

# A Novel Human Fusion Protein for the Treatment of Allergic Diseases

## **Overview**

Drug Name	JZ-603			
Description	JZ-603 is a human fusion protein that co-aggregates the high-affinity			
	immunoglobulin E (IgE) receptor FcεRI to inhibit the IgE-mediated release of			
	inflammatory mediators from mast cells and basophils.			
	JZ-603 is in preclinical development as a dry-powder formulation to be			
	administered by nasal inhalation for the treatment of IgE-mediated allergic			
	diseases, such as allergic asthma and allergic rhinitis.			
Target	IgE			
Drug Modality	Fusion protein			
Indication	Allergic asthma and allergic rhinitis			
Product Category	Anti-IgE therapy			
Mechanism of Action	Regulating IgE-mediated signaling pathways			
Status	Preclinical			
Patent	Granted			

## **Collaboration Opportunity**

Protheragen Inc. is actively seeking partnership for JZ-603. Potential collaboration can be strategic alliance, licensing, or marketing agreement.

We look forward to hearing from you.

# **Target**

#### **IgE**

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Introduction	IgE is a type of immunoglobulins that is located predominantly in tissues and firmly attached to effector cells such as mast cells and basophils through IgE Fc receptors. IgE plays a key role in triggering release of inflammatory modulators are securificated as a contract of the securificated and the securificated and the securificated as a securification as a securificated as a securificat				
	resulting in manifestation of symptoms associated with allergic reactions, such as allergic rhinitis, asthma and eczema.				
Approved Name	Immunoglobulin heavy constant epsilon				
Official Symbol	IGHE				
Gene Type	Immunoglobulin gene				
Synonyms	IgE				
Ensembl	ENSG00000211891				
Gene ID	<u>3497</u>				
Refseq	NG 001019				
OMIM	<u>147180</u>				
UniProt ID	<u>P01854</u>				
Chromosome Location	14q32.33				

#### **Clinical Resources**

Pathway	IgE elicits an immune response by binding to one of two Fc receptors. The high
	affinity receptor FcɛRI is expressed on mast cells and basophils. Aggregation of
	antigens and binding of IgE to the mast cell FcɛRI results in degranulation and the
	release of mediators from the cells, and binding to FccRII on basophils causes
	release of IL-4, IL-13, and other inflammatory mediators. The low affinity receptor
	FcɛRII is constitutively expressed on B cells and inducibly expressed by IL-4 on
	macrophages, eosinophils, platelets, and T cells.
Major Conditions	Allergic diseases, chronic rhinosinusitis, nasal polyp, etc.

# **Drug Modality**

#### **Fusion Protein**

JZ-603 is a human Fc $\gamma$ -Fc $\epsilon$  fusion protein composed of the Fc region of human IgG1 linked to the Fc portion of human IgE by an amino acid linker, which competes with IgE for the binding to Fc $\epsilon$ RI. JZ-603 has the potential

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to treat allergic diseases by inhibiting IgE-mediated signal transduction pathways. Based on the protein dry powder technology, JZ-603 can be administered through nasal inhalation, directly to the lungs, with rapid onset of action, improved drug utilization, and reduced dose required for treatment.

#### Indication

#### **Allergic Asthma and Allergic Rhinitis**

Asthma is an immune-mediated inflammatory disease of the airway wall in which inflammation, goblet cell metaplasia, and physiological as well as pathological airway remodeling lead to bronchial smooth muscle hyperreactivity and airway obstruction. According to the Global Burden of Disease (GBD) study, there were about 262.4 million prevalent cases and 37.0 million incident cases of asthma worldwide in 2019. Allergic asthma is the most common type of asthma, which develops most frequently in childhood. Allergic asthma is triggered by inhaled allergens such as dust mites, pet dander, pollen, mold. Allergy testing can be used to determine which allergens trigger symptoms in individuals with allergic asthma.

Allergic rhinitis is an inflammation of the mucus membranes of the nose that occurs in response to an airborne allergen. This allergic disease is characterized by frequent or repetitive sneezing, runny or congested nose, and itchiness of the nose, eyes and throat. Allergic rhinitis is a highly prevalent chronic disease, affecting 10-40% of the population. In the United States, allergic rhinitis is the most common chronic disease in children and the fifth most common chronic disease in Americans, affecting approximately 60 million people annually.

