Smooth Muscle & Asthma: Bronchial Thermoplasty
-A Smooth Muscle Modifier

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Disclosures

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Lecture Bureau: Boehringer-Ingelheim, Boston Scientific, Genentech, GSK, Merck, Pfizer

Consultant: Boston Scientific, Ception (Cephalon), Genentech, GSK (DSMC), IPS, NKT Therapeutics, Schering

Stock: None
Unmet Need in Severe Persistent Asthma

- Prevalence of severe asthma 5-20% (NAEPP/NHLBI)
- Many patients remain symptomatic despite standard of care medication
- Treatments are limited, require adherence, and may have serious side effects
- New options are needed
RF Energy to Reduce Excess Airway Smooth Muscle

- History of safe use in medical procedures

- Viewpoint CK System for Vision Correction
- Alair System for BT
- Adiana for Contraception
- Halo for Barrett's Esophagus
- Ligasure for Vessel Sealing/Cutting
- Prostive for shrinking Prostate
- COBRA for Cardiac Arrhythmias/Ablation
- Maestro 3000 System for Cardiac Arrhythmias

Increasing Energy
Bronchial Thermoplasty

Rationale

Reduces Airway Smooth Muscle (ASM)

\[ \Downarrow \]

Reduced Ability for Bronchoconstriction

\[ \Downarrow \]

Reduced Asthma Symptoms and Exacerbations

\[ \Downarrow \]

Improved Asthma Control and Quality of Life
Reduced Airway Smooth Muscle
3 years Post-Treatment (Canine Model)
Less Airway Constriction with Reduced ASM

\[ R^2 = -0.54; \quad P < 0.001 \]
Bronchial Thermoplasty

- 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
Bronchial Thermoplasty Procedure Details

- Patient evaluated 1 week prior to procedure to verify ability to undergo bronchoscopy
- Procedures performed in Bronchoscopy or IP Suite
- Lung function evaluated morning of procedure to assess stability
- Prophylactic medication: Prednisone
  - 50 mg/day for 5 days (3 days prior, Day of, and Day after procedure)
- Standard Sedation and Monitoring techniques for Interventional bronchoscopy
  - Pre-medications: Anti-mucolytic, Albuterol, Midazolam, Fentanyl
  - Topical anesthesia: Lidocaine (vocal cords and airways)
  - Moderate levels of Anxiolysis and Analgesia (Midazolam 0.5 - 2.0 mg IV q 3-5 minutes prn, Fentanyl 25 - 50µg IV q 3-5 minutes prn)
Post-BT Procedure/Patient Follow Up

- Patient monitored for 2-4 hours post-op
- Patient discharged from hospital same day:
  - Lung function stable within 80% of pre-procedure post BD FEV1
  - Patient stable, able to take liquids, feeling well
  - Prophylactic OCS continued 1 day after procedure (or longer)
- Patient contacted via phone at 1, 2 and 7 days to assess post procedure status
- Office visit at 2 to 3 weeks to assess clinical stability and schedule subsequent BT procedures as appropriate
- Patient returns to care of primary asthma physician for long term asthma management following BT
**Bronchial Thermoplasty Studies To Date**

- **Over 800** Procedures Performed
- **3** Randomized Controlled Studies
- **Over 10** Publications

**Pivotal Study**
AIR2: n=190 treated patients at 30 sites

1. (Castro, AJRCCM, 2010)  
2. (Pavord, AJRCCM, 2007)  
3. (Cox, NEJM, 2007)  
4. (Cox, AJRCCM, 2006)  
5. (Castro, AAAI, 2011)

AIR = Asthma Intervention Research Study  
RISA = Research in Severe Asthma Study
### Baseline Demographics BT Treated Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Feasibility</th>
<th>AIR Trial</th>
<th>RISA Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Subjects</strong></td>
<td>16</td>
<td>55</td>
<td>15</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>39.0 ± 8.6</td>
<td>39.4 ± 11.2</td>
<td>39.1 ± 13.0</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>F 10 (63%)</td>
<td>F 31 (56%)</td>
<td>F 9 (60%)</td>
</tr>
<tr>
<td><strong>Pre-BD FEV₁ (% Pred)</strong></td>
<td>82.2 ± 14.1</td>
<td>72.65 ± 10.41</td>
<td>62.9 ± 12.2</td>
</tr>
<tr>
<td><strong>ICS Dose (µg/day)</strong></td>
<td>900 ± 424</td>
<td>1351 ± 963</td>
<td>2333 ± 817</td>
</tr>
<tr>
<td><strong>OCS Dose (mg/day)</strong></td>
<td>0</td>
<td>0</td>
<td>14.4 ± 6.2 (N=8)</td>
</tr>
<tr>
<td><strong>% Symptom Free Days</strong></td>
<td>50 ± 33</td>
<td>34 ± 34</td>
<td>5 ± 14</td>
</tr>
</tbody>
</table>
AIR Study
- Reduction in Mild Exacerbations

