The Burden and Treatment of Allergic Rhinitis in the 21st Century

Jee YK
Dankook University, College of Medicine
1. The Epidemiology of Allergic Rhinitis

2. The Impact of Rhinitis on Health Economics and Quality of Life

3. Treatment Approaches to Allergic Rhinitis

4. Unmet Needs and formulation considerations in AR Treatment

6. Ciclesonide; A New Intranasal Corticosteroid
Classification of Rhinitis

Allergic Rhinitis

- IgE-mediated response
- Previous Classification
  - Seasonal allergic rhinitis (SAR)
  - Perennial allergic rhinitis (PAR)
- ARIA Classification
  - Intermittent allergic rhinitis (IAR)
  - Persistent allergic rhinitis (PER)

Nonallergic Rhinitis

- Infectious
- Idiopathic or Vasomotor
- Eosinophilic
- Drug-induced
  - Rhinitis Medicamentosa
- Hormonal
- Anatomical

Allergic Rhinitis and its Impact on Asthma (ARIA) 2008
Increasing Prevalence of Allergic Rhinitis in Developed Countries*

* A cross-sectional study of 15- to 41-year-olds in Copenhagen, Denmark.
** Self-reported diagnosis
† Adjusted odds ratio = 1.94, 95% CI 1.30–2.90. Δ 75%
Prevalence of Allergic Rhinitis in Korea

**Subjects (%)**
- 16.4 ≤35
- 24.7 36-50
- 21.7 ≥51

*Prevalence of Allergic Rhinitis in Korea

*A cross-sectional study of 2,467 adults over 20 yr in Korea.

**Self-reported diagnosis \( p=0.02 \)

Prevalence of Allergic rhinitis in patients with bronchial asthma in KOREA

**Age**

- 16-29 yrs: 82.8%
- 30-49 yrs: 79.4%
- 50-64 yrs: 69.0%
- ≥65 yrs: 59.1%

**Asthma Severity**

- Int: 76.4%
- Mild Per.: 75.3%
- Mod Per.: 65.7%
- Sev Per.: 59.1%

*A cross-sectional study of 460 patients over 16 yr in Korea.

The Impact of Rhinitis on Health Economics and Quality of Life
Degree of Discomfort from Nasal Allergies

93% of subjects can tolerate but symptoms are noticeable. 38% can not tolerate.

Allergies in America Executive Summary. Available at: http://www.mmcpub.com/scsaia/AdultSummary.pdf
Most Bothersome of Symptoms Associated With Allergic Rhinitis*

Available at: http://www.mmcpub.com/scsaia/AdultSummary.pdf

*Characterized as most bothersome
The Magnitude of the Impact on Daily Life of Nasal Allergies

85% OF SUBJECTS

<table>
<thead>
<tr>
<th>Extent of Interference with daily life</th>
<th>Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slight</td>
<td>19</td>
</tr>
<tr>
<td>Some</td>
<td>26</td>
</tr>
<tr>
<td>Moderate</td>
<td>25</td>
</tr>
<tr>
<td>Large</td>
<td>15</td>
</tr>
<tr>
<td>Not Sure</td>
<td>1</td>
</tr>
</tbody>
</table>

Symptoms did not Impact daily life 14

Allergies in America Executive Summary.
Available at: http://www.mmcpub.com/scsaia/AdultSummary.pdf
The Frequency of Impairment of Sleep by Allergic Rhinitis

- **Parameter**

  - **Wake-up during night**: 64
  - **Unable to get to sleep**: 75
  - **Lack of good night sleep**: 78

**Rhinitis and poor sleep lead to..**

- ↑ daytime somnolence
- ↓ quality of life
- ↑ psychiatric disorders
- ↑ depression, anxiety, or alcohol abuse
- ↑ disorders of learning, behavior, or attention in childhood or adolescence
- ↓ cognitive functioning

References:

Comparison of Asthma related Symptoms between asthmatics with AR or without AR in KOREA

Subjects with asthma related symptoms (%)

Night-time asthma Symptoms: 61.9 vs 77.3
Exercise induced asthma symptoms: 69 vs 68
Absent day due to asthma symptoms: 20.7 vs 26.3
Speech limitation due to asthma symptoms: 54 vs 49.4

Asthma alone (n=126) vs Asthma with AR (n=334)

P<0.01 NS NS

*A cross-sectional study of 460 patients over 16 yr in Korea.

