Bronchial thermoplasty or biological targeted therapies for severe uncontrolled asthma

Pascal Chanez,
Pascal.chanez@univ-amu.fr

Aix Marseille Université,
Clinique des bronches, allergie et sommeil/ APHM, Marseille
Laboratoire d’Immunologie /INSERM U1067/CNRS UMR 7733
P.C. has provided consultancy services for SNCF, BI, Centocor, GSK, MSD, AZ, Novartis, Teva, Chiesi, and Boston Sci; has served on advisory boards for ALK, BI, Centocor, GSK, AZ, Novartis, Teva, Chiesi, and Boston Sci; has received lecture fees from ALK, BI, Centocor, GSK, AZ, Novartis, Teva, Chiesi, MSD; and has received industry-sponsored grants from Roche, BI, Centocor, GSK, AZ, Novartis, Teva, Chiesi;.
Severe Asthma Management

- Better Understanding
- Better Management
Limitation: Heterogeneity of SA

Genes
Gene expression
Histology
Lung function
The patient

Phenotyping Asthma
Limitation: Complexity of the network

A coherent approach “from difficult to severe asthma”

- Diagnosis
- Adherence
- Comorbidities

Severe Asthma

Optimisation

Phenotyping

- Anti IgE
- OCS
- RCS
- TH2
- Non TH2

Days
Weeks
Months
A major strength: Definition

International ERS/ATS Guidelines Step 4-5 medications: high-dose ICS and LABA (or leukotriene modifier/theophylline) and/or systemic corticosteroids for ≥50% of the previous year. The definition of high dose ICS is age specific

Uncontrolled defined as any one of the following:
- i. Poor symptom control: ACQ consistently >1.5, ACT<20 (or “not well controlled” by NAEPP/GINA guidelines)
- ii. Frequent severe exacerbations: 2 or more bursts of systemic CS (>3 days each) in the previous year
- iii. Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year
- iv. Presence of airflow limitation: a pre-bronchodilator FEV₁ <80% predicted (in the face of reduced FEV₁/FVC)

Controlled asthma on these high doses of ICS or CS (or additional biologics) places a patient at high future risk for side effects from medications

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ATS, American Thoracic Society; ERS, European Respiratory Society; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting β₂-agonist
ERS / ATS Guidelines on severe asthma

- Revise the definition of severe asthma;
- Discuss phenotypes of severe asthma;
- Provide guidance on management, diagnosis, evaluation and treatment of severe asthma;
- Developed according to GRADE methodology → transparent and trustworthy;
- Need regular updates for optimal validity → living document PERSONALISED?
Definitions

Identifies those with highest unmet need
Provides criteria for referral to expert centers
Allows positioning of new high cost therapies biologics and thermoplasty
Focusses research with attention to phenotyping and personalised medicine

Limitations
Does not identify a specific severe asthma endotype is severe asthma a distinct entity?
Relies on inadequate response to current therapy
Focus on subjective measures of control and exacerbations

Adapted from CE Brightling
Personalise Phenotype Endotype Partnership

- Better Understanding
- Better Management
External Validity of RCTs in Severe Asthma

Pahu L et al., AJRCCM 2015

Selection of RCTs on clinicaltrials.gov:
- Interventional
- Recruiting
- Efficacy primary endpoint

Key words:
- Severe asthma
- Uncontrolled asthma
- Refractory asthma
- Difficult asthma

