Endpoint – AQLQ
  - Powered to show improvement over Sham
- Secondary Endpoints
  - Not powered for secondary endpoints
- Safety

AIR2 Trial
Study Design and Results

Mario Castro, MD, MPH

Castro et al. *AJRCCM*, 2009; In Press

Disclosure

- Investigator in AIR2 Trial with standard reimbursement to my institution
- No stock or financial interest in Asthmatx
- Consultant to Asthmatx
- Travel and lodging reimbursed by Asthmatx

Advisors in the Design of the AIR2 Trial

Medical

- Mario Castro, MD, Washington University, St. Louis
- Gerard Cox, MB, McMaster University
- Elliot Israel, MD, Harvard University
- Nizar Jarjour, MD, University of Wisconsin
- Monica Kraft, MD, Duke University
- Alan Leff, MD, University of Chicago

Statistical

- Donald Berry, PhD and Scott Berry, PhD, Berry Consultants
- John Quiring, PhD, QST Consultations, Ltd.

AIR2 Investigators

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  Division Director, Critical Care Medicine
  University of Toronto

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  Professor and Chairman, Department of Medicine
  University of Wisconsin School of Medicine and Public Health
  Chairman, Expert Panel, National Asthma Education and Prevention Program (NAEPP)

- Robert Schellenberg, MD

  Professor of Medicine, University of British Columbia, Vancouver, BC, Canada

- Scott Berry, PhD

  President and Senior Statistical Consultant, Berry Consultants, LLC

AIR2 Trial
Design

AIR2 Trial

- Purpose: Pivotal US IDE Study
  - Effectiveness and Safety
- Study Population:
  - Severe Persistent Asthma
  - Symptomatic despite high dose ICS + LABA

Study Design

- Sham-controlled, double-blind
  - 2 : 1 randomization; Alair : Sham
  - Alair Group (ICS + LABA + Alair)
  - Sham Group (ICS + LABA + Sham)
- Study Size: 297 Subjects / 30 centers
  (6 countries)
- Length of Follow-up:
  - One year for purposes of PMA submission
  - 5-year safety follow-up for Alair subjects

Endpoints

- Primary Endpoint
  - Asthma Quality of Life Questionnaire (AQLQ) Score
    - Difference between study groups
    - Change from baseline
    - Average of 6-, 9-, and 12-month follow-ups
- Group means compared statistically to demonstrate treatment effect
  - Analysis specified in protocol for Intent-to-Treat (ITT) and Per Protocol (PP) populations

Asthma Quality of Life Questionnaire (AQLQ)

- Self-administered, validated questionnaire
- 32 questions
- 4 domains:
  - Symptoms
  - Activity Limitations
  - Emotional Function
  - Environmental Exposure
- Response Scale of 1 (worst) to 7 (best)

Endpoints

- Key Secondary Endpoints
  - Symptom-Free Days
  - Total Symptom Score
  - Morning PEF
  - Asthma Control Questionnaire (ACQ) Score
  - Rescue medication use (Puffs & Days Used)
  - FEV_1 (for safety)

Endpoints

- Safety and Other Endpoints
  - Adverse events
  - Unscheduled physician office visits for respiratory symptoms
  - Emergency room visits for respiratory symptoms
  - Hospitalizations for respiratory symptoms
  - Days lost from work/school/other activities due to asthma symptoms

Key Inclusion Criteria

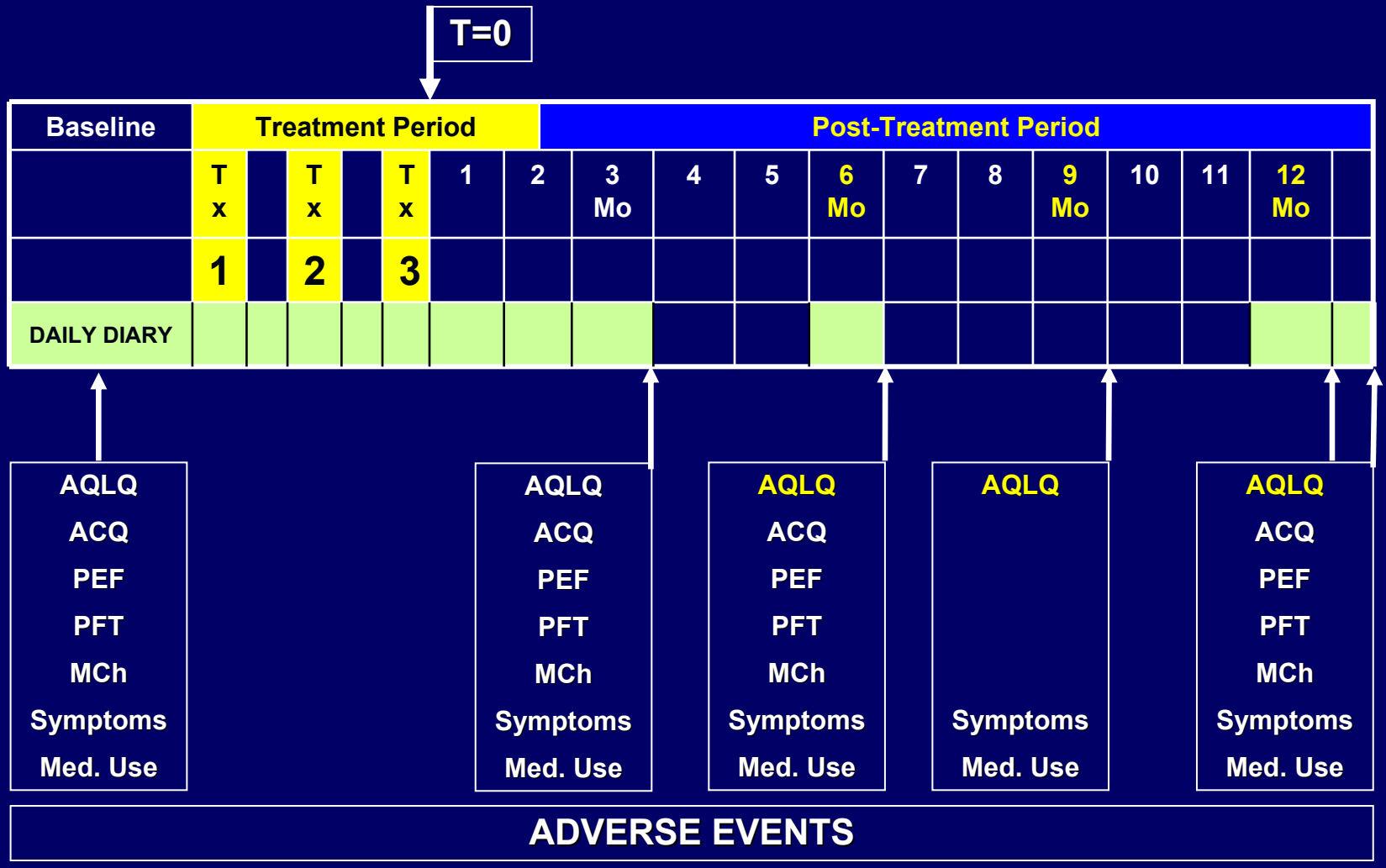
- ICS >1000µg BDP + LABA; ± OCS ≤10 mg/day
- At least 2 symptom days in 4 week baseline
- Pre-bronchodilator FEV_1 ≥ 60% predicted
- ≤ 8 puffs/24h rescue medication, excluding for exercise

Key Exclusion Criteria

- Post-bronchodilator FEV_1 < 65% predicted
- ≥ 3 hospitalizations for asthma in past 12 mths
- > 3 LRTI in the past 12 mths
- ≥ 4 pulses of OCS for asthma in the past 12 mths

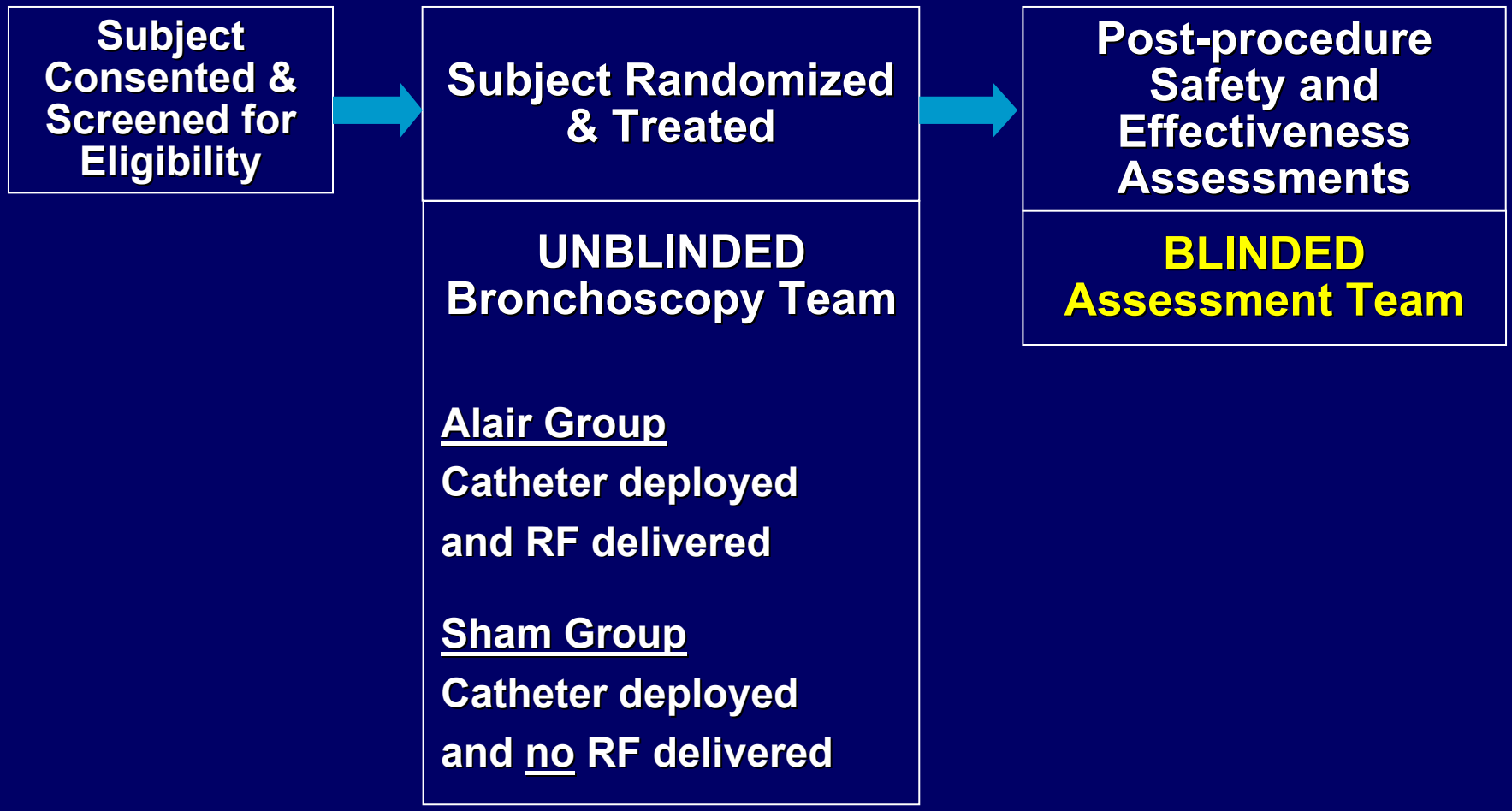
Patient stability at time of bronchoscopy is key