Allergy is the 5th Most Costly Physical and Mental Health Condition


*Assuming a $23.15/hour wage estimate
†Depression, sadness, mental illness

HTN: hypertension; Resp.: respiratory; STD: short-term disability

In United States*
# Economic Burden of Allergic rhinitis in KOREA

<table>
<thead>
<tr>
<th></th>
<th>Direct cost (in 2007, Mil. Won)</th>
<th>Indirect cost (in 2007, Mil. Won)</th>
<th>Total (in 2007, Mil. Won)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-Patient</strong></td>
<td>244,408</td>
<td>54,027</td>
<td>298,435</td>
</tr>
<tr>
<td><strong>Out-Patient</strong></td>
<td>5,059</td>
<td>2,610</td>
<td>7,669</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>249,467</td>
<td>56,637</td>
<td>306,104</td>
</tr>
</tbody>
</table>

**Direct cost** = direct medical care cost + direct non-medical care cost (transportation cost, nursing cost)

**Indirect cost**: Loss of productivity

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Report of the Korea Centers for Disease Control and Prevention (KCDC) 2009
Treatment Approaches to Allergic Rhinitis
ARIA Classification

**Intermittent**
- < 4 days per week
- or < 4 weeks

**Persistent**
- ≥ 4 days per week
- and ≥ 4 weeks

**Mild**
*(all of the following)*
- normal sleep
- no impairment of daily activities, sport, leisure
- normal work and school
- no troublesome symptoms

**Moderate-severe**
*(one or more items)*
- abnormal sleep
- impairment of daily activities, sport, leisure
- abnormal work and school
- troublesome symptoms

Treatment of Allergic Rhinitis (ARIA)

### Mild intermittent

- **Intranasal corticosteroids**
  - Local chromone
  - Oral or local non-sedative H1-blocker
  - Intra-nasal decongestant (<10 days) or oral decongestant
  - Leukotriene receptor antagonists
  - Allergen and irritant avoidance

### Moderate-severe intermittent

### Mild persistent

### Moderate-severe persistent

### Immunotherapy

Rhinitis Management

**Diagnosis of allergic rhinitis**

- **Intermittent symptoms**
  - **Mild**
    - *Not in preferred order*
    - oral H$_1$-blocker or intranasal H$_1$-blocker and/or decongestant or LTRA*

- **Persistent symptoms**
  - **Moderate-severe**
    - *Not in preferred order*
    - oral H$_1$-blocker or intranasal H$_1$-blocker and/or decongestant or intranasal CS or LTRA (or cromone)
  - **Mild**

**Check for asthma especially in patients with severe and/or persistent rhinitis**

- **Moderate-severe**
  - *In preferred order*
  - Intranasal CS, H$_1$-blocker or LTRA

**In preferred order**

- Review the patient after 2-4 weeks

- Improved
  - Step-down and continue treatment for >1 month

- Failure
  - Review diagnosis
  - Review compliance
  - Query infections or other cause

- Add or increase intranasal CS dose
- Rhinorrhea
- Add ipratropium
- Blockage
  - Add decongestant or oral CS (short term)

- Failure referral to specialist

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*LTRA, leukotriene receptor antagonists*

# Pharmacologic Options for Allergic Rhinitis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Sneezing</th>
<th>Itching</th>
<th>Congestion</th>
<th>Rhinorrhea</th>
<th>Ocular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Antihistamine</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Nasal Antihistamine</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td><strong>Intranasal Corticosteroid</strong></td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Oral Decongestant</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Intranasal Decongestant</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Intranasal Mast Cell Stabilizer</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Topical Anticholinergic</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
</tr>
</tbody>
</table>