Allergic rhinitis and allergic asthma can cause intense discomfort and restrict the activities of sufferers. The treatment of a patient with allergic rhinitis and allergic asthma involves identification of the allergen and removing them when possible. In addition, long- or short-term drug therapy or allergen immunotherapy may be required.

### **Mechanism of Action**

#### **Regulating IGE-mediated Signaling Pathways**

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Immunoglobulin E (IgE) is a key mediator of the pathogenesis of allergic asthma and allergic rhinitis, at the top of the allergic cascade. Exposure to an allergen in a susceptible individual causes T lymphocytes to become activated and send a signal to B lymphocytes, initiating the production of IgE antibodies. For each allergen, specific IgE antibodies are produced within a few weeks after the first exposure, and some of them bind to high-affinity FcɛRI receptors on mast cells and eosinophils. Mast cells in the skin and mucosal layers of the respiratory tract contain the inflammatory mediators that cause the symptoms of allergic asthma and allergic rhinitis, including histamine, leukotrienes, and prostaglandins. These mediators are released whenever the allergen crosslinks mast cell-bound IgE through the process of degranulation. Re-exposure to the allergen causes mast cells in the nose and sinuses to be activated by IgE antibodies.

JZ-603 is designed to inhibit IgE-mediated signaling. It is able to compete with IgE for the binding to FcεRI by aggregating FcεRI with FcγRIIb containing an immunoreceptor tyrosine-based inhibition motif on allergic effector cells.

#### **Status**

#### The Status of JZ-603

Pharmacodynamic, toxicological, and pharmacokinetic studies have been completed. The IND application is expected to be submitted within 2 years.

	Discovery/Optimization	Preclinical	Phase I	Phase II	Phase III
JZ-603					

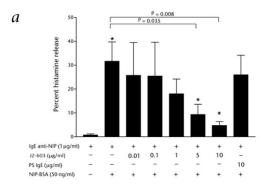
# **Data**

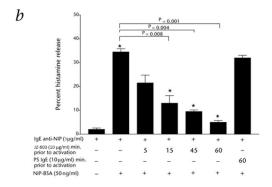
**Inhibition of Basophil Histamine Release** 

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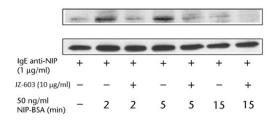
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Basophils were sensitized with 1  $\mu$ g/ml human anti-NIP IgE, plus doses of JZ-603 ranging from 0.01 to 10  $\mu$ g/ml for 1 hour before activation with 50 ng/ml NIP-BSA (Fig. a). Myeloma IgE (PS myeloma) was used as a control. It was found that 1  $\mu$ g JZ-603 at 1  $\mu$ g/ml inhibited almost half of histamine release, whereas at 10  $\mu$ g/ml JZ-603 gave an average of 84% inhibition. 10  $\mu$ g of non-specific PS IgE only decreased histamine release by 19%. Adding the JZ-603 at the same time as the IgE anti-NIP gave optimal inhibition. The longer the delay in JZ-603 addition following sensitization with IgE anti-NIP, the less the inhibition (Fig. b). The results show that the inhibition of antigen-driven histamine release induced by JZ-603 is dependent on time and dosage.



#### Inhibition of FcgRI-mediated Syk Phosphorylation

Tyrosine phosphorylation of Syk is a critical step in human mast cell and basophil mediator release. Cross-linking Fc $\epsilon$ RI on human basophils with IgE directed to NIP (4-hydroxy-3-iodo-5-nitrophenylacetyl) and NIP-BSA induces substantial tyrosine phosphorylation of Syk, which was markedly reduced in cells pre-incubated with JZ-603. Thus, co-aggregation of Fc $\gamma$ RII and Fc $\epsilon$ R1 by JZ-603 inhibits IgE-mediated Syk phosphorylation, which may contribute to the inhibition of histamine release.

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