FDA Briefing Document
Allergenic Products Advisory Committee

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Prevention of Respiratory Allergic Diseases with Allergen Immunotherapy

1.0 Introduction

Allergen immunotherapy (AIT) has been referred to by the Joint Task Force on Practice Parameters as the administration of specific allergen(s) to patients with IgE-mediated conditions for the purpose of attenuating the allergic symptoms and inflammatory reactions associated with natural exposure to the allergen(s) (1). Accumulating evidence from epidemiologic, clinical and pathophysiological studies suggests that the upper and lower airways share a common inflammatory response to allergen triggers, and that the onset of sensitization and/or atopic dermatitis often predates the development of clinical respiratory disease (2). This understanding has raised interest in the use of AIT products and protocols to modulate the allergic response prior to the onset of clinical respiratory allergic disease, with a focus on prevention of asthma[1].

Preliminary published evidence supports the concept that administration of AIT to individuals with allergic rhinoconjunctivitis (ARC) can prevent the development of asthma. For example, in a multicenter, prospective, randomized, open-label study of children with ARC who were skin prick positive to grass and/or birch pollen, fewer children developed asthma after 3 years of treatment with AIT products compared to standard therapy alone (odds ratio 2.52; 95% CI: 1.3-5.1) (4). Such findings have sparked global interest in developing AIT products to prevent the onset of asthma in pediatric populations.

During this meeting, Committee members will be asked to discuss general concepts pertaining to the development of AIT intended to prevent allergic respiratory disease with a focus on asthma. For biological products, including allergenic products, all indications must be supported by substantial evidence of effectiveness with an expectation that the evidence is derived from adequate and well-controlled studies. The effectiveness of AIT for the prevention of asthma should be demonstrated through conducting clinical endpoint studies. The target population of interest is an age group prior to a diagnosis of asthma, including infants and children less than 5 years of age. No product-specific information will be discussed by the Agency during this Allergenic Products Advisory Committee meeting.

In conceptualizing the design of studies in this population, the Agency has identified several challenges:

- Developing criteria for diagnosing asthma in children under 5 years of age who cannot reliably perform spirometry testing
- Reliable identification of children at high risk for development of asthma
- Defining the appropriate period of observation for determining the effectiveness of the product for the prevention of asthma
- Considerations for safety monitoring for adverse reactions associated with AIT in infants and children less than 5 years of age

[1] For the purposes of this document, the term "asthma" refers to allergic asthma, defined by IgE mediated hypersensitivity to environmental allergens (3).

2.0 Clinical Development of AIT for the Prevention of Asthma

2.1 Efficacy Studies

As described above, studies of allergenic products for the prevention of asthma are expected to be adequate and well-controlled with clinical endpoints to support the proposed indication. Studies should be prospective, randomized, blinded and controlled, with a primary endpoint based on case definitions that are clearly defined and consistently applied throughout the study. In addition, the study would need to be adequately powered to detect a clinically meaningful reduction of asthma in the treated group relative to the control group using pre-specified criteria for "success." In conceptualizing the design of a clinical endpoint study for the demonstration of prevention of asthma that meets this standard, the Agency has identified several key challenges as described below.

Selection of Trial Population

To achieve adequate power to detect a clinically meaningful treatment difference in the prevention of asthma between the investigational product and control arms of AIT studies, it is anticipated that subjects at high risk for developing asthma will need to be enrolled.

The challenges in identifying children at risk for developing asthma are highlighted by the fact that recurrent wheezing commonly occurs in children less than 5 years of age. According to long-term, prospective birth cohort studies, up to 50% of young children below the age of 3 years will have at least one episode of wheezing, while roughly 60% of these children will not be diagnosed with asthma at school age (5). In addition, asthma is a heterogeneous disorder with variable expression. Both environmental and host factors influence asthma development and expression; these include family history, allergic sensitization, atopic dermatitis (AD), ARC, sex, obesity, exposure to tobacco smoke, and infection (e.g. respiratory syncytial virus and rhinovirus). Prospective longitudinal studies of population-based birth cohorts indicate that young age at onset, presence of severe symptoms in early childhood, allergic sensitization, atopic dermatitis, ARC, respiratory infection and family history of asthma correlate with persistent asthma (6).