- provides no benefit  
++ provides modest benefit  
+/- provides minimal benefit  
++ provides substantial benefit

Adapted with permission from The AAAAI Allergy Report. Vol. 2, page 19.
Intranasal CS vs. oral H1-Antihistamines

**TOTAL NASAL SYMPTOM SCORE**

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors intranasal CS</th>
<th>Favors antihistamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Géhanno</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronsky</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Munch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schoenwetter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Bavel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berrnstein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beswick</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vervloet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wood</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall effect: $-0.423 (-0.531$ to $-0.315)$

$X^2 = 26.82; df = 8; P < 0.001$

Intranasal CS vs. oral H1-Antihistamines

Χ² = 11.76; df = 13; NS


Favors intranasal CS

Bunnag
Simpson
Brooks
Bernstein
Schoenwetter
Vervloet
Bronsky
Munch
Géhanno
Juniper
Darnell
Beswick
Wood
Robinson

Standardized mean difference (95% CI)

Overall effect -0.628 (-0.729 to -0.527)

Favors antihistamine

Standardized mean difference (95% CI)
Unmet Needs and formulation considerations in AR Treatment
Reasons for Dissatisfaction With AR Medications

- Wasn't effective: 66%
- Bothersome side effects: 21%
- Effectiveness wore off: 12%
- Didn't provide 24 hour relief: 10%
- Not covered: 1%
- Cost/co-pay: 1%
- Hard to administer: 1%
- Other: 4%
- Not sure: 2%

Allergies in America Executive Summary.
Available at: http://www.mmcpub.com/scsaia/AdultSummary.pdf

AR: allergic rhinitis
Perception of Loss of Effectiveness With Chronic Use

- No: 40%
- Yes, one: 15%
- Yes, more than one: 38%
- Not sure: 6%
- Yes, not sure how many: 2%

Allergies in America Executive Summary.
Available at: http://www.mmcpub.com/scsaia/AdultSummary.pdf
Perception of 24-Hour Coverage With Intranasal CS

Loses effectiveness: 48%
Does not lose effectiveness: 46%
Not sure: 6%

Allergies in America Executive Summary.
Available at: http://www.mmcpub.com/scsaia/AdultSummary.pdf
Commonly Reported Side Effects of Allergy Medicines

<table>
<thead>
<tr>
<th>Effect</th>
<th>Occurrence Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning</td>
<td>11</td>
</tr>
<tr>
<td>Bad taste</td>
<td>15</td>
</tr>
<tr>
<td>Headaches</td>
<td>13</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>21</td>
</tr>
<tr>
<td>Dripping down throat</td>
<td>20</td>
</tr>
<tr>
<td>Drying feeling</td>
<td>22</td>
</tr>
</tbody>
</table>

Allergies in America Executive Summary. Available at: http://www.mmcpub.com/scsaia/AdultSummary.pdf
## Patients’ Needs for AR Medications

<table>
<thead>
<tr>
<th>Need</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experience relief within an hour after taking medication</td>
<td>69%</td>
</tr>
<tr>
<td>Maintains its effectiveness to the designated time you are to take another dose</td>
<td>68%</td>
</tr>
<tr>
<td>Non-drowsy</td>
<td>67%</td>
</tr>
<tr>
<td>Lets you wake up with symptoms under control</td>
<td>63%</td>
</tr>
<tr>
<td>Provides relief all day and into the next morning</td>
<td>62%</td>
</tr>
<tr>
<td>Fewer doses of medication needed to control allergy symptoms</td>
<td>45%</td>
</tr>
<tr>
<td>Comes in various forms</td>
<td>23%</td>
</tr>
</tbody>
</table>

### Total allergy sufferers (n=1,000)

- Experience relief within an hour after taking medication: 69%
- Maintains its effectiveness to the designated time you are to take another dose: 68%
- Non-drowsy: 67%
- Lets you wake up with symptoms under control: 63%
- Provides relief all day and into the next morning: 62%
- Fewer doses of medication needed to control allergy symptoms: 45%
- Comes in various forms: 23%