Study Schema for AIR2 Trial



Total office visits =12; Additional phone contacts with study team =31

Double Blind Carefully Maintained



SUBJECTS REMAINED BLINDED THROUGH ENTIRE STUDY PERIOD

AIR2 Trial

Demographics and Execution

Patient Demographics Well-Matched

Parameter	Alair	Sham
Number of Subjects	190	98
Age (years)	40.7 ± 11. 9	40.6 ± 11.9
Gender, n (%)	Male 81 (43%) Female 109 (57%)	Male 38 (39%) Female 60 (61%)
Race, n (%)	White 151 (80%) Black 19 (10%) Hispanic 6 (3%) Asian 4 (2%) Other 10 (5%)	White 72 (74%) Black 15 (15%) Hispanic 4 (4%) Asian 2 (1%) Other 6 (6%)

Baseline Characteristics Well-Matched

Parameter	Alair	Sham
Number of Subjects	190	98
Pre-Bronchodilator FEV_1 (% predicted)	77.8 ± 15.7	79.7 ± 15.1
Inhaled Corticosteroid (beclomethasone equivalent, µg/day)	1961	1835
Long-Acting β_2-Agonist (µg/day)	117	110
AQLQ Score	4.30 ± 1.17	4.32 ± 1.21
Symptom-Free Days (%)	16.4 ± 24.0	16.8 ± 23.1
Number and (%) of Subjects on Additional Asthma Maintenance Medications	59 (31.1)	25 (25.5)

Data are Poolable

- Same protocol executed at all sites
- Study administered identically at all sites
- Data were found to be poolable based on pre-specified analysis for pooling
- No site was an outlier with respect to a difference in the AQLQ between the study groups

Evaluable Subjects

	Alair	Sham	Total
Randomized	196	101	297
Intent-to-Treat (ITT)	190	98	288
Per Protocol (PP)	173	95	268 (93% of ITT)
Safety Population		Same as ITT (288)	

9 subjects withdrew after randomization and prior to any bronchoscopy

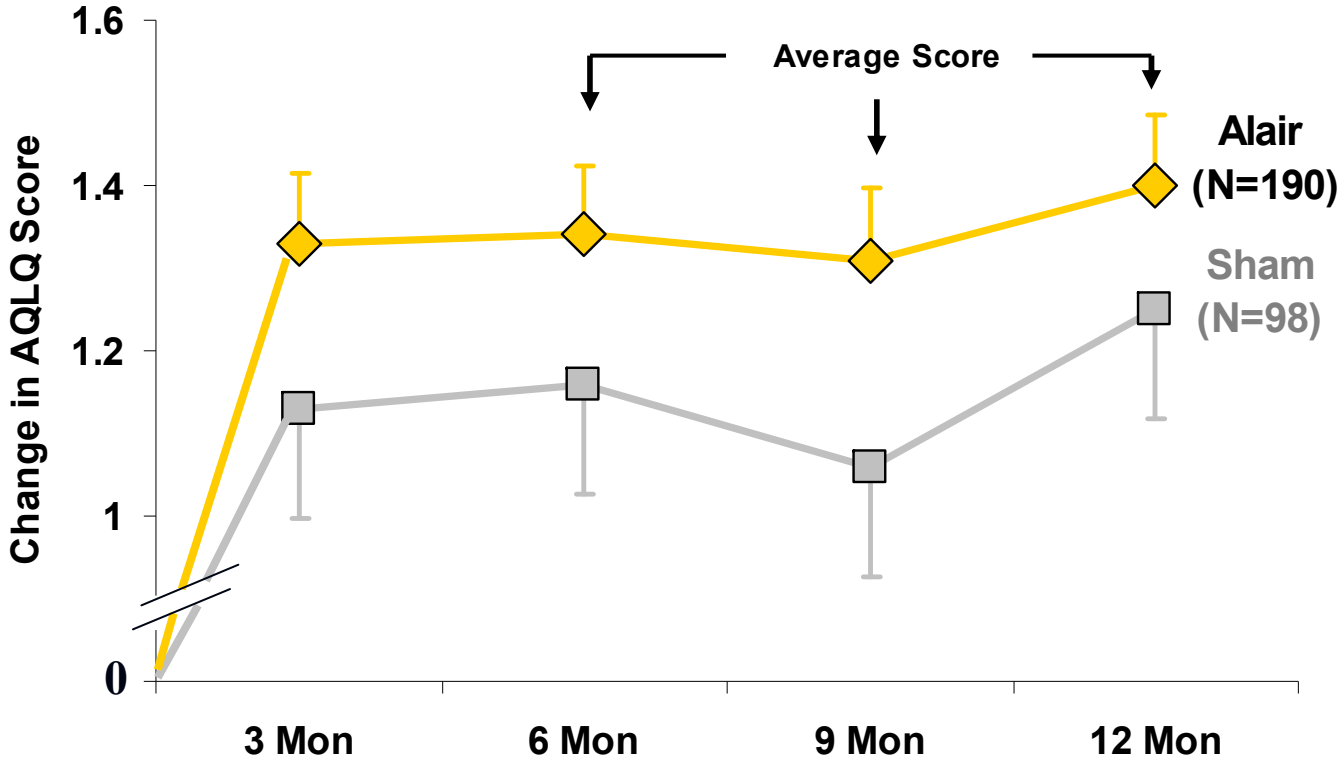
ITT: Randomized subjects with at least ONE bronchoscopy

PP: Subjects who completed all 3 bronchoscopies and the 6-, 9-, 12-month visits.

AIR2 Trial

Effectiveness

Primary Endpoint: AQLQ
Alair superior to Sham



ITT

Mean Difference= 0.21

PP Sup.= 96.0%

PP

Mean Difference= 0.24

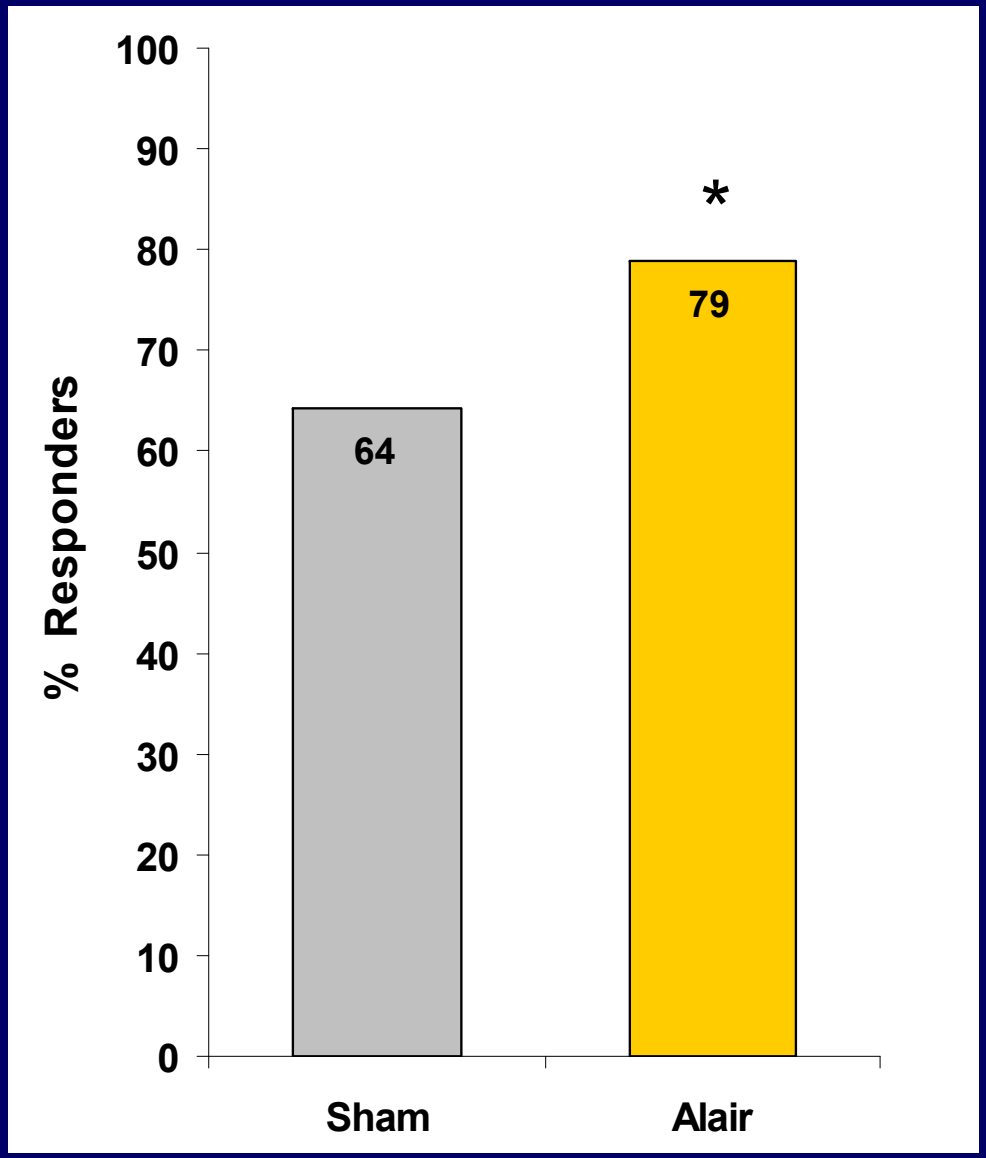
PP Sup.= 97.9%

Clinical Meaningfulness

- Minimal important difference (MID) for AQLQ validated for *within-patient* change
- Change in *within-patient* score of 0.5 is the threshold for clinically meaningful
- Responder analysis - % of patients in each group achieving MID (not pre-specified)

