

## A Small Molecule Agonist Targeting VISTA

### Overview

<b>Drug Name</b>	Compound-0056
<b>Description</b>	VISTA, or V-type immunoglobulin domain-containing suppressor of T-cell activation, is a negative checkpoint regulator expressed on naïve T cells. Compound-0056 is an agonist binding to extracellular domain protein of VISTA via virtual screening based the homology modeling. Compound-0056 can inhibit the inflammatory response of T cells and the transformation of naive T cells by enhancing the function of VISTA protein. In addition to psoriasis, compound-0056 can be developed as treatments for other autoimmune diseases.
<b>Target</b>	V-domain Ig suppressor of T cell activation (VISTA)
<b>Drug Modality</b>	Small molecule
<b>Indication</b>	Psoriasis
<b>Product Category</b>	Checkpoint receptor agonist
<b>Mechanism of Action</b>	Enhancing the function of VISTA to suppress T cell-mediated immune responses
<b>Status</b>	Preclinical
<b>Patent</b>	Granted

### Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for compound-0056. Potential collaboration can be strategic alliance, licensing, or marketing agreement.

We look forward to hearing from you.

### Target

#### V-domain Ig Suppressor of T Cell Activation (VISTA)

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<b>Introduction</b>	VISTA is an immunoregulatory receptor primarily expressed on naive T lymphocytes, which inhibits the T cell response and maintain peripheral tolerance. As a type I transmembrane protein of approximately 50kDa, VISTA consists of a single N-terminal immunoglobulin (Ig) V domain, a stalk, a transmembrane domain, and a cytoplasmic tail.
<b>Approved Name</b>	V-set immunoregulatory receptor
<b>Official Symbol</b>	VSIR
<b>Gene Type</b>	Protein coding
<b>Synonyms</b>	Stress induced secreted protein 1; V-domain Ig suppressor of T cell activation; PDCD1 homolog
<b>Ensembl</b>	<a href="#">ENSG00000107738</a>
<b>Gene ID</b>	<a href="#">64115</a>
<b>mRNA Refseq</b>	<a href="#">NM_022153</a>
<b>Protein Refseq</b>	<a href="#">NP_071436</a>
<b>OMIM</b>	<a href="#">615608</a>
<b>UniProt ID</b>	<a href="#">Q9H7M9</a>
<b>Chromosome Location</b>	10q22.1

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## Clinical Resources

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<b>Gene Function</b>	Unlike other negative checkpoint regulators identified to date, VISTA is expressed on naive T cells and genetic deletion of VISTA culminates in T cell-mediated autoimmunity. Studies have shown that within the naive T cell compartment, loss of VISTA disrupted the major quiescent naive T cell subset and enhanced self-reactivity.
<b>Pathway</b>	Cell adhesion molecules (CAMs); NF-kappaB Signaling
<b>Major Conditions</b>	Ichthyosis, congenital, autosomal recessive 6, and monckeberg arteriosclerosis

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## Drug Modality

### Small Molecule

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Compound-0056 is a small molecule agonist with high VISTA affinity, screened out from thousands of chemical compounds through two rounds of screening and binding affinity verification.

## Indication

### Psoriasis

Psoriasis is a chronic, immune-mediated, inflammatory disorder, primarily involving the skin and joints. It affects approximately 2-3% of the world population. It is generally accepted that an interaction between components of innate and adaptive immune systems and resident cutaneous cells is associated with the pathogenesis of psoriasis.

According to results of the global burden of disease (GBD) study, there were more than 58 million prevalent cases of psoriasis worldwide in 2013. Other studies estimated a much higher prevalence of >125 million worldwide. Psoriasis generally does not impair patients' normal functions, but has significant negative impact on self-esteem and social interaction.

Conventional topical treatments for psoriasis have a favorable efficacy/safety ratio but with a suboptimal treatment adherence. Systemic agents, including cytotoxic agents, immunosuppressants, retinoids, fumaric acid esters, and phototherapy, are preferred for the disease that generally does not respond to topical therapies.

## Mechanism of Action

### Enhancing VISTA Function to Suppress T Cell-mediated Immune Responses

Psoriasis is considered to be a T cell-dependent autoimmune disease and the IL-23/Th17/IL-17 axis plays an important role. Resident dendritic cells (DCs) in psoriatic lesions secrete IL-23 and TNF-alpha, cytokines involved in Th17 cell (CD4+ T cell subset) generation. Produced by the Th17 cells, IL-17 and IL-22 drive the chronic cutaneous inflammation, together with tumor necrosis factor (TNF)-alpha.

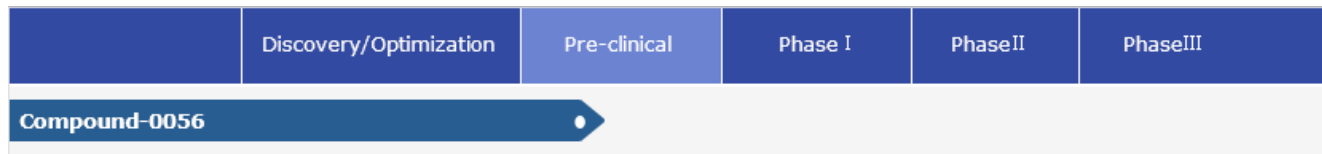
Previous studies have reported that VISTA controls the production of IL-23 in DCs and suppresses activation of

an array of immune cell types, such as CD4+ and CD8+ T cells, and Foxp3+CD4+ Tregs. Compound-0056, as an agonist, can enhance the anti-inflammatory function of VISTA to benefit the treatment of psoriasis.

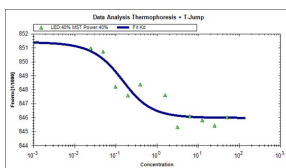
## Status

### The Status of Compound-0056

Pharmacodynamics tests in vitro and in vivo have been applied to assess the therapeutic effect of compound-0056 in treating psoriasis.

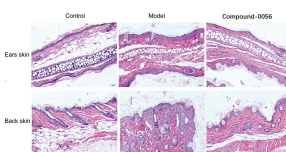


## Data



### Compound-0056's Kd Value for VISTA-ECD Protein

The binding rate of compound-0056 with VISTA was 10.44%, determined by ELISA. Microscale Thermophoresis (MST) was performed to further evaluate compound-0056's Kd value. The calculated Kd value for compound-0056 with human VISTA-ECD was  $12.60 \pm 3.84 \mu\text{M}$ .



### Histopathological Evaluation in Mice Psoriasis Model

H&E staining showed that mice psoriasis model induced applying Imiquimod to the skin resulted in vasodilation, infiltration of inflammatory cells, and increased epidermal thickening. Compared with the Model group, mice skin thickness was

significantly reduced and inflammatory symptoms was significantly improved in Compound-0056 group.

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