### Methodology
- Online interviews (16-item questionnaire)
- Adults (aged >18 years) with physician-diagnosed allergic rhinitis in the United States

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Ciclesonide

A New Intranasal Corticosteroid
Mechanisms of GCS

(a) Prereceptor ligand metabolism

Cortisol

11β-HSD1

11β-HSD2

Cortisone

(b) GR domain organization

Dimerization

Chaperones

Coactivators

Glucocorticoids

Importin
Mechanisms of GCS
**Mechanisms of GCS**

**Inflammatory cells**
- Eosinophil: Numbers (apoptosis)
- T-lymphocyte
- Mast cell: Numbers
- Macrophage
- Dendritic cell: Numbers

**Structural cells**
- Epithelial cell: Cytokines
- Endothelial cell: Leak
- Airway smooth muscle: β2-receptor
- Mucus gland: Mucus secretion

Cytokines and mediators connect these cells to GCS.
<table>
<thead>
<tr>
<th>System</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>brain</td>
<td>loss of brain tissue, loss of cognition</td>
</tr>
<tr>
<td>bone</td>
<td>avascular necrosis of the bone, osteoporosis, osteonecrosis</td>
</tr>
<tr>
<td>endocrine</td>
<td>suppression of adrenal response, widespread endocrine dysfunction, Cushing's Syndrome, diabetes, fluid retention</td>
</tr>
<tr>
<td>eyes</td>
<td>cataracts, glaucoma, range of other side effects,</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td>gastrointestinal hemorrhage, indigestion, worsening of peptic ulcer</td>
</tr>
<tr>
<td>muscle</td>
<td>loss of skeletal muscle, myopathy (muscle weakness)</td>
</tr>
<tr>
<td>psychological</td>
<td>dementia, changes in mood</td>
</tr>
<tr>
<td>sexual, female</td>
<td>menstruation disturbance</td>
</tr>
<tr>
<td>sexual, male</td>
<td>decrease testosterone</td>
</tr>
<tr>
<td>skin</td>
<td>skin atrophy, thinning, bruising</td>
</tr>
<tr>
<td>others</td>
<td>impaired healing, weight gain, increased risk of infection</td>
</tr>
</tbody>
</table>
Directions of development

Developments of new steroid—Changes of structures

<table>
<thead>
<tr>
<th>Effectiveness ↑</th>
<th>ADR ↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding affinity</td>
<td>Route of administration</td>
</tr>
<tr>
<td>Delivery</td>
<td>Less mineralocorticoid action</td>
</tr>
</tbody>
</table>

- Rapid systemic metabolism
- Low oral bioavailability
- Proactive forms
Requirements for New AR Medications

**Effective**
- Fast acting
- 24-hour coverage
- No tachyphylaxis

**Minimal side effects**
- Little burning, drying, and bad taste
- No systemic side effects

**Comfortable to use**
- Less run out of nose
- Less drip down throat

Bioactivation of Ciclesonide and Fatty Acid Lipid Conjugation of Des-Ciclesonide

Ciclesonide (Inactive Parent Compound)

Des-Ciclesonide (Active Metabolite)

O-fatty acid esters

C-21-lipid conjugates

des-CIC: desisobutyryl-ciclesonide
CIC, Des-CIC vs Fluticasone Oropharyngeal Deposition