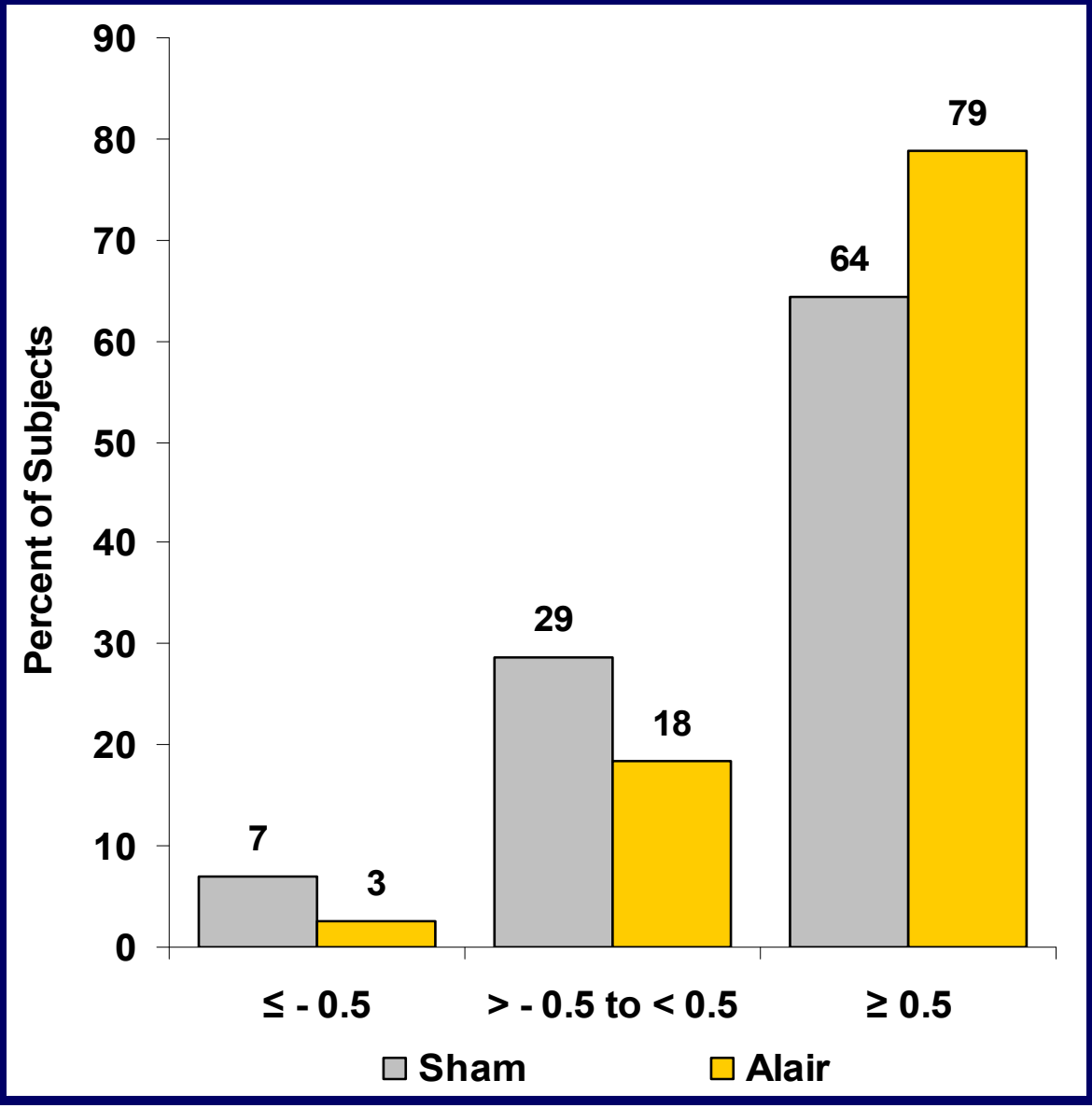
Juniper et al. *J Clin Epidemiol* 1994; 47: 81-87

AQLQ Responder Analysis (ITT)
(% Subjects with ≥ 0.5 Increase)



* Posterior Probability of Superiority = 99.6%

AQLQ Responder Net Benefit (ITT)
(≥ 0.5 Increase; ≤ -0.5 Decrease)



Net benefit:

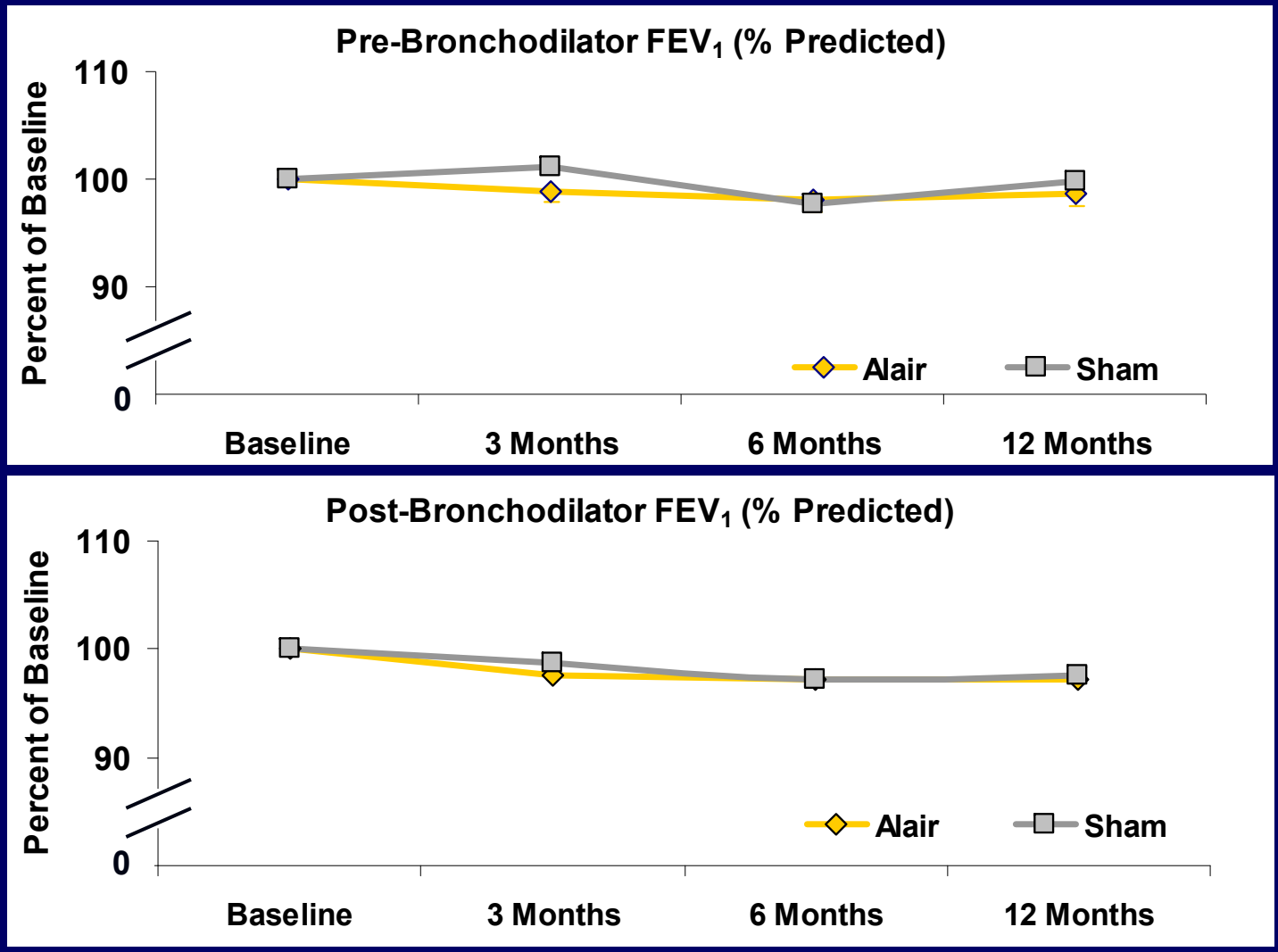
Posterior Probability of Superiority >99.9%

Secondary Endpoints at 12 Months: Changes from Baseline (ITT)

Endpoint	Alair	Sham	Trend in favor of Alair	PP Superiority (%)
% Symptom Free Days	24.4	21.0	+	77.6
Total Symptom Score	- 1.7	- 1.6	+	63.7
Rescue Med Use (Puffs/7days)	- 6.0	- 4.3	+	81.3
% Days Rescue Med Used	- 24.0	- 22.0	+	68.0
ACQ Score	- 0.82	- 0.77	+	63.8
am PEF (L/min)	27.8	22.3	+	80.6

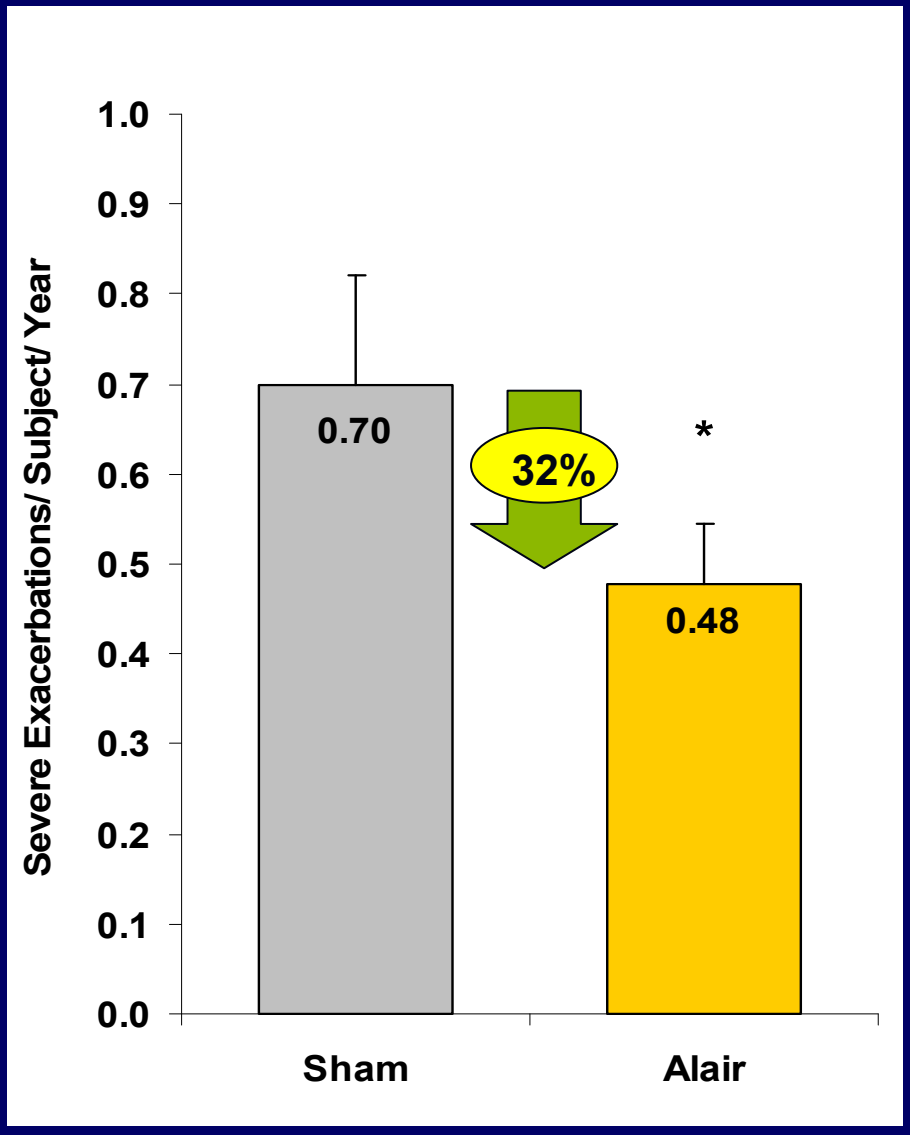
Effectiveness benefits are concordant

Safety: FEV_1 Stable Over Time (ITT)