RCTs

COBRA Cohort: 593 asthmatic patients

GINA

Severe asthmatics

Eligibility criteria

Eligible patients
Injury

SPDEF NOTCH

EGFR

TSLP IL25 IL33

DC

IL-8

TH1

TNF

IL-17

CXCR2

TH2

IL-5

IL-3 IL-5 IL-9 GMCSF IL-4/IL-13

IgE

eosinophils

Mast cells, basophils

thermoplasty

neutrophils

Biomarkers and response to therapy for $T_H^2$ and non-$T_H^2$ asthma

<table>
<thead>
<tr>
<th>Pathobiology and biomarkers</th>
<th>Response to therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset allergic Specific IgE; $T_H^2$ cytokines; thick SBM</td>
<td>Corticosteroid-responsive; $T_H^2$-targeted</td>
</tr>
<tr>
<td>Late-onset eosinophilic Corticosteroid-refractory eosinophilia; IL-5</td>
<td>Responsive to antibody to IL-5 and cysteinyll leukotriene modifiers; corticosteroid-refractory</td>
</tr>
<tr>
<td>Exercise-induced Mast-cell activation; $T_H^2$ cytokines; cysteinyll leukotrienes</td>
<td>Responsive to cysteinyll leukotriene modifiers, beta agonists and antibody to IL-9</td>
</tr>
<tr>
<td>Obesity-related Lack of $T_H^2$ biomarkers; oxidative stress</td>
<td>Responsive to weight loss, antioxidants and possibly to hormonal therapy</td>
</tr>
<tr>
<td>Neutrophilic Sputum neutrophilia; $T_H^17$ pathways; IL-8</td>
<td>Possibly responsive to macrolide antibiotics</td>
</tr>
</tbody>
</table>

IgE, immunoglobulin E; IL-5, interleukin 5; IL-8, interleukin 8; IL-9, interleukin 9; SBM, sub-basement membrane; $T_H^2$, T helper 2

Sputum eosinophil-guided asthma management

Cumulative numbers of exacerbations

Conclusions: Eosinophilic inflammation of the airways is correlated with the severity of asthma. These cells are likely to play a part in the epithelial damage seen in this disease (N Engl J Med 1990;323:1033–9)

Conclusions: Mepolizumab administered either intravenously or subcutaneously significantly reduced asthma exacerbations and was associated with improvements in markers of asthma control (N Engl J Med 2014;371:1198–207)
Results: reduction in exacerbations

- IV group: Exacerbation rate reduced by 47% versus placebo (95% CI: 29–61%)
- SC group: Exacerbation rate reduced by 53% versus placebo (95% CI: 37–65%)

Mepolizumab Withdrawal
Halder et al JACI 2014

- Sputum eosinophils (Eos)
- Blood eosinophils
- Exacerbation frequency per quarter (EXA)
- Forced Expiratory Volume in 1 second (FEV1s)
- Asthma Control Questionnaire (ACQ)
- Exhaled Nitric Oxide (eNO)
Therapeutic Targets for Eosinophilic Asthma: Reslizumab
# Reslizumab: Published Clinical Trials in Asthma

<table>
<thead>
<tr>
<th>First author/year</th>
<th>Disease Severity</th>
<th>N</th>
<th>Dosage/Delivery</th>
<th>Outcome summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kips et al, 2003¹</td>
<td>Severe asthmatics</td>
<td>18</td>
<td>0.03–1 mg/kg i.v. single dose</td>
<td>Safe; ↓Blood Eos</td>
</tr>
<tr>
<td>Castro et al, 2011²</td>
<td>Poorly controlled eosinophilic asthma</td>
<td>53</td>
<td>3 mg/kg i.v. every 4 weeks for 12 weeks</td>
<td>↓Blood Eos; ↑FEV₁; ↑ACQ-5 score; Particularly in patients with nasal polyps; 30% had nasal polyps</td>
</tr>
<tr>
<td>Castro et al, 2015³,⁴</td>
<td>Inadequately controlled asthma with elevated eosinophils</td>
<td>953 (N=477 in Study 1; N=476 in Study 2)</td>
<td>3 mg/kg i.v. every 4 weeks for 1 year</td>
<td>↓Exacerbation frequency</td>
</tr>
<tr>
<td>Bjerner et al, 2016⁴</td>
<td>Inadequately controlled asthma with elevated eosinophils</td>
<td>315</td>
<td>0.3 or 3.0 mg/kg every 4 weeks for 16 weeks</td>
<td>↑FEV₁; ↑ACQ-5; ↑AQLQ</td>
</tr>
<tr>
<td>Corren et al, 2016⁵</td>
<td>Poorly controlled asthma with a range of eosinophil counts</td>
<td>492</td>
<td>3.0 mg/kg or placebo once every 4 weeks for 16 weeks</td>
<td>↑FEV₁; ↑ACQ-7; ↓Rescue SABA use; no improvement in FEV₁ with baseline eosinophil &lt;400 cells/μL</td>
</tr>
</tbody>
</table>