Steroid concentration in rinsing solution, nmol/L

Time, hours

CIC

des-CIC

FP

<table>
<thead>
<tr>
<th>Drug</th>
<th>R Binding Affinity</th>
<th>Lung delivery (%)</th>
<th>Protein binding (%)</th>
<th>Oral Bioavailability (%)</th>
<th>Systemic Clearance (L/h)</th>
<th>Distribution (L)</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate/17-monopropionate(^{b})</td>
<td>0.4/13.5</td>
<td>50–60</td>
<td>87</td>
<td>20/40</td>
<td>150/120</td>
<td>20/424</td>
<td>0.5/2.7</td>
</tr>
<tr>
<td>Budesonide</td>
<td>9.4</td>
<td>15–30(^{c})</td>
<td>88</td>
<td>11</td>
<td>84</td>
<td>280</td>
<td>2.8</td>
</tr>
<tr>
<td>Ciclesonide/de sciclesonide(^{b})</td>
<td>0.12/12.0</td>
<td>50</td>
<td>99/99</td>
<td>&lt;1/&lt;1</td>
<td>152/228</td>
<td>207/897</td>
<td>0.36/3.4</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>1.8</td>
<td>68</td>
<td>80</td>
<td>20</td>
<td>58</td>
<td>96</td>
<td>1.6</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>18</td>
<td>20(^{c})</td>
<td>90</td>
<td>≤1</td>
<td>66</td>
<td>318–859</td>
<td>7.8</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>23(^{d})</td>
<td>11(^{d})</td>
<td>99</td>
<td>&lt;1</td>
<td>53</td>
<td>152</td>
<td>5.0</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>3.6</td>
<td>22</td>
<td>71</td>
<td>23</td>
<td>45–69</td>
<td>103</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Metabolism of Ciclesonide in Human Nasal Epithelial Cells

Formulation Aspect of INCS; Hypotonic Intranasal Delivery System

**Hypotonic suspension**

- Shrinking matrix
- Adherence to nasal mucosa

- Longer retardation of ciclesonide on mucosa
- High local ciclesonide concentration and increased its absorption into mucosal tissue
- Increased des-CIC in mucosal tissue

**Isotonic suspension**

- Water diffuses with drug
- Collapse of matrix

- Rapid clearance into esophagus with drug diffusion
- Insufficient ciclesonide absorption
- Lower concentration of ciclesonide and des-CIC in mucosal tissue

Persistence of Hypotonic Ciclesonide Formulation in Rabbit Nasal Mucosa

Formulation-Dependent Run-off Into the Rabbit Esophagus


Statistical analysis not performed
### Formulation Aspect of INCS

#### Intranasal CS Formulation Comparisons

<table>
<thead>
<tr>
<th>Intranasal CS</th>
<th>BKC</th>
<th>Potassium Sorbate</th>
<th>Alcohol</th>
<th>Polysorbate</th>
<th>Propylene-glycol</th>
<th>CMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclesonide (Omnaris)</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Fluticasone propionate (Flixonase)</td>
<td>+</td>
<td></td>
<td>+*</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Triamcinolone acetonide (Nasacort AQ)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Mometasone furoate (Nasonex)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Budesonide (Rhinocort Aqua)</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Fluticasone furoate (Avamys)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

*BKC, benzalkonium chloride; CMC, carboxymethylcellulose

* Phenylethyl alcohol

Clinical Studies 1

Pivotal SAR Study
Efficacy and Safety of Ciclesonide Nasal Spray for the Treatment of Seasonal Allergic Rhinitis (SAR)

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER, PARALLEL-GROUP STUDY

SAR patients

Baseline Period
(Day -10 ~ -1)

Placebo (n=163)

Ciclesonide 200 μg/d QD (n=164)

Treatment Period
(Day 1 ~ 28)

Patient-assessed total nasal symptom score (TNSS)
Physician-Assessed overall Nasal signs and symptoms Severity (PANS)
Rhinconjunctivitis Quality-of-Life Questionnaire (RQLQ)
Adverse events

Significantly Improved rTNSS in SAR

Placebo:
-1.87

Ciclesonide 200μg/d:
-2.69

*P < 0.001 vs placebo

Change from Baseline in the Average of AM + PM reflective TNSS (Day1-28)

TNSS: Total Nasal Symptom Score (Runny nose, Congestion, Sneezing, Itching)