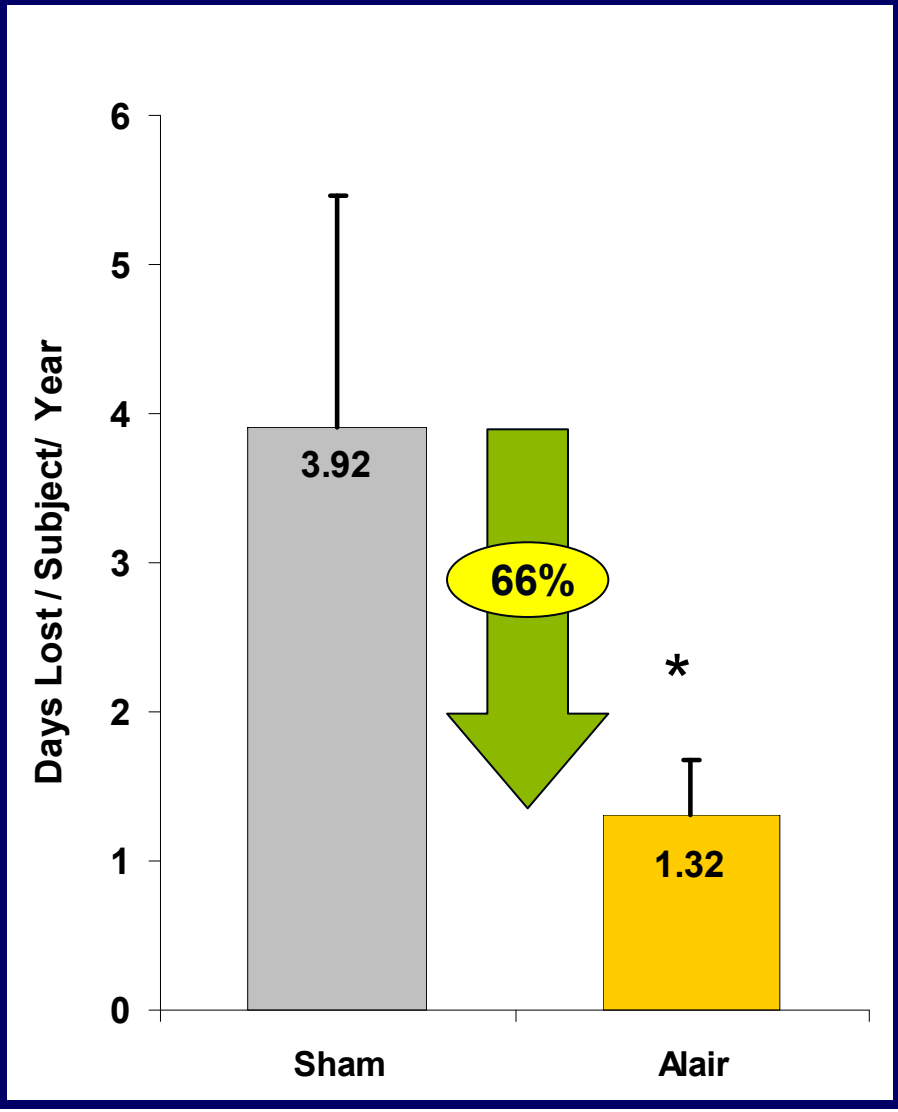
Methacholine PC_{20}: 1.2 doublings in both Alair and Sham groups

Severe Exacerbations
Post-Treatment Period



* Posterior Probability of Superiority = 95.6%

Days Lost from Work/School/ Other Activity due to Asthma
Post-Treatment Period (ITT)



* Posterior Probability of Superiority = 99.3%

AIR2 Trial: Effectiveness Summary

- Alair Therapy is superior to Sham at improving AQLQ
  - 96.0% pp superiority (ITT) ; 97.9% pp superiority (PP)
- 79% of Alair patients are AQLQ responders
  - More Alair patients are responders*
- 32% reduction in severe exacerbations compared to Sham*
- 66% reduction in days lost compared to Sham*

---

* PP Superiority >95.0%

AIR2 Trial

Safety

Safety

- Timeframes for Safety assessments
  - Short-term: Treatment Period
    - First bronchoscopy till 6 weeks after 3rd bronchoscopy (~12 week period)
  - Long-term: Post-Treatment Period
    - >6 weeks till 12 Months (~46 week period)
- Safety Data
  - Adverse events
  - Unscheduled physician office visits for respiratory symptoms
  - Emergency room visits for respiratory symptoms
  - Hospitalizations for respiratory symptoms

Respiratory Adverse Events

Overall Adverse Events With > 3% Incidence

Adverse Event	Treatment Period (~12 weeks)	
	Alair (N=190) %	Sham (N=98) %
Asthma (Multiple Symptom)	52.1	38.8 *
Wheezing	15.3	6.1 *
Atelectasis	4.7	0 *
Hemoptysis	3.2	0 *
Lower Respiratory Tract Infection	7.9	2.0 *
Upper Respiratory Tract Infection	20.0	11.2 *
Throat irritation	4.7*	12.2

* PP Superiority >95.0%

Respiratory Adverse Events

Overall Adverse Events With > 3% Incidence

Adverse Event	Treatment Period (~12 weeks)		Post-Treatment Period (~46 weeks)	
	Alair (N=190) %	Sham (N=98) %	Alair (N=187) %	Sham (N=98) %
Asthma (Multiple Symptom)	52.1	38.8 *	27.3 *	42.9
Wheezing	15.3	6.1 *	4.3	3.1
Atelectasis	4.7	0 *	0	0
Hemoptysis	3.2	0 *	0	0
Lower Respiratory Tract Infection	7.9	2.0 *	3.2	6.1
Upper Respiratory Tract Infection	20.0	11.2 *	29.9	25.5
Nasopharyngitis	4.7	7.1	10.7	5.1 *
Throat irritation	4.7*	12.2	1.1	3.1

* PP Superiority >95.0%

Hemoptysis AEs in Alair Group
(defined as >5 mL of blood)

Total of 7 events following 558 bronchoscopy procedures (1.25%)

Time after Procedure	No. of Events (No. of Subjects)	How Treated
Day of Procedure	2 (2)	None - Self Limiting
2 - 3 days	2 (2)	None - Self Limiting
~ 2 weeks	2 (1)	Medication for Cough
31 days	1 (1)	Embolization

Treatment Period Hospitalizations for Respiratory Symptoms

Alair (N=190) 19 Hospitalizations in 16 Subjects No. of Events (Incident Rate %)		Sham (N=98) 2 Hospitalizations in 2 Subjects No. of Events (Incident Rate %)	
Asthma Aggravated	12 (6.3%)	Asthma Aggravated	2 (2.0%)
Atelectasis	3 (1.6%)		
Lower Resp. Tract Infect.	1 (0.5%)		
Hemoptysis	1 (0.5%)		
Low FEV_1	1 (0.5%)		
Aspirated prosthetic tooth in airway	1 (0.5%)		

Respiratory-Related Hospitalization Following Procedure

Respiratory-Related Hospitalizations during Treatment Period	Alair (N=190)	Sham (N=98)
Events / Bronchoscopy (%)	19*/558 (3.4%)	2/292 (0.7%)

* 10/19 (53%) occurred on the day of the procedure
  13/19 (68%) occurred within one day of the procedure

Absence of Major Events

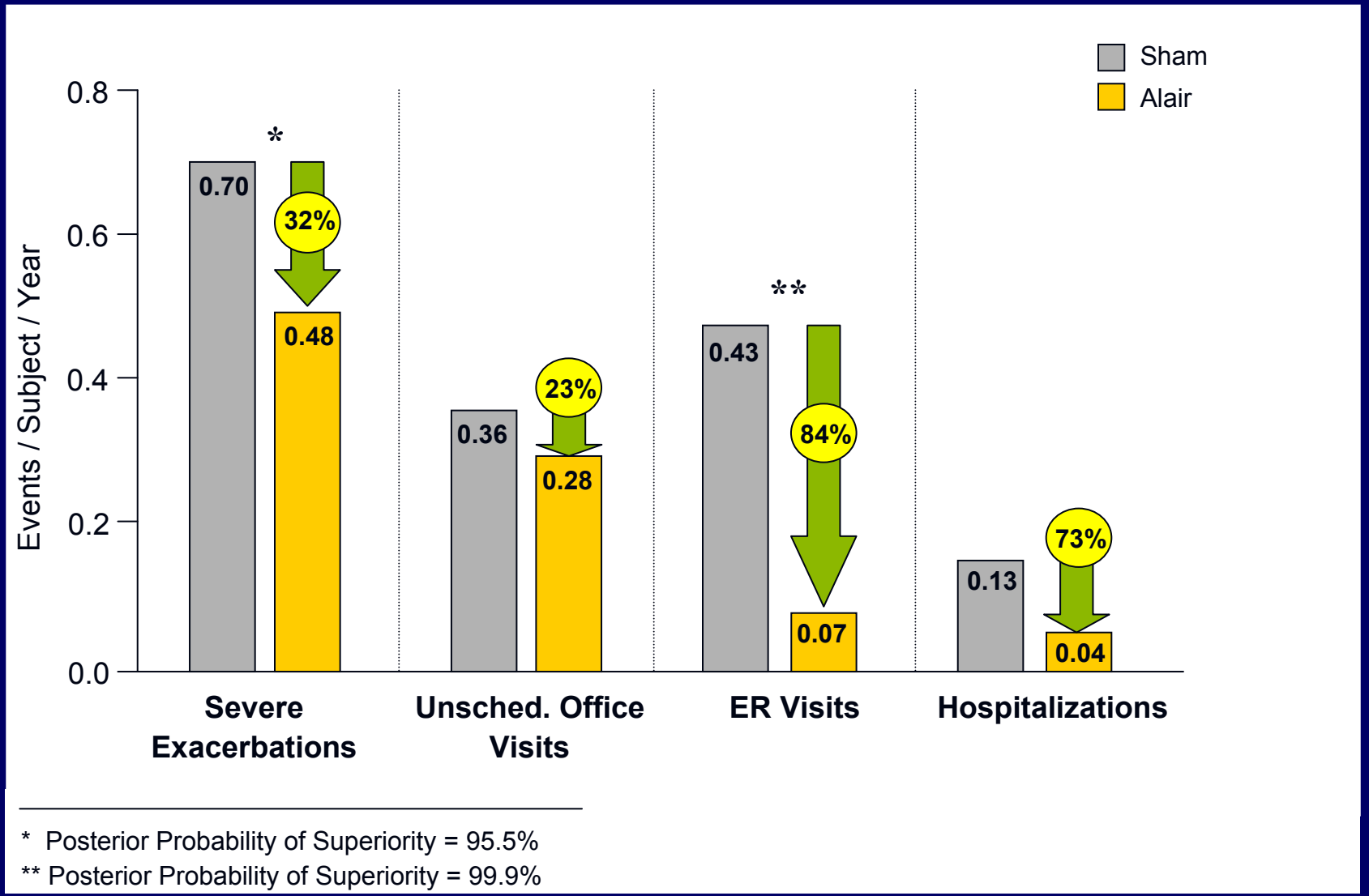
- 850 Bronchoscopy procedures performed in subjects with severe asthma
- No incidences of:
  - Intubation
  - Mechanical ventilation
  - Pneumothorax
  - Airway stenosis or focal narrowing
  - Cardiac arrhythmias
  - Death

HRCT: Changes from Baseline to 1 Year

- Blinded assessments by independent radiologist and pulmonologist of 100 Alair and 50 Sham baseline and follow-up CT pairs
- Conclusions
  - No structural changes in the lung at 1-Year in Alair subjects
  - Increased bronchial wall thickening was observed at 1-Year in Sham subjects
  - No evidence of bronchial dilation, bronchiectasis, bronchiolitis obliterans, or pulmonary emphysema in any Alair subjects

