Prevention of Respiratory Allergic Disease with Allergen Immunotherapy (AIT)

Allergenic Products Advisory Committee

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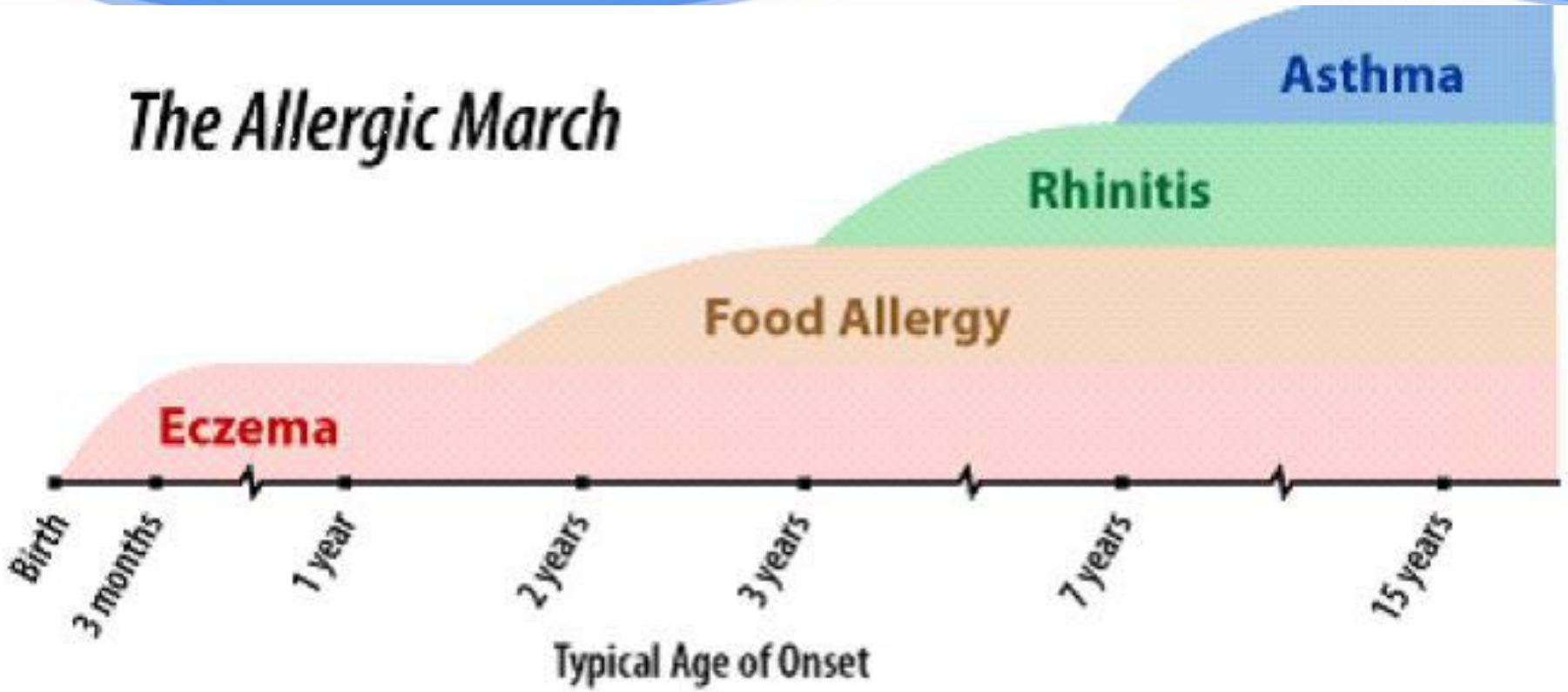
OUTLINE

- **Background**
- **Regulatory considerations**
- **Clinical development**
  - Efficacy
  - Safety
- **Summary**

Background



(Diagram courtesy of LEAP Study, Evelina Children's Hospital, London)

Investigators are exploring the administration of allergen immunotherapy ***EARLY*** in life to interrupt the progression of the allergic march to prevent asthma.

Study	Study Design	N = # of subjects; Age	Inclusion criteria	Treatment; Study duration
Learning Early About Peanut (LEAP) study suggests EARLY oral introduction of peanuts decreases risk of developing peanut allergy in infants at increased risk of peanut allergy.				
Du Toit et al. 2015; **L**earning **E**arly **A**bout **P**eanut study	Randomized, open-label, controlled	N=640; **4-11 months old**	Existing egg allergy and/or severe eczema	Consumed 6 grams peanut protein/week until 5 years of age

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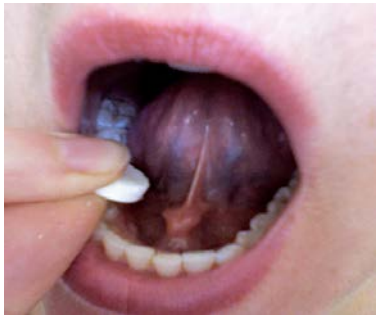
Examples of published studies that suggests AIT may decrease risk of developing asthma.				
Moller et al. 2001; **P**reventive **A**llergy **T**reatment study	Randomized, open-label, controlled	N=208; **6-14 years old**	Seasonal allergic rhinoconjunctivitis to grass and/or birch pollen; + Skin prick test to grass and/or birch only	3 year course of subcutaneous immunotherapy (SCIT) with grass/birch pollen extract with additional follow-ups at 5 and 10 years
Novembre et al. 2004	Randomized, open-label, controlled	N=113; **5-14 years old**	Seasonal allergic rhinoconjunctivitis to grass pollen + Skin prick test to grass only	4 months/year of sublingual immunotherapy (SLIT) with grass pollen extracts x 3 years