As described in Section 1.0, investigators are exploring the administration of AIT to interrupt the often-observed clinical progression of individual patients from AD to ARC to asthma. This progression has sometimes been referred to as the "atopic march" (also called "allergic march" (7). Evidence from both cross-sectional and longitudinal studies supports the concept of "atopic march." For example, a pooled meta-analysis of 13 prospective cohort studies reported an odds ratio for the risk of asthma after AD, compared to children without AD, of 2.14; 95% CI: 1.67-2.75 (8). Some authors have proposed that young children with evidence for sensitization to aeroallergens or food may be an appropriate population to study whether an early intervention can attenuate or prevent the "atopic march" (9).

Multiple risk profile tools have been developed to identify children at high risk of developing persistent asthma symptoms, including the Asthma Preventive Index (API), Isle of Wight and the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Index (10). Each of these indices varies with respect to the number of risk factors queried and statistical criteria for

determining a 'positive' result. The PIAMA risk score is estimated to be the most sensitive, while the API is the most specific (10). In order to improve the sensitivity of the API, there have been several modifications, such as substituting the clinical diagnosis of allergic rhinitis with objective testing for allergic sensitization, or including fraction of exhaled nitric oxide (FeNO) (11, 12).

Criteria for Asthma Diagnosis and Endpoints

The primary endpoint for a clinical study to support licensure should be based on an asthma case definition that is prospectively specified and applied consistently; the case definition should be well-accepted as clinically meaningful. The pathophysiology of asthma and challenges in the diagnosis of asthma complicate attempts to develop a case definition for asthma in infants and young children. Since asthma is diagnosed by a history of respiratory symptoms, associated with bronchial hyperresponsiveness varying in intensity over time, the National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma – Full Report 2007 (EPR-3) emphasizes that the diagnosis of asthma should include objective measurements of pulmonary function obtained before and after a patient inhales a short-acting bronchodilator (13). Although spirometry tests can be reliably used in most children as young as 5 years of age, the majority of children less than 5 years of age are unable to perform acceptable and reproducible spirometry.

Since there are no objective tests to diagnose asthma with certainty in children less than 5 years of age, current clinical practice guidelines (EPR-3, Global Initiative for Asthma (GINA) 2015, PRACTALL 2008) recommend that clinicians diagnose asthma based on the pattern of symptoms, physical examination, and therapeutic response to a 2-3 month trial of as-needed, a short-acting beta 2-adrenergic agonist, and inhaled corticosteroids (5, 13, 14). Marked clinical improvement during treatment and deterioration when treatment is stopped, support a diagnosis of asthma (5, 13, 14).

Potential approaches to evaluating efficacy of products for prevention of asthma in children less than 5 years of age could include:

1) Clinical efficacy studies for prevention of asthma that would continue until children are able to perform pulmonary function testing (after 5 years of age); or

2) Shorter-term follow-up (i.e., through less than 5 years of age) clinical efficacy studies that would rely on an asthma diagnosis based on symptoms and potentially other laboratory tests (e.g. FeNO) with adjudication by a committee with appropriate expertise.

2.2 Safety Evaluation

Evaluation of safety to support FDA approval of AIT intended for prevention of asthma in children younger than 5 years of age presents unique and challenging issues. Common adverse reactions to AIT may be difficult to monitor in young children, which may prevent or delay the recognition of severe adverse reactions. In an effort to improve the tolerability of AIT in young children, sublingual, oral and/or nasal routes of administration may be investigated. Specifically,

with regard to products administered by the sublingual or oral routes, monitoring for common adverse reactions, such as pruritus, mouth edema, throat irritation and oropharyngeal pain may be difficult for parents and investigators to reliably detect and assess in infants and young children. Furthermore, the risk of severe or fatal adverse reactions involving laryngopharyngeal swelling may be higher because of the small caliber of airways in infants and young children.

Finally, monitoring for occurrence of eosinophilic esophagitis (EoE), a chronic inflammatory, immune/antigen-mediated esophageal disease and known complication of SLIT and oral immunotherapy, will be an important component of the study design for these products. The detection of EoE in a clinical trial can be challenging for a variety of reasons. The clinical presentation of EoE in children may be subtle and include nonspecific symptoms (failure to thrive, feeding difficulty, nausea, vomiting, and heartburn); childhood subclinical disease may be unrecognized for years (15). Definitive diagnosis of EoE involves invasive methods such as endoscopy and esophageal biopsy.

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