³Pool analysis.
4ACQ-5 asthma control questionnaire 5-item version; AQLQ=asthma quality of life questionnaire; Eos=eosinophils; FEV₁=forced expiratory volume in 1 second; SABA=short-acting beta agonist.
Eosinophil’s Role Remains Uncertain as Anti–Interleukin-5 only Partially Depletes Numbers in Asthmatic Airway

Patrick T. Flood-Page,* Andrew N. Menzies-Gow,* A. Barry Kay, and Douglas S. Robinson  

Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics

Patrick Flood-Page,1 Andrew Menzies-Gow,1 Simon Phipps,1 Sun Ying,2 Arun Wangoo,1 Mara S. Ludwig,3 Neil Barnes,4 Douglas Robinson,1 and A. Barry Kay1

JCI 2003

AJRCCM 2003
Benralizumab

IL-5 Receptors antagonist
Therapeutic Targets for Eosinophilic Asthma: Benralizumab
Depletion of bronchial eosinophils
Laviolette M et al. J Allergy Clin Immunol 2014

A

Placebo

Benralizumab 1 mg/kg IV

Airway eosinophils (mm$^3$)

Screening → Dosing → Day 28

B

Placebo

Benralizumab 1 mg/kg IV

Airway eosinophils (mm$^3$)

Screening → Dosing → Day 28

ULN
## Benralizumab: Published Clinical Trials in Asthma

<table>
<thead>
<tr>
<th>First author/year</th>
<th>Disease Severity</th>
<th>N</th>
<th>Dosage/Delivery</th>
<th>Outcome summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busse et al, 2010¹</td>
<td>Mild atopic asthma</td>
<td>44</td>
<td>0.0003–3 mg/kg i.v. single dose</td>
<td>↓Blood Eos at dose 0.03–3 mg; Eosinopenia lasted 8–12 weeks; Transient, mild decrease in WBC; CRP increased 5.5-fold; Interleukin-6 increased CPK of peripheral muscular origin increased</td>
</tr>
<tr>
<td>Laviolette et al, 2013²</td>
<td>Eosinophilic asthma</td>
<td>26</td>
<td>1 mg/kg i.v.; 100 mg s.c. every month for 3 doses; 200 mg s.c. every month for 3 doses</td>
<td>↓Eos in blood, sputum and bronchial mucosa; ↓Basophils; Nasopharyngitis 25%; Headache 25%; Nausea 22%</td>
</tr>
<tr>
<td>Castro et al, 2014³</td>
<td>Eosinophilic asthma</td>
<td>384</td>
<td>2–20–200 mg 2 s.c. every 4 weeks for the first 3 doses, then every 8 weeks for 1 year</td>
<td>20 mg and 100 mg ↓Exacerbations; ↑FEV₁</td>
</tr>
<tr>
<td>Nowak et al, 2015⁴</td>
<td>Asthma after acute attack</td>
<td>72</td>
<td>Single dose 0.3 mg/kg i.v. 1 mg/kg i.v. Evaluated up to 6 months</td>
<td>↓Blood Eos; ↓Exacerbations</td>
</tr>
<tr>
<td>Pham et al, 2016⁵</td>
<td>Eosinophilic asthma</td>
<td>N=14 (Study 1); N=24 (Study 2)</td>
<td>100 or 200 mg, multiple doses (Study 1); 25, 100, 200 mg every 4 weeks (Study 2)</td>
<td>↓Blood Eos; ↓EDN; ↓ECP</td>
</tr>
</tbody>
</table>

CPK=creatine phosphokine; CRP=C-reactive protein; ECP=eosinophil cationic protein; EDN=eosinophil-derived neurotoxin; Eos=eosinophils; FEV₁=forced expiratory volume in 1 second; WBC=white blood cell.