Potential routes of administration include:

Subcutaneous

Sublingual



Oral

Regulatory Considerations

Demonstration of effectiveness

- 21 CFR 201.57: "… all indications must be supported by substantial evidence of effectiveness."
- Expectation that demonstration of effectiveness is based on *adequate and well-controlled clinical studies*

Some characteristics of adequate and well-controlled studies include:

- Methods of selection of subjects provide adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed

- Methods of assessment of subjects' response are well-defined and reliable

Efficacy

Evaluating the effectiveness of AIT for prevention of asthma

- Selecting the trial population and control group
- Choosing criteria for asthma diagnosis and endpoints
- Defining the timing of the assessment of asthma endpoints

Evaluating the effectiveness of AIT for prevention of asthma

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Selecting the trial population

- In order to develop a product to prevent the development of asthma, subjects at increased risk for developing asthma need to be studied
- Start treatment EARLY for prevention of asthma
- Population of interest is infants and children < 5 years of age

Challenges of identifying target population

- Asthma is a heterogeneous disorder with variable expression influenced by many factors:

- Host
  - Genetic predisposition
  - Family history
  - Atopic dermatitis
  - Food allergy
  - Allergic rhinoconjunctivitis
  - Airway hyperresponsiveness
  - Sex
  - Race/ethnicity
  - Obesity
- Environmental
  - Allergic sensitization
    - Indoor allergens
    - Outdoor allergens
  - Tobacco smoke
  - Air pollution
  - Respiratory infections
  - Diet
  - Drugs
  - Socioeconomic status

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Evaluating the effectiveness of AIT for prevention of asthma

- Selecting the trial population and control group
- **Choosing criteria for asthma diagnosis and endpoints**
- Defining the timing of the assessment of asthma endpoints

Guidelines for diagnosing asthma in adults*

- Medical history of wheeze, shortness of breath, chest tightness, and cough
- Physical examination
- ***Spirometry*** that documents airflow limitation

*The National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) and Global Initiative for Asthma (GINA) guidelines

Special considerations for diagnosis of asthma in children < 5 years of age

- **Pulmonary function testing is difficult to perform**
  - Majority of children less than 5 years of age are unable to perform acceptable and reproducible spirometry
- **Not all children who wheeze develop asthma**

Common causes of wheezing in young children

- Asthma
- Viral upper respiratory tract infections
- Gastroesophageal reflux disease
- Obstructive sleep apnea
- Almost any respiratory disorder that leads to airway narrowing or obstruction can be associated with wheezing

Guidelines for diagnosing asthma in children < 5 years of age*

- Pattern of symptoms (e.g. wheeze, cough)
- Presence of risk factors for asthma
- Physical examination
- A therapeutic response to a 2-3 month trial of as-needed short-acting beta 2-adrenergic agonist and inhaled corticosteroids

*The National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) and Global Initiative for Asthma (GINA) guidelines

Additional tools to assist in the diagnosis of asthma in children < 5 years of age

- Tests for atopy:
  - Skin prick testing
  - Allergen-specific serum Immunglobulin E (IgE) testing
- Use of risk profile tools
  - Asthma Predictive Index (API)
  - Isle of Wight
  - Prevention and Incidence of Asthma and Mite Allergy (PIAMA) index
- Measure of the fraction of exhaled nitric oxide (FeNO)
- Imaging to exclude structural abnormalities

FeNO

- Normal reference values have been published for children aged 1-5 years
  - Van Der Heijden HH, Brouwer ML, Hoekstra, Van der Pol P, Merkus PJ. Reference values of exhaled nitric oxide in health children 1-5 years using off-line tidal breathing. Pediatr Pulmonol 2013; 49:291-5.

- FeNO has been shown to be elevated in eosinophilic airway inflammation

- An elevated FeNO in pre-school children with recurrent cough and wheeze is associated with a subsequent diagnosis of asthma

Evaluating the effectiveness of AIT for prevention of asthma

- Selecting the trial population and control group
- Choosing criteria for asthma diagnosis and endpoints
- **Defining the timing of the assessment of asthma endpoints**

Defining the timing of the assessment of asthma endpoints

- Depends on age of asthma diagnosis
- Consider number of years subjects need to be on treatment to assess the prevention of asthma
- If applicable, consider number of years subjects need to be off treatment

Study designs and endpoints based on age – examples

1) Continue clinical efficacy studies until children are able to perform pulmonary function testing (e.g. 5 years of age or older); or

2) Assess children < 5 years of age based on clinical symptoms and other laboratory tests or diagnostic tools (e.g. FeNO)

Safety

Safety monitoring in infants and young children

- Adverse events depend on the route of administrations
  - Oral and sublingual immunotherapy are more likely to be accepted by patients and parents than conventional subcutaneous immunotherapy
- Adverse reactions following oral and sublingual immunotherapy may be difficult to reliably detect and treat
  - Pruritus, mouth edema, throat irritation, and oropharyngeal pain
  - Risk of severe or fatal laryngopharyngeal swelling is greater due to narrow airways
  - Important to monitor for Eosinophilic Esophagitis (EoE)

Assessment of Eosinophilic Esophagitis in young children

- Reported adverse event that has been described with sublingual immunotherapy (SLIT) products
- Symptoms of EoE in infants and young children may be subtle and the disease may be unrecognized for years
- Definitive diagnosis involves invasive methods (e.g. endoscopy and esophageal biopsy)

Summary

- Clinical development of AIT products to prevent the development of asthma presents challenges including selection of the study population, criteria and timing of assessment of asthma endpoints, and safety monitoring in infants and young children.

- To support labeling, agreement is needed between the applicant and the FDA on the study design, study population and clinical parameters for demonstrating prevention of the development of asthma.