A Histamine Receptor H3 Antagonist for the Treatment of Excessive Daytime Sleepiness

Overview

Drug Name	PTH-0349
Description	PTH-0349 is a histamine receptor H3 antagonist currently in clinical development for the treatment of excessive daytime sleepiness in patients with obstructive sleep apnea. This small molecule can regulate various neurobehavioral functions of the central nervous system and has the potential to treat multiple central and peripheral nervous disorders. The completed clinical trial showed that PTH-0349 had favorable pharmacokinetic characteristics and safety, and no addiction risk.
Target	Histamine receptor H3 (HRH3)
Drug Modality	Small molecule
Indication	Excessive daytime sleepiness
Product Category	Antagonist
Mechanism of Action	Binding to the HRH3 to inhibit its mediated physiological processes
Status	Phase 2
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for PTH-0349. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

Histamine Receptor H3 (HRH3)

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Introduction	Four histamine receptor subtypes (H1, H2, H3 and H4) have been identified, which are all G-protein-coupled receptors. Among them, histamine receptor H3 (HRH3) couples to Galphai/o proteins, resulting in inhibition of cAMP formation, consequent enhancement of calcium mobilization, and activation of MAPKs and ion channels. The HRH3 is expressed primarily in the nervous system. It can act as a presynaptic autoreceptor and control histamine turnover or as a heteroreceptor in dopamine-, serotonin-, norepinephrine-, GABA- and ACh-containing neurons. Activation of HRH3 depresses adrenergic neurotransmission in the mesenteric artery and attenuates spinal cord- or medulla oblongata-stimulated pressor and tachycardic responses. HRH3 modulation may be effective in the treatment of narcolepsy. The HRH3 may also play a role in memory formation and pharmacological blockage of central H3 receptors has been shown to enhance cognition suggesting a potential efficacy for these agents in the treatment of cognitive dysfunction in Alzheimer's disease.
Approved Name	histamine receptor H3
Official Symbol	HRH3
Gene Type	gene with protein product
Synonyms	GPCR97
Ensembl	ENSG00000101180
Gene ID	11255
mRNA Refseq	NM_007232
Protein Refseq	NP_009163
OMIM	604525
UniProt ID	Q7Z7D3
Chromosome Location	20q13.33

Clinical Resources

Pathway	adenylate cyclase-inhibiting G protein-coupled acetylcholine receptor signaling pathway, cAMP metabolic process, chemical synaptic transmission, cognition, etc.
Major Conditions	Narcolepsy; Sleep disorder; Obesity; Cognitive disorders

Drug Modality

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Small Molecule

PTH-0349 is a small molecule antagonist with independent intellectual property. The pharmacokinetic studies in vivo showed that PTH-0349 can be completely absorbed orally, with a high exposure level. PTH-0349 could penetrate the blood-brain barrier and exhibited a wide distribution throughout the body. After multiple administrations, no accumulation was observed. Additionally, no significant inhibition or induction of the CYP450 enzymes by PTH-0349 was observed, nor were drug-drug interactions observed.

Indication

Excessive Daytime Sleepiness

According to the International Classification of Sleep Disorders, Third Edition, Text Revision (ICSD-3-TR), excessive daytime sleepiness (EDS) is defined as the inability to remain awake and alert during the main waking period of the day, and the occurrence of unintentional or inappropriate sleep almost every day for at least 3 months. Patients with EDS have difficulty maintaining wakefulness or alertness at appropriate times during the day, thus experiencing functional impairment. EDS can occur secondary to sleep deprivation, the effects of medication, the use of illegal substances, obstructive sleep apnea (OSA), and other medical and psychiatric conditions. EDS caused by a primary hypersomnia of central origin such as narcolepsy and idiopathic hypersomnia is less common.

EDS is the most common symptom of OSA. An estimated 936 million adults worldwide suffer sleep apnea of any severity, 425 million of whom have moderate to severe apnea. OSA is the most common form of sleep apnea, accounting for approximately 85% of all cases. The American Academy of Sleep Medicine reported in 2016 that approximately 5.9 million adults in the United States were diagnosed with OSA, and an additional 23.5 million people remained undiagnosed with this condition. OSA is a sleep disorder caused by obstruction of the upper respiratory tract, which leads to episodes of breathing cessation (apnea) or reduced airflow (hypopnea). These events cause repeated hypoxia and repeated awakenings from sleep.

Mechanism of Action

Binding to HRH3 to Inhibit Its Mediated Physiological Processes

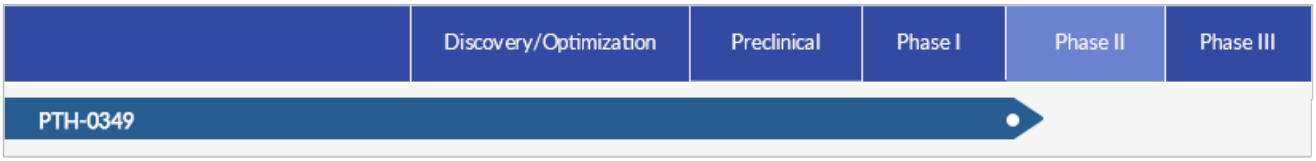
The histamine system plays a crucial role in promoting and maintaining a state of wakefulness. Histamine receptor H3 (HRH3) functions as an autoreceptor, inhibiting the synthesis and release of histamine. It also functions as an heteroreceptor, regulating the release of other important neurotransmitters, including dopamine, acetylcholine, norepinephrine, serotonin, gamma-aminobutyric acid, glutamate, and substance P. Histaminergic neurons interact anatomically and functionally with hypocretin neurons, and this interaction has been found to play an important role in the pathophysiological process of hypersomnia. Studies on patients with excessive daytime sleepiness have confirmed the reduction of histamine turnover and the impairment of histaminergic neurotransmission.

The HRH3 controls the release, synthesis, and turnover of histamine, as well as the neural activity of histaminergic cells. The HRH3 is expressed on neurons of the cerebral cortex, hippocampus, amygdala, nucleus accumbens, globus pallidus, striatum, and hypothalamus, and is widely distributed throughout the central nervous system. Therefore, the specific characteristics and location of HRH3 provide favorable conditions for it to become the most promising target for the treatment of sleep-wake disorders.

Status

The Status of PTH-0349

In the preclinical studies, PTH-0349 showed a significant arousal-promoting effect on C57BL/6J mice, and the duration of this effect was 1 to 9 hours. In the Phase I clinical trial, results from single ascending dose (SAD) and multiple ascending dose (MAD) studies indicated that PTH-0349 exhibited a favorable safety and tolerability profile.



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