Novel Phosphodiesterase 9 Inhibitor for the Treatment of Heart Failure

Overview

Drug Name	BioLink2022
Description	Phosphodiesterase 9 (PDE9), a specifically hydrolytic enzyme with the highest affinity for cyclic guanosine monophosphate (cGMP) among the phosphodiesterase family, controls cGMP in cardiac myocytes and is strongly upregulated in human heart failure, suggesting its potential as a promising therapeutic target in heart failure. BioLink2022 is a highly selective oral PDE9 small molecule inhibitor in early clinical development for the treatment of chronic heart failure.
Target	PDE9
Drug Modality	Small molecule
Indication	Heart failure
Product Category	Inhibitor
Mechanism of Action	Inhibiting PDE9 to regulate cGMP level
Status	Phase I
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for BioLink2022. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

PDE9

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Introduction	The family of phosphodiesterases (PDEs) are regulatory hydrolase enzymes that play a crucial role in modulating cyclic nucleotides, including cGMP and cAMP, which are involved in a wide range of physiological processes. Eleven phosphodiesterase subfamilies have been identified. Among all PDEs, PDE9 has the highest affinity for cGMP, making it an attractive target for inhibitors that regulate cGMP levels. PDE9 has a high affinity for cGMP (Km = 70 nM) and a high selectivity for cAMP (Km = 230 μM). The subtype PDE9A is the only known form of the PDE9 enzyme. The human PDE9A gene is located on chromosome 21q22.3 and encompasses more than 20 exons spanning 122 kb. More than 20 splice variants of PDE9A have been identified, exhibiting distinct subcellular distributions, which allow for modulation of cGMP degradation in microdomains and fine control of specific signal transduction pathways.
Approved Name	Phosphodiesterase 9A
Official Symbol	PDE9A
Gene Type	Protein coding
Synonyms	HSPDE9A2
Ensembl	ENSG00000160191
Gene ID	5152
mRNA Refseq	NM_001001567
Protein Refseq	NP_001001567
OMIM	602973
UniProt ID	O76083
Chromosome Location	21q22.3

Drug Modality

Small Molecule

BioLink2022 is an orally bioavailable small molecule. It is a potent PDE9 inhibitor that characterized by high selectivity, low brain penetration, and target tissue distribution. Preclinical data showed that BioLink2022 remarkably improved cardiac function and reversed ventricular remodeling in heart failure.

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Indication

Heart Failure

Heart failure is a serious condition and a major cause of morbidity and mortality worldwide. The condition can be caused by any structural or functional abnormality that leads to elevated intracardiac pressure or to reduced cardiac output, whether at rest or during stress. As a result, cardiac output is inadequate to meet the body's metabolic needs and/or to accommodate venous return. Heart failure occurs when a sufficient number of myocardial cells are lost following injury or insult to the heart, such as that caused by ischemic heart disease, hypertension or diabetes. Heart failure may develop as a result of left- and/or right-sided ventricular failure. Left-sided heart failure is further divided into heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF).

According to the Global Burden of Disease (GBD) study, the total number of patients with heart failure worldwide was 61.7 million in 2013, and the number of patients with heart failure worldwide increased 96.4% from 1990 to 2013. More than half of those were classified as severe. Heart failure morbidity is closely associated with disease severity. In patients with mild and well controlled disease, the disease can have little or no effect on quality of life. However, severe heart failure can limit even simple activities and generally proves fatal. In 2018, heart failure was the underlying cause in 83,616 deaths in the United States and was a contributing factor in 366,464 deaths, according to the American Heart Association.

Drug therapy is the mainstay of treatment for all patients with heart failure but should be accompanied by lifestyle modification (e.g., severe sodium restriction) and, if necessary, surgical intervention or device implantation. Although there is no definitive cure for heart failure, drugs can improve cardiac function and relieve symptoms, significantly prolonging survival and improving quality of life for patients.

Mechanism of Action

Inhibiting PDE9 to Regulate cGMP Level

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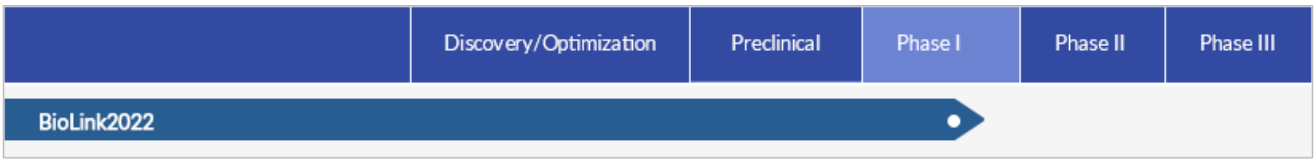
The cyclic nucleotides cAMP and cGMP participate in the main pathways regulating cardiac and vascular functions and they act as second messengers for sympathetic and parasympathetic systems, nitric oxide (NO) and natriuretic peptides (NPs). The cardioprotective effect of NPs released in response to increased ventricular stretch in heart failure is mediated by the cGMP. PDE9 has the greatest affinity for cGMP of all the PDEs with specific affinity for the NP/cGMP signaling pathway. PDE9 is strongly upregulated in human heart failure and catabolizes cGMP leading to reduced intracellular cGMP concentration, suggesting that inhibition of PDE9 activity is a promising therapeutic target in heart failure. BioLink2022 inhibits PDE9 activity to increase circulating cGMP levels, promoting cGMP signaling.

Status

The Status of BioLink2022

BioLink2022 is being evaluated in the phase 1 clinical study in the United States for safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy volunteers.



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