AIR2 Trial
Healthcare Utilization

Healthcare Utilization for Respiratory Symptoms Post-Treatment Period



* Posterior Probability of Superiority = 95.5%

** Posterior Probability of Superiority = 99.9%

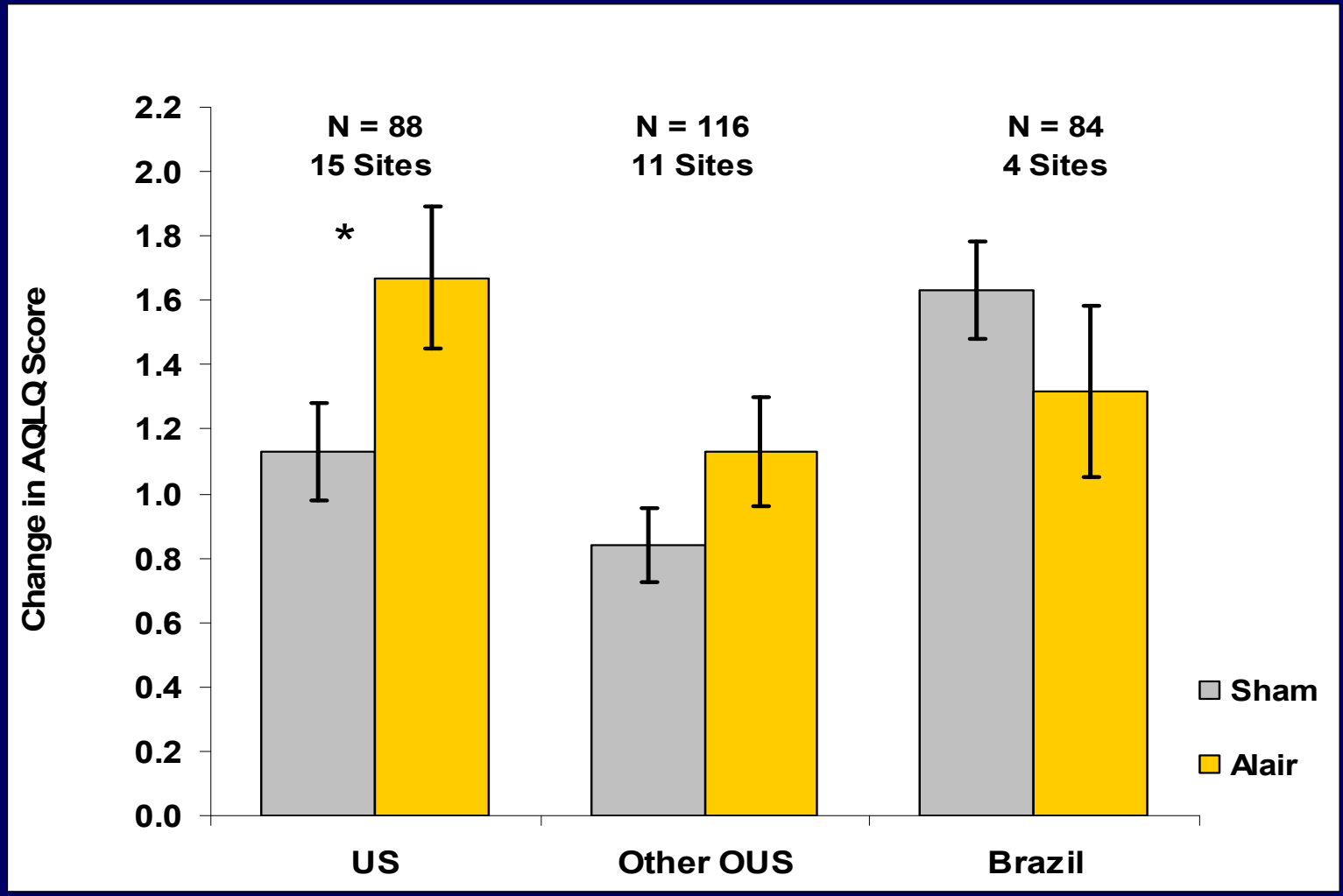
Safety Summary

- Early predictable procedural respiratory AEs
  - Treatment Period (~12 week period)
    - Alair > Sham
    - Majority occurred within 1 day of procedure
    - Most resolved within 7 days with standard care
    - Most common were related to transient worsening of asthma
    - No unanticipated device-related adverse events
- Later reductions in AEs and ER visits due to asthma symptoms
  - Post-Treatment Period (~46 week period)
    - Sham > Alair
    - 36% reduction in % subjects with Asthma (multiple symptoms)
    - 84% reduction in ER visits due to respiratory symptoms

FDA Questions

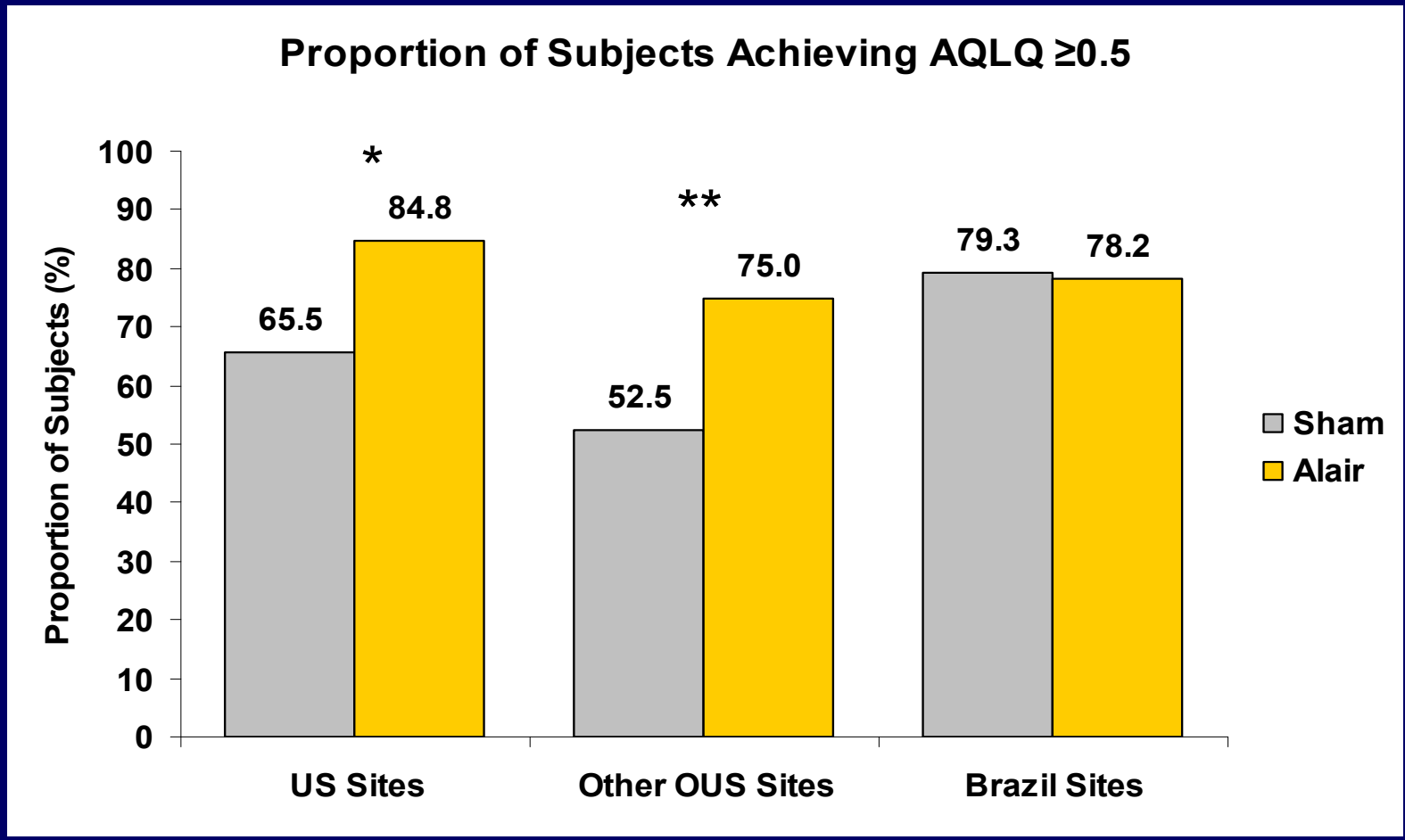
Outcome by Geography
US vs Brazil vs Other Outside US (OUS)

AQLQ Score Change from Baseline US vs Brazil vs Other OUS



* PP Superiority (Alair>Sham): 99.8%

Responder Analysis: US vs Brazil vs Other OUS



PP Superiority (Alair>Sham): * 97.9%; ** 99.3%

AIR2 Trial

Summary

AIR2 Summary

- Alair provides a net benefit
- Short-term risks:
  - Treatment adverse events related to transient worsening of asthma
  - Typically occur within one day and resolve within one week with standard care
- Long-term benefits:
  - Improved AQLQ
  - 32% decrease in severe exacerbations
  - 84% decrease in ER visits
  - 66% decrease in days lost from work/school/activities
  - 36% decrease in asthma (multiple symptoms) adverse events

Conclusion

- AQLQ primary endpoint
  - Alair statistically superior to Sham
  - Demonstrates treatment effect
- AQLQ results clinically meaningful
  - Validated for within-subject changes, requiring responder analysis
  - Alair statistically superior to Sham in responder analysis (not pre-specified)
- The totality of the evidence demonstrates that Alair is safe and effective for the treatment of patients with severe asthma

Debera Brown

Vice President, Regulatory Affairs and Quality Assurance

Asthmatx, Inc., Sunnyvale, CA

Maximizing Patient Safety Post-Approval

- Controlled product launch
  - User and facility prerequisites
  - Training program – device/procedure/labeling
- Post-approval vigilance
- Post-approval long-term follow-up
  - AIR, RISA, and AIR2 Trials
- New post-marketing registry

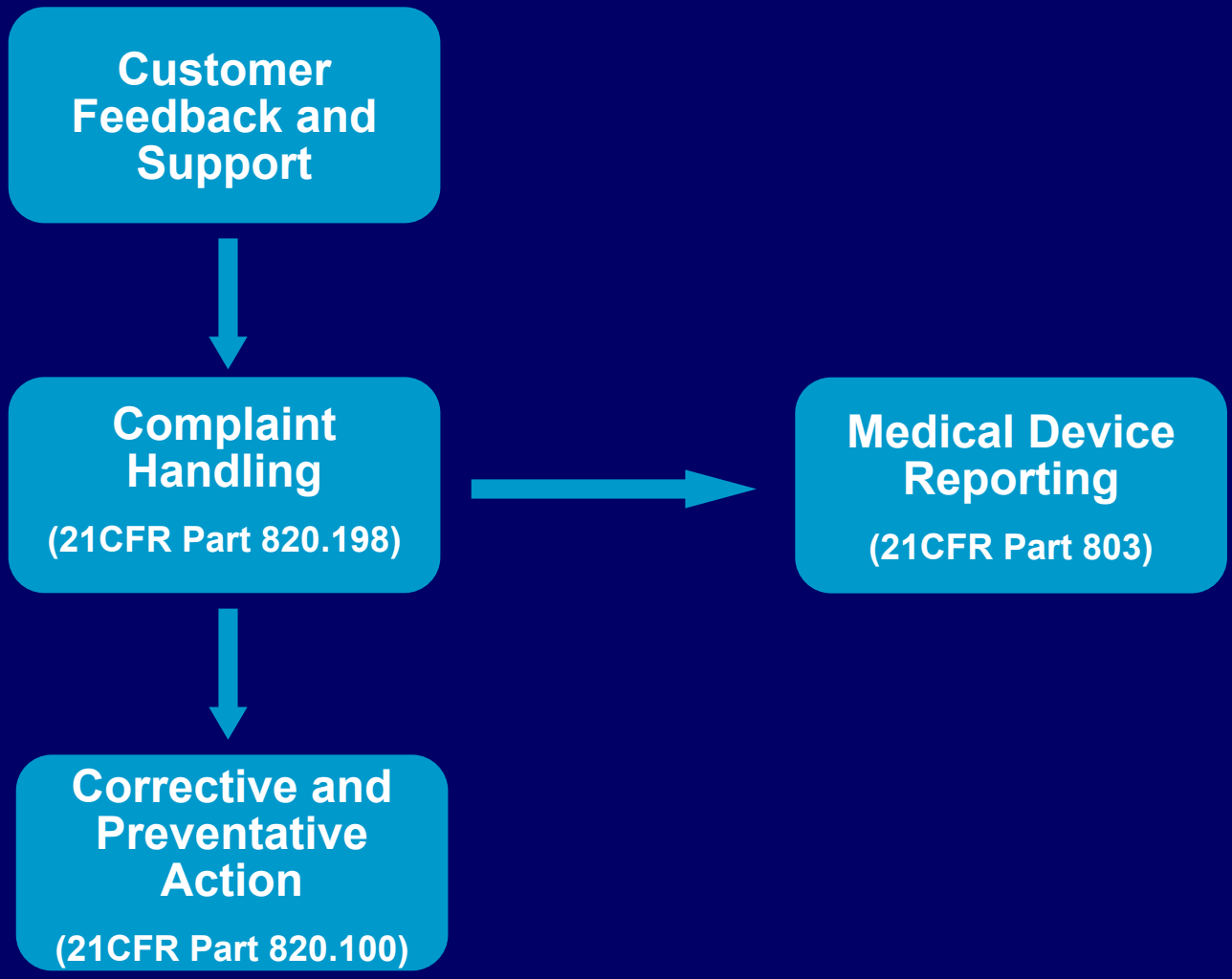
User and Facility Prerequisites

- Users will be physicians who:
  - Have bronchoscopy experience
  - Have experience in managing patients with asthma
  - Have received appropriate Alair System training
- Facilities will provide:
  - Appropriate equipment for bronchoscopy
  - Capability to manage respiratory complications