Omalizumab

*Anti-IgE mab*

Exacerbations per Patient (mean)

- **Adult (US)**
  - Omalizumab: 0.28
  - Placebo: 0.54

- **Adult (US and International)**
  - Omalizumab: 0.28
  - Placebo: 0.66

- **Pediatric**
  - Omalizumab: 0.3
  - Placebo: 0.4
### Table 4—Rates and AHRs of Severe Exacerbations Following Exposure or Not to Omalizumab

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rate per 100 Person-y</th>
<th></th>
<th></th>
<th>UHR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>AHR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Absence of Omalizumab</td>
<td>During Omalizumab Use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization and ED visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire cohort (n = 767, 1,208 person-y)</td>
<td>30.6</td>
<td>33.4</td>
<td>20.8</td>
<td>0.56</td>
<td>0.57 (0.43-0.78)</td>
</tr>
<tr>
<td>In users of omalizumab at least once (n = 374, 564.9 person-y)</td>
<td>26.2</td>
<td>32.3</td>
<td>20.8</td>
<td>0.53</td>
<td>0.40 (0.28-0.58)</td>
</tr>
<tr>
<td>(n = 374, 564.9 person-y) during omalizumab use (298.9 person-y) and in the absence of omalizumab use (265.9 person-y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic patients only (n = 486, 750 person-y)</td>
<td>28.0</td>
<td>31.9</td>
<td>20.2</td>
<td>0.50</td>
<td>0.53 (0.39-0.75)</td>
</tr>
<tr>
<td>Use of oral corticosteroids (entire cohort)</td>
<td>...</td>
<td>73.8</td>
<td>49.2</td>
<td>P &lt; .001</td>
<td>...</td>
</tr>
</tbody>
</table>

AHR = adjusted hazard ratio; UHR = unadjusted hazard ratio. See Table 1 legend for expansion of other abbreviation.

<sup>a</sup>Cox proportional hazard model.

<sup>b</sup>Andersen-Gill extension of the Cox proportional hazard model for correlated data, adjusted with a propensity score for age, sex, smoking history, BMI, gastroesophageal reflux, allergic status, allergic rhinitis, use of oral corticosteroids or LTRAs, and recent severe exacerbations.
Biomarkers for anti-IgE treatment

Patients with high FeNO, eosinophils and periostin benefit more from anti-IgE treatment

Anti-IgE and exacerbations (one year)

Treatment duration?

Busse WW et al. ATS 2014

Time to First Protocol-Defined Asthma Exacerbation

Number at risk
Xolair Continuation 88 85 81 77 73 69 68 68 67 65 63 62 60 45
Placebo 88 79 75 67 60 56 54 53 52 48 44 43 43 31
Lebrikizumab
Tralokinumab
m-AB anti-IL13
Anti-IL13 in asthma: Periostin as a crucial factor?


Total cohort

High-periostin subgroup  Low-periostin subgroup

Lebrikizumab (n = 106)  Placebo (n = 112)

Lebrikizumab (n = 51)  Placebo (n = 59)

Lebrikizumab (n = 51)  Placebo (n = 50)
Tralokinumab
Réduction des exacerbations n=300
*C Brightling et al Lancet Respir 2015*
Dupilumab

m-AB anti-IL-4R
Dupilumab in Asthma
Dupilumab in Asthma

Percentage reduction relative to placebo

Adjusted annualised severe exacerbation rate, estimate (95% CI)