Change in Exacerbations/Year

Cox, G, et. al., Asthma control during one year after bronchial thermoplasty, 
## BT Clinical Results

<table>
<thead>
<tr>
<th>Feasibility (n=16)</th>
<th>AIR (RCT, n=109)</th>
<th>RISA* (RCT, n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well tolerated</td>
<td>AQLQ score</td>
<td>AQLQ score</td>
</tr>
<tr>
<td>Lung function</td>
<td>Exacerbations</td>
<td>ACQ score</td>
</tr>
<tr>
<td>Symptom Free Days</td>
<td>Rescue medications</td>
<td>Rescue medications</td>
</tr>
<tr>
<td>Persistent</td>
<td>Symptom Free Days</td>
<td>Oral steroids</td>
</tr>
</tbody>
</table>

*Pavord, ID, et. al., Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med, 2007; 176: 1185-1191*
RISA Study

-Ability to Wean Patients Off Oral Steroids

**Percent of Baseline Oral Steroid Dose**

- **Control** (n = 7)
  - 26.2%↓
  - p = 0.12

- **Alair** (n = 8)
  - 50.1%↓
  - 63.5%↓

AIR2 Trial Design

- Primary Endpoint: Asthma Quality of Life Questionnaire (AQLQ)

- Study Design: Sham Controlled, Double Blind
  - 2 : 1 randomization; BT: Sham
  - BT Group (ICS + LABA + BT)
  - Sham Group (ICS + LABA + Sham)

- Study Size: 297 Subjects / 30 centers (International)

- Length of Follow-up: - One year
  - 5-year safety follow-up for BT subjects

AIR2 Trial
- Key Inclusion Criteria

- ICS >1000 ug BDP equiv + LABA; ± OCS ≤10 mg/day
- At least 2 symptom days in 4 week baseline
- Pre-bronchodilator FEV₁ ≥ 60% Predicted
- ≤ 8 puffs/24h rescue medication, excluding for exercise

Double Blind Carefully Maintained

- **Subject Consented & Screened for Eligibility**
- **Subject Randomized & Treated**
  - Alair Group: Catheter deployed and RF delivered
  - Sham Group: Catheter deployed, but NO RF delivered
- **UNBLINDED Bronchoscopy Team**
- **BLINDED Assessment Team**
- **Post-procedure Safety and Effectiveness Assessments**

SUBJECTS REMAINED BLINDED THROUGH ENTIRE STUDY PERIOD

## AIR2 Patient Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BT</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>190</td>
<td>98</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.7 ± 11.89</td>
<td>40.6 ± 11.85</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>81 (43%)</td>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
<td>109 (57%)</td>
<td>Female</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>151 (80%)</td>
<td>White</td>
</tr>
<tr>
<td>Black</td>
<td>19 (10%)</td>
<td>Black</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6 (3%)</td>
<td>Hispanic</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (2%)</td>
<td>Asian</td>
</tr>
<tr>
<td>Other</td>
<td>10 (5%)</td>
<td>Other</td>
</tr>
</tbody>
</table>

## AIR2: Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BT</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>190</td>
<td>98</td>
</tr>
<tr>
<td>Pre-Bronchodilator FEV$_1$ (% predicted)</td>
<td>77.8 ± 15.7</td>
<td>79.7 ± 15.1</td>
</tr>
<tr>
<td>Inhaled Corticosteroid (beclomethasone equivalent, µg/day)</td>
<td>1961</td>
<td>1835</td>
</tr>
<tr>
<td>Long-Acting β$_2$-Agonist (µg/day)</td>
<td>117</td>
<td>110</td>
</tr>
<tr>
<td>AQLQ Score (scale 1-7)</td>
<td>4.30 ± 1.17</td>
<td>4.32 ± 1.21</td>
</tr>
<tr>
<td>Symptom-Free Days (%)</td>
<td>16.4 ± 24.0</td>
<td>16.8 ± 23.1</td>
</tr>
<tr>
<td>Number and (%) of Subjects on Other Asthma Medications:</td>
<td>59 (31.1)</td>
<td>25 (25.5)</td>
</tr>
<tr>
<td>OCS</td>
<td>7 (3.7)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Leukotriene Modifiers (e.g., Singulair)</td>
<td>47 (24.7)</td>
<td>18 (18.4)</td>
</tr>
<tr>
<td>Omalizumab (Xolair)</td>
<td>2 (1.1)</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Other</td>
<td>21 (11.1)</td>
<td>14 (14.3)</td>
</tr>
</tbody>
</table>
Primary Endpoint: AQLQ