Training Program
Device/Procedure/Patient Selection

- Product overview and virtual procedure simulation
- Didactic and interactive procedure training
  - Careful review of instructions for use
  - Patient selection and patient management
- Technical support of initial clinical cases
- Ongoing technical and customer support

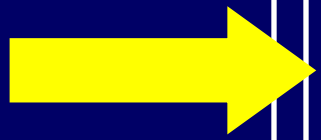
Post-Approval Vigilance



Post-Approval Long-Term Follow-up

5-Year Follow-up of Existing Patients (Safety)

- AIR2 Trial (n=190)
  Completed 1 yr F/U
- RISA Trial (n=15)
  Completed 3 yr F/U
- AIR Trial (n=43)
  Completed 4 yr F/U
- Feasibility Study (n=16)
  Completed 5 yr F/U



Post-Approval Studies

- AIR2 Trial Extended Follow-Up
  - Long-term (>1 year) durability of effectiveness
- Post-Marketing Registry
  - Safety study (250 subjects)
  - Real-world experience in the US Intended use population

AIR2 Trial Extended Follow-Up

- Objective: Longer-term durability (>1 year) of Alair treatment
- Study Design: 5 years follow-up of AIR2 Trial patients treated with Alair
- Endpoint of interest:
  - % of patients with ER visits for respiratory symptoms during the annual post-treatment periods (2, 3, 4, and 5 years)
  - Non-inferiority margin of 20% for the lower 95% confidence limit of the difference between the subsequent 12-month rate and the first 12-month rate
    - 30% of AIR2 patients had ER visits in the year prior to study entry

New Post-Marketing Registry

- Objective: Safety of Alair treatment in US intended use population
- Study Design: 250 Alair treated patients, open label, single arm, follow-up for 5 years
- Patient enrollment consistent with labeling
- Endpoints of interest:
  - % of patients with hospitalizations during the first 12 months post-treatment
    - Not to exceed proportion reported in Severe Asthma Research Program (SARP), 30% of subjects in one year
  - Safety measures over 5 years
    - Hospitalizations for respiratory symptoms
    - Emergency room visits for respiratory symptoms
    - Other respiratory AEs
    - Maintenance asthma medications
    - FEV_1 (pre- and post-bronchodilator)

Rationale for Single Arm Post-Marketing Registry

- Difficult / impossible to enroll untreated controls in a 5-year study once treatment is approved
- Likely high rate of dropouts in untreated control group during long-term follow-up
- Unethical to withhold effective therapy from a needy patient population

Maximizing Patient Safety Post-Approval

- Controlled product launch
  - User and facility prerequisites
  - Training program – device/procedure/labeling
- Post-approval vigilance
- Post-approval long-term follow-up
  - AIR, RISA, AIR2 Trials
- New post-marketing registry

Michael Wechsler, MD, MMSc.

Assistant Professor of Medicine
Harvard Medical School, Boston, MA

Associate Director, Asthma Research Center
at Brigham & Women's Hospital, Boston, MA

- Investigator in AIR2 Trial
- Pulmonary and critical care specialist
- Basic and clinical research in asthma and allergy
- Member Steering Committee, Asthma Clinical Research Network (ACRN – NIH)

Putting AIR2 into Context

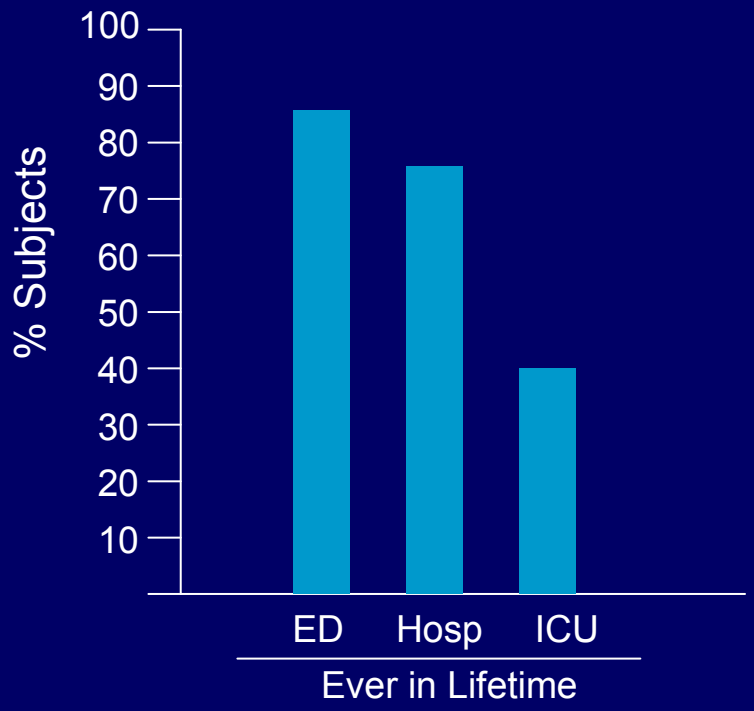
Disclosure

- Investigator in AIR2 Trial with standard reimbursement to my institution
- No stock or financial interest in Asthmatx
- Consultant to Asthmatx
- Travel and lodging reimbursed by Asthmatx

Putting AIR2 into Context

Need for New Treatment Options

Urgent Healthcare Utilization in Severe Asthma



Adapted from Moore WC et al (SARP). J Allergy Clin Immunol 2007;119:405-13

- There is no cure or long lasting treatment for asthma
  - The majority of severe asthma patients on 2 or 3 drugs
  - Adherence to prescribed dosing regimen is essential
- New options to address severe asthma are needed

AIR2 Clinical Trial Design

- Rigorously designed and executed
- Designed in collaboration with FDA
- Based on two earlier RCTs vs. the standard of care
- Enrollment was rapid despite a sham control, three procedures, at least 12 office visits, and more than 30 additional contacts (reflects substantial need)
- Minimal loss to follow-up (~3%) in a complex and involved clinical trial

Primary Outcome - Alair Superior to Sham

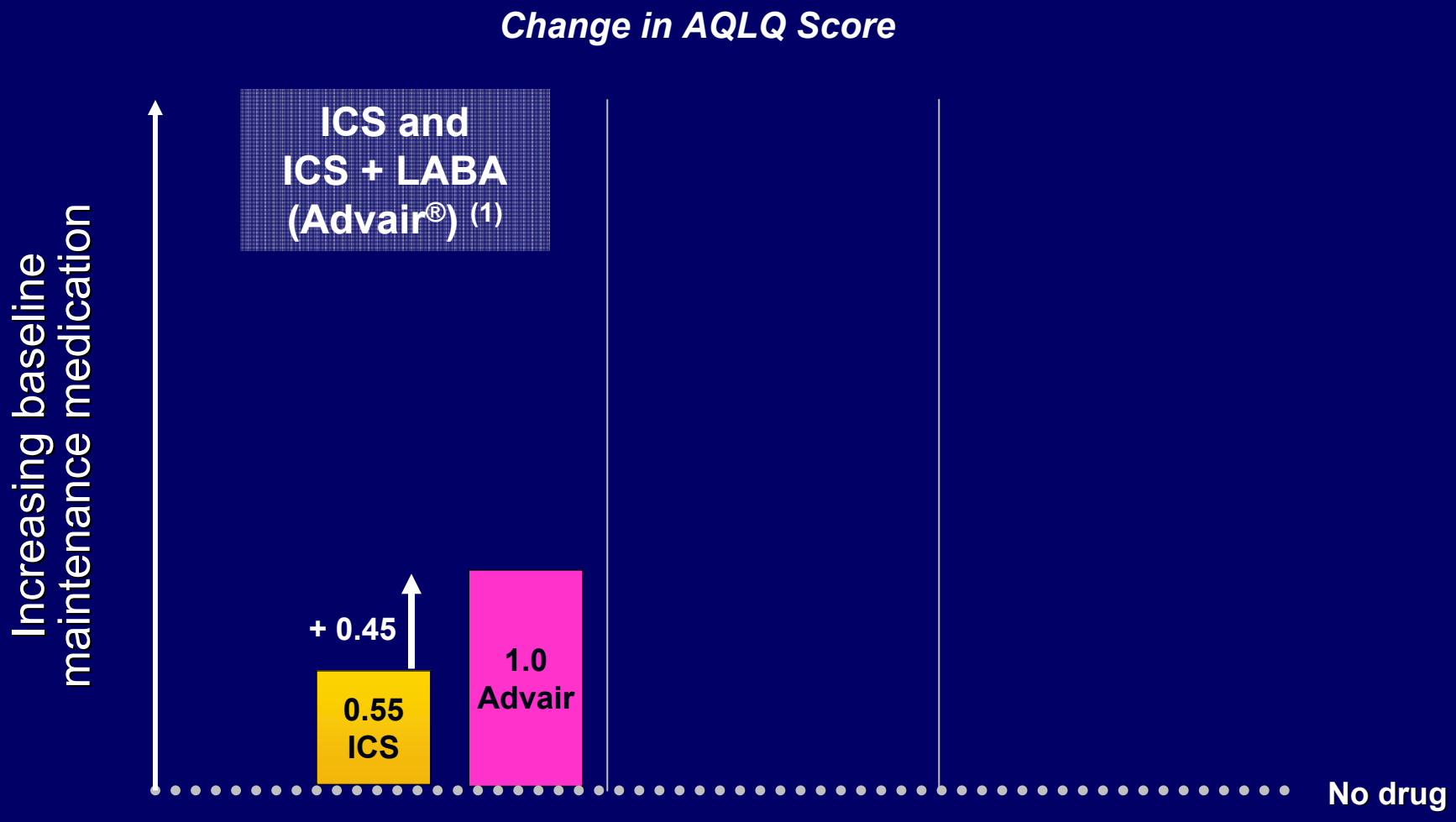
- AQLQ is well validated and broadly used
- Sham-control was essential
- Sham effect was expected, but was larger than projected
- Despite sham effect, Alair group still achieved a greater increase in AQLQ score (96% pp superiority)
- AQLQ score increased 1.38 over baseline

Quote from Dr. Elizabeth Juniper

"I am not aware of any other therapy for severe asthma that has demonstrated this degree of clinically meaningful benefit based on the results of the AQLQ."