- Placebo (n=90): (0.493-12.31)
- 200 mg every 4 weeks (n=91): (0.252-0.786)  (-43%)
- 300 mg every 4 weeks (n=91): (0.286-0.837)  (-37%)
- 200 mg every 2 weeks (n=84): * (0.124-0.516)  (-68%)
- 300 mg every 2 weeks (n=92): † (0.170-0.576)  (-60%)
<table>
<thead>
<tr>
<th>Compound</th>
<th>MoA</th>
<th>Development status</th>
<th>Administration (dose, frequency)</th>
<th>Phase III populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupilumab (Sanofi/Regeneron)</td>
<td>Anti-IL-4/13</td>
<td>Phase III</td>
<td>200 mg or 300 mg SC Q2W and Q4W being assessed in Phase IIb</td>
<td>≥18 yrs, mod/severe (Phase IIb: blood eos ≥300 cells/μL group)</td>
</tr>
<tr>
<td>Reslizumab (Teva)</td>
<td>Anti-IL-5</td>
<td>Registration US</td>
<td>3.0 mg/kg IV Q4W</td>
<td>≥12–75 yrs, mod/severe, blood eos ≥400 cells/μL</td>
</tr>
<tr>
<td>Mepolizumab (GSK)</td>
<td>Anti-IL-5</td>
<td>Registration US-EU</td>
<td>100 mg SC Q4W</td>
<td>≥12 yrs, severe, blood eos ≥150 cells/μL OR ≥300 cells/μL at some point in previous year</td>
</tr>
<tr>
<td>Benralizumab (AZ/MedImmune)</td>
<td>Anti-IL-5</td>
<td>Phase III underway</td>
<td>Phase IIb: 2, 20 and 100 mg SC Q4W for first 3 doses, then Q8W Up to 3 doses being assessed in Phase III</td>
<td>≥12–75 yrs, severe (Phase IIb: severe eos phenotype defined by ELEN index)</td>
</tr>
<tr>
<td>Lebrikizumab (Roche/Genentech)</td>
<td>Anti-IL-13</td>
<td>Phase III</td>
<td>Phase IIb: 37.5, 125 and 250 mg SC Q4W High and low doses being assessed in Phase III</td>
<td>≥18–75 yrs, severe (Phase IIb: high/low periostin groups)</td>
</tr>
<tr>
<td>Tralokinumab (AZ/MedImmune)</td>
<td>Anti-IL-13</td>
<td>Phase III underway</td>
<td>Phase IIb: 300 mg SC Q2W or Q2W for 12 wks then Q4W Two doses, including 300 mg SC Q2W being assessed in Phase III</td>
<td>≥12–75 yrs, severe (Phase IIb: high/low periostin and high/low DPP4 groups)</td>
</tr>
</tbody>
</table>
### Biomarkers and response to therapy for T\(_H\)2 and non-T\(_H\)2 asthma

<table>
<thead>
<tr>
<th>Pathobiology and biomarkers</th>
<th>Response to therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset allergic</td>
<td>Specific IgE; T(_H)2 cytokines; thick SBM</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid-responsive; T(_H)2-targeted</td>
</tr>
<tr>
<td>Late-onset eosinophilic</td>
<td>Corticosteroid-refractory eosinophilia; IL-5</td>
</tr>
<tr>
<td></td>
<td>Responsive to antibody to IL-5 and cysteiny leukotriene modifiers; corticosteroid-refractory</td>
</tr>
<tr>
<td>Exercise-induced</td>
<td>Mast-cell activation; T(_H)2 cytokines; cysteiny leukotrienes</td>
</tr>
<tr>
<td></td>
<td>Responsive to cysteiny leukotriene modifiers, beta agonists and antibody to IL-9</td>
</tr>
<tr>
<td>Obesity-related</td>
<td>Lack of T(_H)2 biomarkers; oxidative stress</td>
</tr>
<tr>
<td></td>
<td>Responsive to weight loss, antioxidants and possibly to hormonal therapy</td>
</tr>
<tr>
<td>Neutrophilic</td>
<td>Sputum neutrophilia; T(_H)17 pathways; IL-8</td>
</tr>
<tr>
<td></td>
<td>Possibly responsive to macrolide antibiotics</td>
</tr>
</tbody>
</table>

IgE, immunoglobulin E; IL-5, interleukin 5; IL-8, interleukin 8; IL-9; interleukin 9; SBM, sub-basement membrane; T\(_H\)2, T helper 2 Wenzel SE, et al. Nat Med 2012; 18 (5): 716-25
Macrolide antibiotics in severe asthma

No specific intervention on bronchial epithelium and mucus production
No specific intervention on bronchial nerves
No specific intervention on vascular remodeling
No specific action on SM Cells
Phenotyping severe asthma

Clinical approaches
- A priori hypothesis
- Unsupervised clustering

Endotyping
- TH2 low
- TH2 high

Omalizumab
- Atopic Total IgE
- Anti TSLP GATA3 DNazyme

Mepolizumab
- Eos > 300
- Dupilumab
- Eos > 400
- Benra
- Resli
- Periostin
- Lebrikizumab

Reversible Anti IL17

Smooth Muscle Thermoplasty

Viral Exacerbation
- β-IFN

Neutrophilic
- Azithromycine
- Anti CXCR2

Paucigranulocytic
- Thermoplasty?
Thermoplasty in severe asthma

BRONCHIAL THERMOPLASTY FOR ASTHMA

Bronchial thermoplasty for asthma: evidence is lacking

Angshu Bhowmik  
respiratory physician

Homerton University Hospital, London E9 6SR, UK
HRCT-Scan 24 H after BT

Petrolani et al AJRCCM 2015

- Treated RL SL
- Non treated RML
Smooth muscle Cells and BT
Petrolani et al AJRCCM 2015
Remodeling affected by BT


Typical examples of histological features observed on bronchial biopsies at Baseline (A) and visit 2 (B). Note the decrease in ASM area following BT.

