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 and 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	3497
Refseq	NG_001019
OMIM	147180
UniProt ID	P01854
Chromosome Location	14q32.33

Clinical Resources

Pathway	IgE elicits an immune response by binding to one of two Fc receptors. The high affinity receptor FcεRI is expressed on mast cells and basophils. Aggregation of antigens and binding of IgE to the mast cell FcεRI results in degranulation and the release of mediators from the cells, and binding to FcεRII on basophils causes release of IL-4, IL-13, and other inflammatory mediators. The low affinity receptor FcεRII 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 Fcγ-Fcε 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 FcεRI. JZ-603 has the potential

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

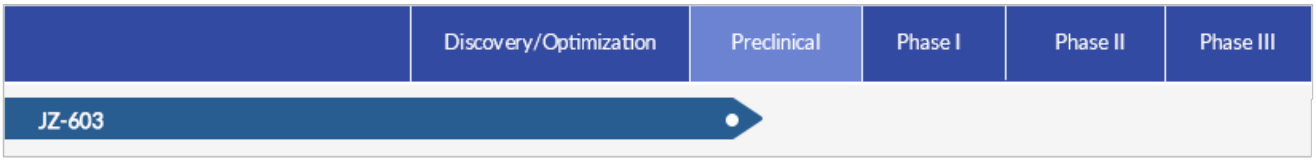
Regulating IGE-mediated Signaling Pathways

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 FcεRI 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.



Data

Inhibition of Basophil Histamine Release

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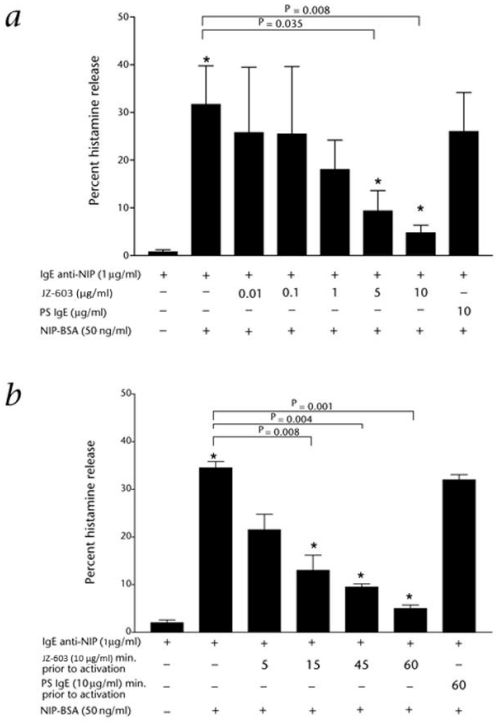
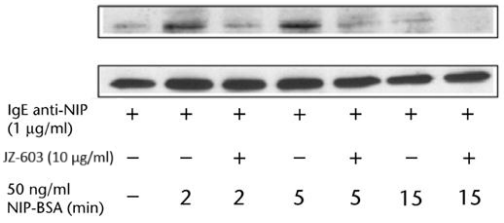


Basophils were sensitized with 1 μg/ml human anti-NIP IgE, plus doses of JZ-603 ranging from 0.01 to 10 μg/ml for 1 hour before activation with 50 ng/ml NIP-BSA (Fig. a). Myeloma IgE (PS myeloma) was used as a control. It was found that 1 μg JZ-603 at 1 μg/ml inhibited almost half of histamine release, whereas at 10 μg/ml JZ-603 gave an average of 84% inhibition. 10 μg 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 FcεRI-mediated Syk Phosphorylation

Tyrosine phosphorylation of Syk is a critical step in human mast cell and basophil mediator release. Cross-linking FcεRI 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 FcγRII and FcεR1 by JZ-603 inhibits IgE-mediated Syk phosphorylation, which may contribute to the inhibition of histamine release.

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