### Changes in Individual components of the TNSS

#### Improvement in Individual Symptom

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ciclesonide</th>
<th>Placebo</th>
<th>Treatment difference</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestion</td>
<td>-0.58 (0.04)</td>
<td>-0.32 (0.04)</td>
<td>0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Itching</td>
<td>-0.61 (0.04)</td>
<td>-0.41 (0.04)</td>
<td>0.20</td>
<td>0.002</td>
</tr>
<tr>
<td>Sneezing</td>
<td>-0.61 (0.05)</td>
<td>-0.41 (0.05)</td>
<td>0.20</td>
<td>0.003</td>
</tr>
<tr>
<td>Runny Nose</td>
<td>-0.63 (0.05)</td>
<td>-0.41 (0.05)</td>
<td>0.24</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TNSS: Total Nasal Symptom Score

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Clinical Studies 2

Pivotal PAR Study
Efficacy and Safety of Ciclesonide for the treatment of perennial allergic rhinitis (PAR)

**RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER, PARALLEL-GROUP STUDY**

**PAR patients**

**Baseline Period**
*(Day -14 ~ -1)*

**Placebo** *(n=233)*

**Ciclesonide 200 μg/d QD** *(n=238)*

**Treatment Period**
*(Day 1 ~ 42)*

- Patient-assessed total nasal symptom score (TNSS)
- Physician-assessed overall nasal signs and symptoms severity (PANS)
- Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ)
- Adverse events

Significantly Improved reflective TNSS in PAR

Change From Baseline in the Avg. of AM and PM Reflective TNSS (Days 1-42, ITT Population)

**Placebo**
-1.89

**Ciclesonide 200μg/d**
-2.51

*P < 0.001 vs. placebo


TNSS: Total nasal symptom score.
Changes in Individual Components of the TNSS

** Improvement in Individual Symptom

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ciclesonide</th>
<th>Placebo</th>
<th>Treatment difference</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestion</td>
<td>-0.55 (0.04)</td>
<td>-0.47 (0.04)</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Itching</td>
<td>-0.64 (0.04)</td>
<td>-0.46 (0.04)</td>
<td>0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sneezing</td>
<td>-0.65 (0.03)</td>
<td>-0.46 (0.03)</td>
<td>0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Runny Nose</td>
<td>-0.68 (0.04)</td>
<td>-0.50 (0.04)</td>
<td>0.17</td>
<td>0.001</td>
</tr>
</tbody>
</table>

TNSS: Total nasal symptom score.

Clinical Studies 3

Onset of Action
Onset of Action of Ciclesonide in SAR Treatment

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SINGLE-CENTER, PARALLEL-GROUP STUDY

Environmental Exposure Chamber (EEC) Single treatment

Screening Phase

Priming Phase

Placebo (n=251)

Ciclesonide 200μg/d QD (n=251)

iTNSS assessed at hourly intervals for 12hrs


* iTNSS: instantaneous Total Nasal Symptom Score
*Significant difference vs. placebo at 1 hour after administration

**Title:** Time to Onset of Action

*One-sided \( P \leq 0.025 \) versus placebo

iTNSS: instantaneous Total Nasal Symptom Score
Clinical Studies 4

Long-term Safety and Efficacy
Need for Long Term Safety and Efficacy Study

- Intranasal steroids: mainstay treatment for moderate-severe AR
- Dissatisfaction with AR medication
  - Long-term effectiveness and concern for tachyphylaxis
  - Concern for adverse effect, especially to intranasal steroids
- Intranasal Ciclesonide
  - Safe and effective in SAR and PAR up to 6 week duration
  - No long term safety, tolerability and efficacy data

Long Term Safety and Efficacy of Intranasal Ciclesonide

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER, PARALLEL-GROUP STUDY

Baseline Period (7-14 days)

Ciclesonide 200 μg/d (n=441)

Placebo (n=222)

Treatment Period (Day 1 to Week 48/52)

Treatment-emergent adverse events
Ocular exam: IOP, lens opacification
24-hour urine and plasma cortisol
24-hour reflective TNSS, PANS, RQOL


- IOP: intraocular pressure,
- TNSS: total nasal symptom score
- PANS: physician assessed nasal symptom
- RQOL: rhinoconjunctivitis quality of life questionnaire
Improvement of rTNSS and QOL