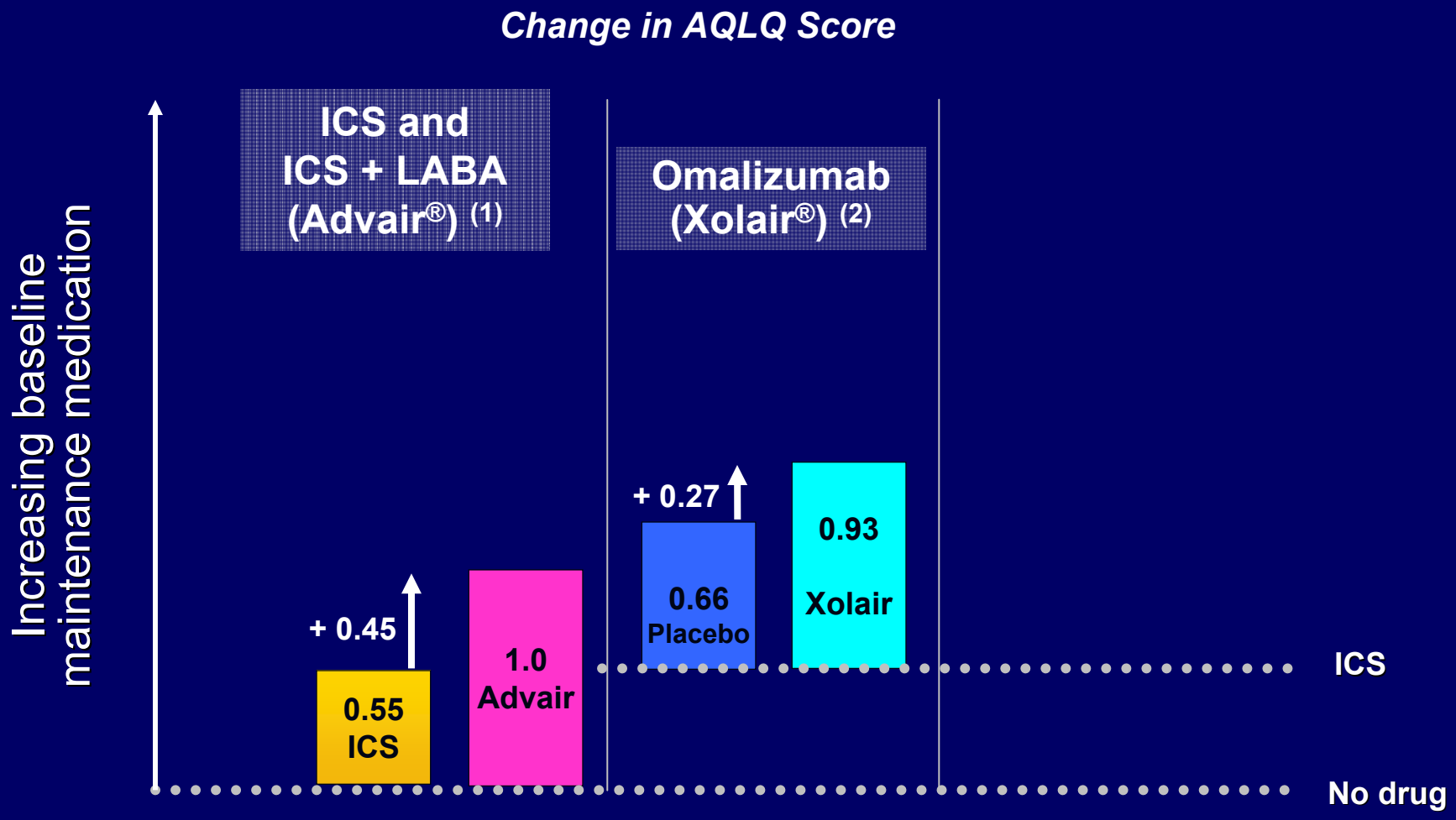
Letter dated June 2, 2009

Conceptualizing the Impact of Adding Alair



(1) NDA 21-077 Study 3003: Placebo, ICS (Fluticasone 250), and ICS + LABA (Advair 250/50)

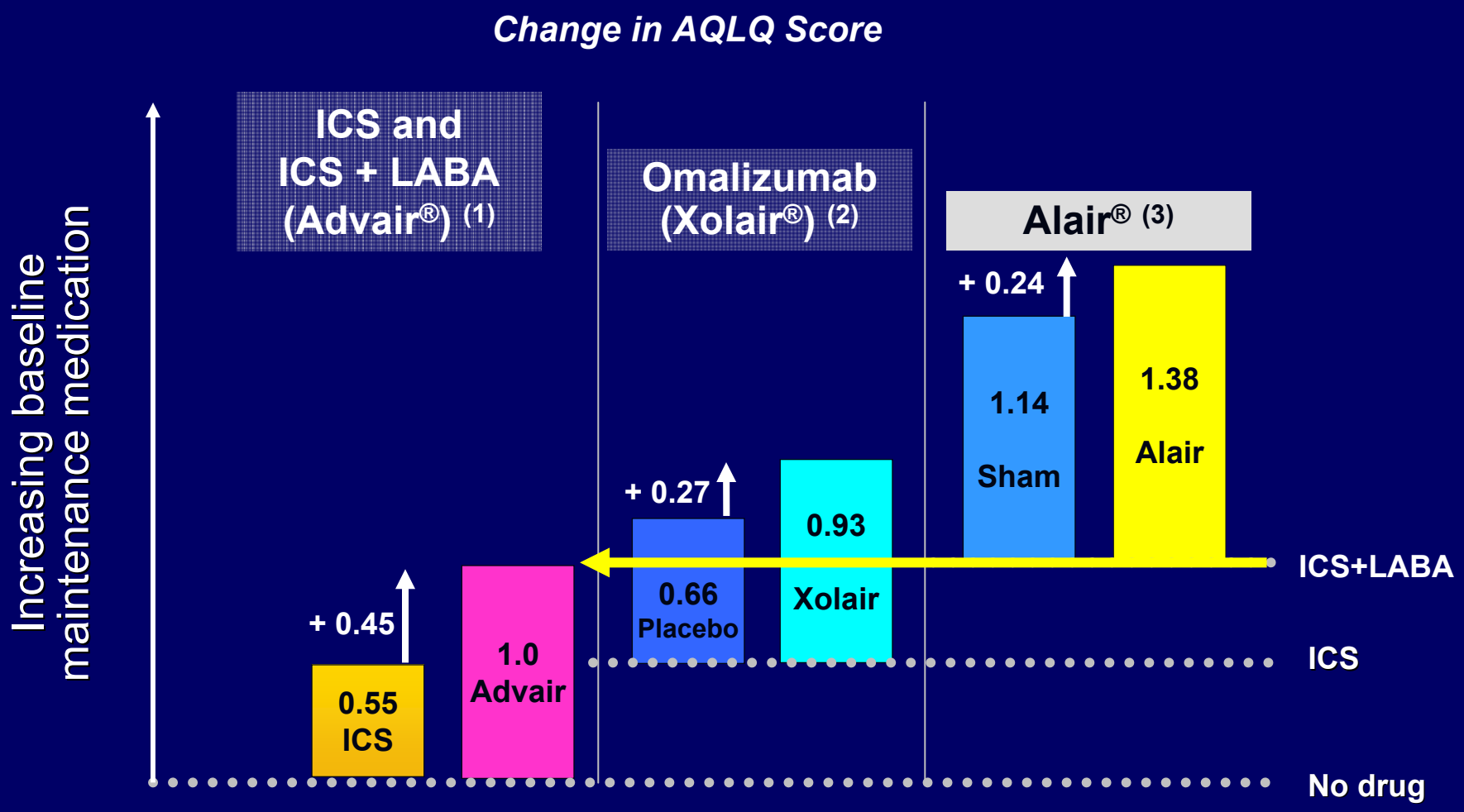
Conceptualizing the Impact of Adding Alair



(1) NDA 21-077 Study 3003: Placebo, ICS (Fluticasone 250), and ICS + LABA (Advair 250/50)

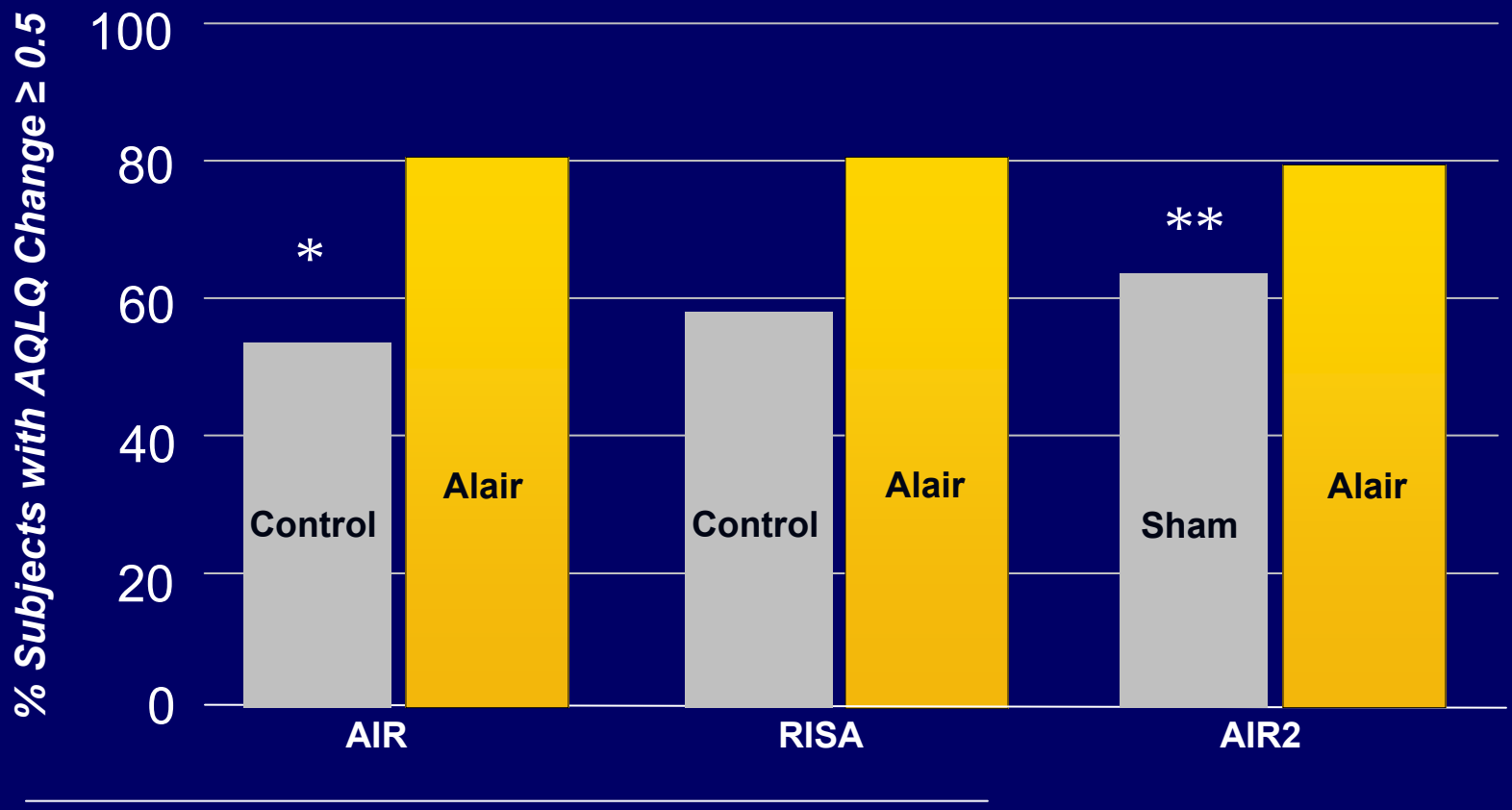
(2) BB IND 5369, Study 009: Omalizumab (Xolair), placebo; for allergic asthma only

