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Fact Sheet

GIBH117

A Therapy for Treating Resistant Strains of Malaria

Innovation in the DDP

GIBH's Drug Candidate 117 for the Treatment of Malaria

Product Description

GIBH-117 belongs to a new class of antimalarial drugs developed to combat the rising levels of drug-resistant strains of P. falciparum. Compound 117 is an aspartic protease inhibitor with selectivity for plasmepsins, which play key roles in the survival of the parasite in its human host. Drug 117 spares human aspartic proteases (BACE, CatD and CatE), has moderate stability in human liver microsomes and is orally bioavailable in rats with a half-life of 2.9 h. GIBH-117 represents a promising lead as a new antimalarial drug with a low molecular weight, modest lipophilicity, antimalarial potency, protease selectivity, and oral bioavailability in rats

Indication and Market

In 2009, 225 million cases of malaria resulted in 781,000 deaths according to the World Health Organization. Recent estimates place the malaria death toll at 1 to 1.5 million annually. Significant strides towards eradication were made during the early to mid-1900s via the introduction of fast-acting antimalarial agents such as chloroquine, sulphadoxinepyrimethamine and other antimalarial drugs. However, the rise of resistance to chloroquine and other antimalarial drugs led to a resurgence of the disease in the developing world during the latter half of the 20th century. Therefore, it is crucial that additional antimalarial drugs be developed with novel mechanisms of action as the next line of defense to combat developing resistance to known drugs.

Product Rationale

The Plasmodium parasite has a complex lifecycle including sexual replication in the mosquito stage and asexual replication in the human liver and blood stages. These lifecycle stages involve numerous potential opportunities for intervention. Plasmodium has multiple aspartic proteases (termed "plasmepsins") that play key roles in the survival of the parasite in its human host. Recently discovered plasmepsin V (PM-V) is expressed in the endoplasmic reticulum and is an essential protein for the survival of the parasite as it is responsible for the processing of hundreds of proteins, many of which are essential themselves, destined for export into the host's red blood cells. Thus, there is an opportunity for exploiting the potential of aspartic protease inhibition of plasmepsins as novel and potent antimalarial drugs.

Preclinical Development

Lead compound 117 demonstrates antimalarial activity in the SYBR Green assay of P. falciparum 3D7 strain-infected red blood cells and has equivalent potency against the multi-drug resistant Dd2 strain of P. falciparum. Compound 117 demonstrated dose dependent efficacy in P. chabaudi ASS (Chloroquine sensitive line) and P. chabaudi ASCQ (Chloroquine resistant line) murine suppressive models of malaria. Once a day oral dosing of compound 117 suppressed parasitemia at a similar level as CQ. No significant side effects were observed following dosing of compound 117 in rodents other than a modest increase in animal activity.

Intellectual Property

GIBH has filed intellectual property rights for composition of matter, production and medical use of compound 117 for the treatment of malaria and other diseases mediated by parasites that employ aspartic proteases in their life cycle.

Product

GIBH-117 is a non-peptidic small molecule that falls well within the drug-like chemical space (MW < 400 and a cLogP of < 4).

Indication

Primary: Malaria

Secondary: Aspartic acid requiring parasites

Design

Compound 117 is formulated as a tablet suitable for oral dosing.

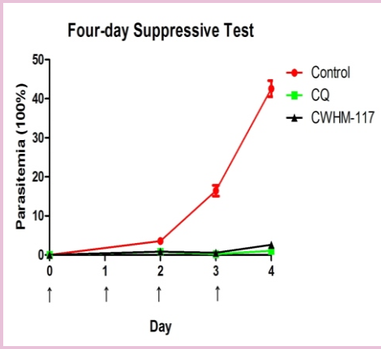
Development Status

Lead optimization: Preclinical proof-of-concept in industry-standard models of malaria established. Candidate selection of the drug is scheduled for 2013 and IND filing is to be initiated in 2014.

Commercialization Strategy

Commercial partners are being sought for development and marketing in Asia and Africa.

Proof of Concept in rodent malaria model



Evaluation of compound 117 in P. chabaudi ASS, mouse model. 4-day suppressive test. Arrows represent day of dosing.