**24-Hr Reflective TNSS Over Days 2-365**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ciclesonide 200μg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean change from baseline in the average of 24-Hour reflective TNSS</td>
<td>-1.8</td>
<td>-2.3*</td>
</tr>
</tbody>
</table>

*P < 0.001 vs placebo

**RQLQ Assessment**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ciclesonide 200μg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean change from baseline</td>
<td>-0.88</td>
<td>-1.07*</td>
</tr>
</tbody>
</table>

*P = 0.003 vs placebo

Long-term Efficacy of Intranasal Ciclesonide

No Evidence of Tachyphylaxis

*One-sided $P \leq 0.025$ versus placebo

iTNSS: instantaneous Total Nasal Symptom Score

No Clinically Relevant Effects on HPA axis

24-Hour Urinary Free Cortisol at Endpoint

- **Placebo**
- **Ciclesonide 200μg/d**

Change from baseline in 24-hour urinary free cortisol (mg/day)

AM Spot Plasma Cortisol at Endpoint

- **Placebo**
- **Ciclesonide 200μg/d**

Change from baseline in plasma cortisol (mcg/dL)

* No significant difference between treatment groups

No Treatment Differences in Lens Opacity Findings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Ciclesonide</th>
<th>Treatment Difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intraocular Pressure</strong></td>
<td>-0.10 (0.16)</td>
<td>-0.00 (0.12)</td>
<td>-0.10 (-0.50, 0.30)</td>
</tr>
<tr>
<td>Nuclear Color</td>
<td>0.14 (0.03)</td>
<td>0.14 (0.02)</td>
<td>0.00 (-0.06, 0.06)</td>
</tr>
<tr>
<td>Nuclear Opalescence</td>
<td>0.08 (0.03)</td>
<td>0.11 (0.02)</td>
<td>-0.03 (-0.09, 0.03)</td>
</tr>
<tr>
<td>Posterior Subcapsular Cataract</td>
<td>0.02 (0.01)</td>
<td>0.01 (0.01)</td>
<td>0.01 (-0.01, 0.02)</td>
</tr>
<tr>
<td>Cortical Cataract</td>
<td>0.00 (0.02)</td>
<td>-0.01 (0.01)</td>
<td>0.01 (-0.02, 0.05)</td>
</tr>
</tbody>
</table>

*LS mean changes

Clinical Studies 5

ICS/INCS HPA-Axis Data
Intranasal Ciclesonide Co-administration with Inhaled FP-SAL in Allergic Rhinitis Patients

RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO- AND ACTIVE-CONTROLLED NON-INFERIORITY STUDY

Screening Phase

pre-ICS 24-hr cortisol profiles → Placebo nasal spray
ICS (FP/SAL) → post-ICS 24-hr cortisol profiles → Placebo nasal spray + ICS (n=75)

Ciclesonide nasal spray +ICS (n=75) → post-nasal spray + ICS 24-hr cortisol profiles → post-dexa 24-hr cortisol profiles

Change in plasma cortisol AUC (0-24 hr)


ICS: inhaled corticosteroid
FP/SAL: fluticasone propionate/ salmeterol


Mean Plasma Cortisol AUC (0, 24h)

No Additive Inhibitory Effects on the HPA axis


FP-SAL, fluticasone propionate-salmeterol
<table>
<thead>
<tr>
<th>Adverse Event Preferred Term</th>
<th>Placebo (n = 163)</th>
<th>Ciclesonide 200 µg/d (n = 164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>8.0%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Increased White Blood Cell Count</td>
<td>0.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Increased Blood Glucose</td>
<td>0.0%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>2.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Pharyngolaryngeal Pain</td>
<td>2.7%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Effective relief of rhinitis symptoms and quality of life
Maintained effectiveness over the full 24-hour dosing interval
Onset of action as early as 1 hr after administration
Decreased run-off into esophagus, less drying feeling and bad taste
No evidence of tachyphylaxis over 1 year treatment period
No clinically relevant differences in adverse events, systemic safety, and ocular examination
No additive effects on cortisol suppression when coadministered with [ICS+LABA]

Thank you!