Conceptualizing the Impact of Adding Alair



(1) NDA 21-077 Study 3003: Placebo, ICS (Fluticasone 250), and ICS + LABA (Advair 250/50)
(2) BB IND 5369, Study 009: Omalizumab (Xolair), placebo; for allergic asthma only
(3) PMA P080032, AIR2 Trial, Bronchial Thermoplasty (Alair), Sham (PP, n=268)

Consistent Benefit At 12 Months Across Three RCTs



* p = 0.021

** PP Superiority = 99.6%

Other Outcomes

- Significant improvements (vs Sham) in clinical outcomes important to physicians and patients
  - 36% reduction in asthma related adverse events
  - 32% reduction in severe exacerbations
  - 84% reduction in ER visits
  - 66% reduction in time lost from work/school and other activities

Multiple Studies Support Effectiveness

AIR
(RCT; n = 109)

- AQLQ score
- Exacerbations
- Rescue meds
- Symptom Free Days
- Lung Function (PEF)

NEJM, v356, Mar 2007

RISA
(RCT; n = 32)

- AQLQ score
- Rescue meds
- Lung Function (FEV_1)

AJRCCM, v176, Sep 2007

AIR2
(RCT- Sham; n = 297)

- AQLQ score
- Exacerbations
- ER Visits
- Time Lost from Work/School
- Asthma AEs

AJRCCM, In Press, 2009

Short-Term Safety

- AIR2 safety consistent with prior two RCTs
  - No deaths nor major adverse events such as intubations, pneumothorax, etc.
  - Worsening of asthma symptoms
    - Predictable - type and onset (median time to occurrence 1 day)
    - Manageable with standard therapies (median time to resolution 7 days)

Putting Hospitalization Risk in Severe Asthma Patients into Context

Source	Percent of Subjects with Hospitalizations over a 3 Month Period
AIR2 Trial (Treatment Bronchoscopies)	8.4%

Putting Hospitalization Risk in Severe Asthma Patients into Context

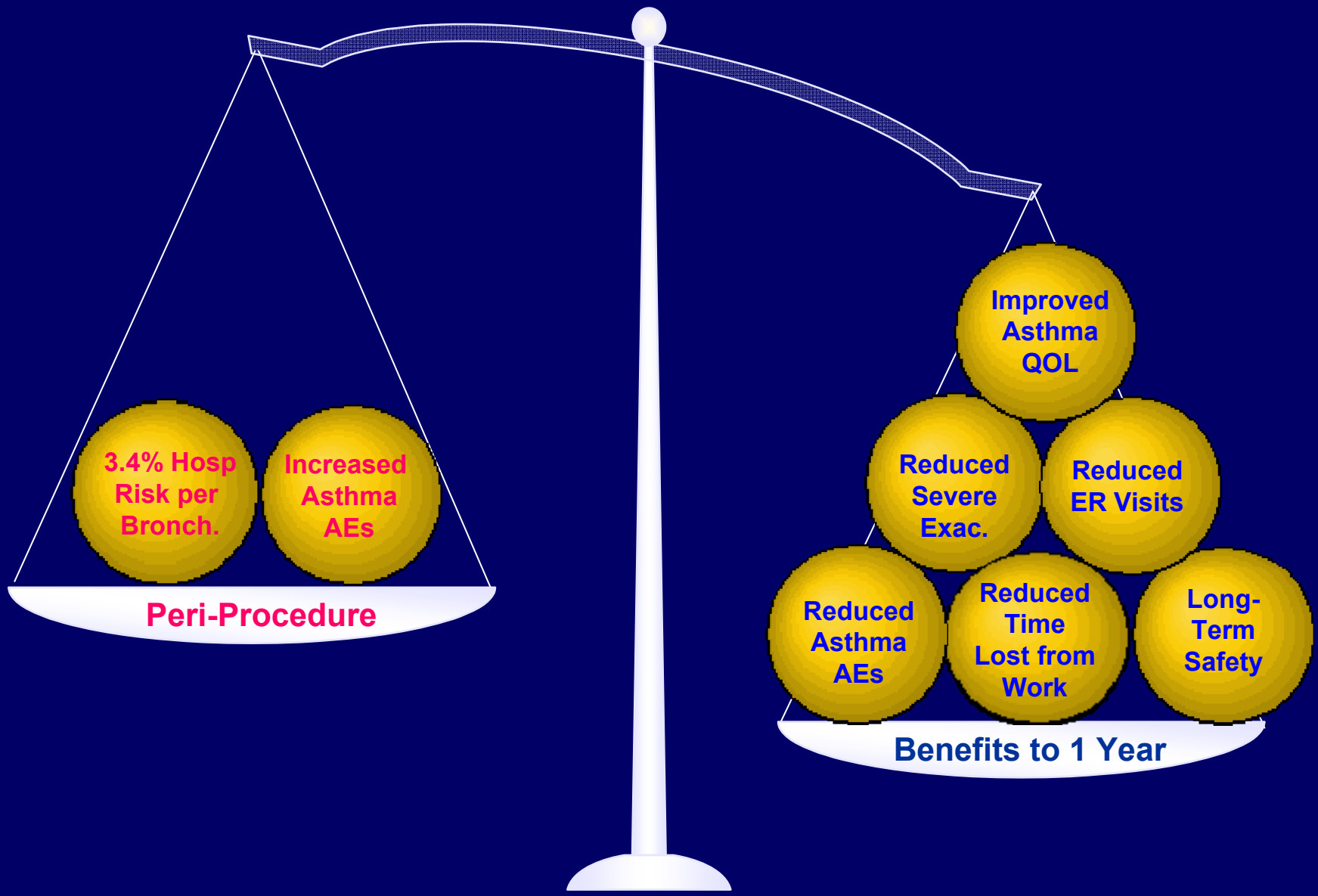
Source	Percent of Subjects with Hospitalizations over a 3 Month Period
AIR2 Trial (Treatment Bronchoscopies)	8.4%
TENOR Study[1]	10.0%

[1] Dolan et al. *Ann Allergy Asthma Immunol* 2004; 92: 32-39

Multiple Studies Support Long-Term Safety

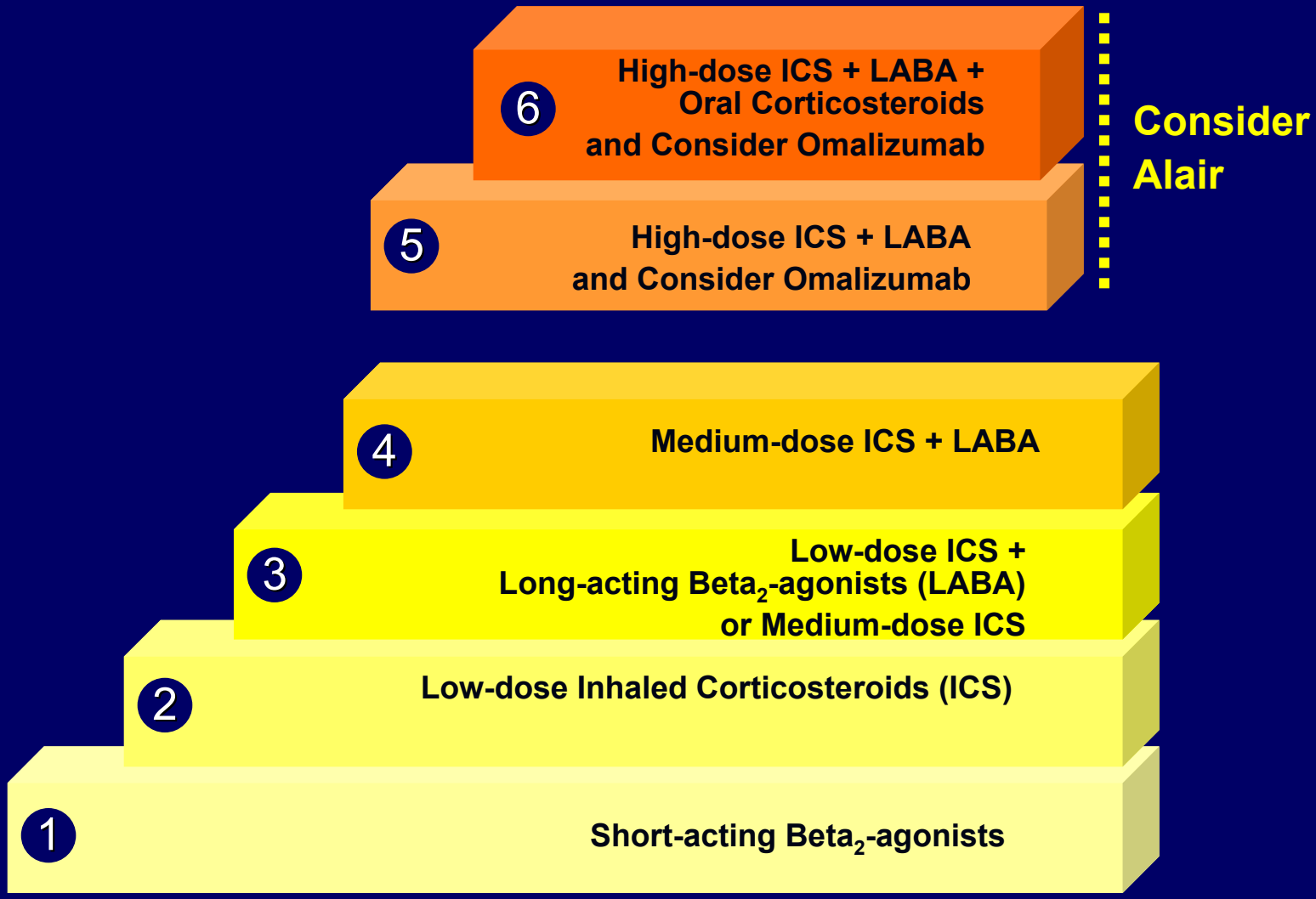
- Alair treatment has a consistent and excellent safety profile over the long-term
- ≥ 3 year follow-up in 3 different studies (Feasibility, AIR, RISA) and 1 year follow-up in AIR2
  - Stable pulmonary function based on spirometry
  - No clinical complications related to the device
- Annual HRCT scans for 5 years (Feasibility Study), and 1 year in AIR2
  - No radiographic evidence of structural changes / bronchiectasis

Risk-Benefit Profile



Where Does Alair Fit In?

Stepwise Approach for Managing Asthma



Adapted from National Asthma Education and Prevention Program (NAEPP) Guidelines. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute, NIH Publication No. 07-4051, Revised August 2007

Summary

- Indisputable unmet medical need
- Treatment with the Alair System elevates the presently attainable level of control in patients with severe asthma
- Compelling evidence of effectiveness and safety from 3 RCTs
  - 2 vs. standard of care medications
  - 1 vs. standard of care medications + Sham
- Significant and persistent benefits
- Safety profile well characterized
  - Events are manageable
  - Safety data available out to as many as 5 years of follow-up (~500 patient years)

Conclusion

The totality of the evidence demonstrates that the Alair System represents a clinically meaningful treatment option for patients suffering from severe asthma.