Intent-to-Treat (ITT) Population

Mean Difference = 0.21 (ITT); 0.24 (PP)
Post Prob Sup = 96.0% (ITT); 97.9% (PP)
Bronchial Thermoplasty

**AIR2 Trial**
Net Benefit = 19%
PPS (Alair - Sham) = 100.0%

**Results**
- Percent of Subjects
- Severe Exacerbations: Sham = 0.7, Alair = 0.48 (32% reduction)
- Unscheduled Office Visits: Sham = 0.36, Alair = 0.28 (23% reduction)
- ER Visits: Sham = 0.43, Alair = 0.07 (84% reduction)
- Hospitalizations: Sham = 0.13, Alair = 0.04 (73% reduction)

*PPS = 95.6%, **PPS = 95.6%

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

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

## Respiratory Adverse Events

### Overall Adverse Events With > 3% Incidence

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

* pp superiority >95.0%

# Treatment Period Hospitalizations for Respiratory Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Alair (N=190)</th>
<th>Sham (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events (Incident Rate %)</td>
<td>No. of Events (Incident Rate %)</td>
</tr>
<tr>
<td>Asthma Aggravated</td>
<td>12 (6.3%)</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>3 (1.6%)</td>
<td></td>
</tr>
<tr>
<td>Lower Resp. Tract Infect.</td>
<td>1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Low FEV₁</td>
<td>1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Aspirated tooth in airway</td>
<td>1 (0.5%)</td>
<td></td>
</tr>
</tbody>
</table>

*Castro, Am J Respir Crit Care Med. 2010;181(2):116-24*
AIR2 Summary at 1-Year

- Improved asthma-related quality of life compared to control (AQLQ score)
  - 79% of BT treated patients achieved ≥ 0.5 increase
  - Effect persistent across 6, 9, and 12 months

- Improved clinical outcomes compared to control:
  - 32% decrease in severe exacerbations
  - 84% reduction in ER visits for respiratory symptoms
  - 73% reduction in hospitalization for respiratory symptoms
  - 66% less days lost from work, school and other daily activities due to asthma

- 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

No difference found in the asthma control for BT-treated subjects in Year 2 versus Year 1 following treatment.

<table>
<thead>
<tr>
<th>Percent of Subjects</th>
<th>Year Prior to Study Entry&lt;sup&gt;a&lt;/sup&gt; (n=288)</th>
<th>Year 1 BT (n=181)</th>
<th>Year 2 BT (n=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe exacerbations</td>
<td>53.4</td>
<td>30.9 (56)</td>
<td>23.0 (38)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ED Visits</td>
<td>29.8</td>
<td>5.0 (9)</td>
<td>6.6 (11)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>5.5</td>
<td>3.3 (6)</td>
<td>4.2 (7)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> patient reported for all subjects (BT + Sham) prior to study entry
<sup>b</sup> Year 2 BT comparison to Year 1 BT: Not significant by Fisher’s Exact Test
Conceptualizing the Impact of Bronchial Thermoplasty

Change in AQLQ Score

ICS and ICS + LABA (Advair®) (1)

Omalizumab (Xolair®) (2)

Bronchial Thermoplasty (Alair®) (3)

+ 0.24

1.14

0.93

Sham

Xolair

1.38

Alair

ICS+LABA

ICS

No drug

Increasing baseline maintenance medication

(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)
Stepwise Approach for Managing Asthma

1. Short-acting Beta$_2$-agonists

2. Low-dose Inhaled Corticosteroids (ICS)

3. Low-dose ICS + Long-acting Beta$_2$-agonists (LABA) or Medium-dose ICS

4. Medium-dose ICS + LABA

5. High-dose ICS + LABA and Consider Omalizumab

6. High-dose ICS + LABA + Oral Corticosteroids and Consider Omalizumab

Bronchial Thermoplasty
Conclusions

1. Offers a novel treatment for severe asthma where alternative treatments are limited, of unproven efficacy, and have side effects

2. Proven efficacy for reducing severe exacerbations, healthcare utilization, days lost from school/work and improving QOL with acceptable short-term AE profile > NET positive health outcome

3. Long term safety established out to 5 years

4. Since FDA approval over 100 pts have been treated outside of an investigational setting with an acceptable AE profile

   (CTAF testimony Oct 19, 2011)

5. BT is ready for “prime time” in the hands of experienced trained bronchoscopist working in conjunction with clinician with special expertise in evaluation and management of severe asthma