22x6mm (300 x 300 DPI)

Type 1 Collagen

Mean sub-epithelial collagen 1 deposition at each visit. Collagen 1 thickness significantly decreased at visits 2 and 3 compared to visit 1.
60x49mm (300 x 300 DPI)

Airway Smooth Muscle

(A) Mean ASM surfaces significantly decreased after BT
62x52mm (300 x 300 DPI)
Table 2: Changes of epithelium morphology observed after BT

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 (n = 17)</th>
<th>Visit 2 (n = 17)</th>
<th>Visit 3 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MUC5AC staining (%)</strong></td>
<td>19.6 ± 2.2</td>
<td>12.2 ± 1.2*</td>
<td>21.2 ± 2.5†</td>
</tr>
<tr>
<td>Acute inflammation (n, %)</td>
<td>1 (6)</td>
<td>12 (80)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Goblet cell metaplasia (n)</td>
<td>10 (59)</td>
<td>12 (80)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Squamous metaplasia (n)</td>
<td>2 (12)</td>
<td>6 (40)</td>
<td>0</td>
</tr>
</tbody>
</table>

* p = 0.003 compared to visit 1
† p = 0.99 compared to visit 1
¶ n = 15 at visit 2 and 7 at visit 3
BT and ASM
(n = 15 severe french patients)
Petrolani et al submitted

Before BT

After BT

ASM area (% of biopsy area)

P < 0.001

Before BT

After BT
Effect on Nerves (PGP)

Petrolani et al submitted

**Before BT**

**After BT**

**P < 0.001**

**P = 0.02**

Before

After
Clinical Correlates
M Aubier et al unpublished

<table>
<thead>
<tr>
<th>Pathology Criteria</th>
<th>ACT</th>
<th>AQLQ</th>
<th>Exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface ASM</td>
<td>&lt; 0.001</td>
<td>0.02</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BM size</td>
<td>0.005</td>
<td>0.07</td>
<td>0.04</td>
</tr>
<tr>
<td>Nerves</td>
<td>0.04</td>
<td>0.33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ASM associated nerves</td>
<td>0.32</td>
<td>0.83</td>
<td>0.03</td>
</tr>
<tr>
<td>Neuroendocrine cells</td>
<td>0.004</td>
<td>0.01</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Similar Results at 3 and 12 months
A coherent approach to management for severe asthma

- TTT trials
- Centre of excellence For SA
- Health care system
- Real SA Phenotypes
- Treatment
- Clinical Research Cohorts
- EBM Grading recommendations
- Ethics
- Patient partnership
Dedicated Severe Asthma Services Improve Health-care Use and Quality of Life

- 346 patients with severe asthma

- Significant reductions in health-care use in terms of primary care or ED visits (66.4% vs 87.8%, P<0.0001) and hospital admissions (38% vs 48%, P=0.0004)

- No difference was noted in terms of those requiring maintenance oral corticosteroids, there was a reduction in steroid dose (10 mg [8-20 mg] vs 15 mg [10-20 mg], P =0.003 ), and fewer subjects required short-burst steroids (77.4% vs 90.8%, P=0.01).

- Significant improvements were seen in QoL and control using the Asthma Quality of Life Questionnaire and the Asthma Control Questionnaire.
New approaches in severe asthma?

- Customization of health care
  - Tailored to individual patient

- New innovative treatments:
  - Optimized prescribing
    - Right dose
    - Right drug or intervention
    - Right time
Fluka

Assorted Swiss Chocolates

Aldrich Materials Science Guarantee

100% edible

- Sensitive to heat
- Tested for human beings
- For good customers only
- For perfect pleasure

Protect from sunlight
Thank you !!!!