Pharmacokinetics and Pharmacodynamics of GBT440, a Novel Hemoglobin S Polymerization Inhibitor for the Treatment of Sickle Cell Disease, in Healthy Volunteers and SCD Patients

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Introduction

Sickle cell disease (SCD) is an inherited disorder caused by a point mutation in the β-globin gene leading to the formation of hemoglobin S (HbS). A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of deoxymethemoglobin S into long, rigid polymer (HbS) oligomers and the resulting sickling of red blood cells (RBCs). Sickling and/or polymerization has been demonstrated to increase oxidative stress, inflammation, and sickle cell damage, resulting in progression and organ damage with a clinical course of lifelong pain, morbidity, and early death. A drug that inhibits HbS polymerization and has a good pharmacodynamic profile has the potential to provide efficacy. Because hemolytic anemia is a patient inhibitor of HbS polymerization, reduction of hemoglobin S into nonpolymerizable HbF on a steady-state basis is likely to slow efficacy. GBT440, an orally administered, small-molecule drug used to slow cell destruction, was developed by hemolytic anemia and nonpolymerizable HbF, leading to progressively worsening organ damage with a clinical course of lifelong pain, morbidity, and early death.

Purpose

To determine the Pharmacokinetics of GBT440 in Healthy Volunteers and SCD patients.

To evaluate Oxygen Equilibrium Curves in a pharmacodynamic model.

To determine Hb and F relationship

Pharmacokinetic Model of GBT440

Methods

SI blood

Carboxyhemoglobin (COHb) and oxyhemoglobin (HbO2) concentrations from whole blood samples were determined using a co-oximeter. Hemoglobin (Hb) and hematocrit (Hct) were measured using a hemoglobinometer (Cobas C501, Roche Diagnostics, Indianapolis, IN). The results were expressed as percentage of the normal value.

Dose and Patients

Healthy volunteers and SCD patients were enrolled in a phase 1 clinical trial. Healthy volunteers were enrolled with a single dose of 500 mg of GBT440 and SCD patients were dosed with either a single dose of 100 mg and with multiple doses of 500 mg and 700 mg of GBT440 for 14 days.

Analysis of Blood and Plasma GBT440 Concentrations

Concentrations of GBT440 in whole blood and plasma were determined using validated LC-MS methods. Concentrations of GBT440 in RED were calculated using the GBT440 concentrations in blood and plasma.

In vivo Hemolytic

GBT440 (in red blood cells) was administered at 700 mg or 1000 mg orally (PO) to 6 volunteers who were enrolled in a phase 1 clinical trial. Hemolytic SCD patients were administered at 700 mg or 1000 mg PO. Plasma concentrations were determined using LC-MS methods. Hemolysis was determined using a hemolysis assay (DMM, Inc., Cambridge, MA) and compared to a positive control (hemolytic SCD patients treated with 700 mg PO). Point of care analysis was carried out using a point of care hematology analyzer

Clinical Hemolysis

Blood samples collected in vacutainers containing ethylenediaminetetraacetic acid (EDTA). Hemolysis was determined using a hemolysis assay (DMM, Inc., Cambridge, MA) and compared to a positive control (hemolytic SCD patients treated with 700 mg PO). Point of care analysis was carried out using a point of care hematology analyzer

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Oxygen Equilibrium Curves of GBT440 in SS Blood and the Correlation to % Hb modification

Pharmacokinetics Studies

GBT440 demonstrates linear, dose-proportional PK in Healthy Volunteers and SCD patients (see poster P271). GBT440 has a half-life of 2.9 and 1.6 days in Healthy Volunteers and SCD Patients, respectively, which supports once daily dosing.

The relatively high hSCV in SCD patients (40%) compared to Healthy Volunteers is likely due to differences in RBC turnover and hemolytic rates.

At the predicted therapeutic range (10-30 Hb modification), pO2 is a more sensitive indicator of the GBT440-induced left shift in the HbO2 than pH.

A dose-dependent decrease in pO2 and pH is observed, indicating that increasing GBT440 blood levels lead to increased oxygen affinities.

% Hb modification using GBT440 PK/blood levels is a good predictor of changes in oxygen affinity based on OECs measurements.