Absorption, Metabolism, and Excretion of GBT440, a Novel Hemoglobin S (HbS) Polymerization Inhibitor for the Treatment of Sickle Cell Disease (SCD), in Healthy Male Subjects

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INTRODUCTION

- GBT440 is an oral, once-daily therapy that modulates hemoglobin affinity for oxygen, thereby inhibiting hemoglobin polymerization in sickle cell disease
- The goal of this open-label study is to determine the absorption, metabolism, and elimination routes of GBT440

METHODS

Clinical study design
- The pharmacokinetics, mass balance, and metabolite profile of [14C]GBT440 were evaluated in 7 healthy male subjects
- To evaluate the disposition kinetics of GBT440 at steady-state concentrations, a loading/maintenance dose schedule was used
- Each subject received an oral loading dose of 2000 mg GBT440 on day 1 followed by oral maintenance doses of 400 mg once daily from days 2 to 4
- Once the target steady-state was achieved, a single [14C]GBT440 400 mg dose (approximately 100 µCi) was administered orally on day 5
- Blood, plasma, urine, and feces were collected serially to day 27 or when subjects met the discharge criteria

Analysis of blood and plasma GBT440 concentrations
- Blood and plasma samples were analyzed for GBT440 concentrations using liquid chromatography-tandem mass spectrometry
- The analytical range was 50 to 100,000 ng/mL for blood and 10 to 20,000 ng/mL for plasma samples
- GBT440 concentration in red blood cells (RBCs) was calculated from the whole blood and plasma concentrations and hematocrit values

Determination of total radioactivity
- Total radioactivity (TRA) levels in whole blood, plasma, urine, and feces samples were measured using liquid scintillation counting (LSC)
- Whole blood and homogenized feces samples were submitted to combustion analysis before LSC
- Plasma and urine samples were analyzed directly by LSC
- TRA in RBCs was derived from the whole blood and plasma TRA data and hematocrit values

RESULTS AND DISCUSSION

Pharmacokinetics (Figure 2; Table 1)
- After oral administration, GBT440 reached maximum concentration (C max) in plasma and whole blood with median time to maximum concentration (T max) values of 2 hours
- GBT440 rapidly partitions into the RBC with high specificity with blood/plasma ratio of ~32.1, which corresponded to an RBC/plasma ratio of ~7:1
- After reaching C max, GBT440 concentrations decreased in a monophasic manner, with terminal elimination phase
- The major metabolic pathway was via phase 1 and phase 2 metabolism
- Because GBT440 was not excreted directly into the urine, the pharmacokinetics are unlikely to be affected in patients with renal disorders

Metabolite identification in plasma, whole blood, urine, and feces (Figures 4 and 5)
- Whole blood
  - In whole blood, most of the TRA was unchanged GBT440 (97.5%), whereas 3 metabolites accounted for the remaining TRA (2.5%)
  - Two potential active metabolites (M5, M6) were identified but only accounted for 2.5% of the dose in whole blood
- Plasma
  - In plasma, unchanged GBT440 was the prominent circulating radioactive component, accounting for 48.8% of the TRA
  - There was 1 major phase 2 metabolite (M2, GBT440 O-dealkylation-sulfation), accounting for 16.8% of the TRA

CONCLUSIONS
- Although GBT440 has high specific binding to hemoglobin, it was completely excreted from the body, with a T 1/2 of approximately 3 days in healthy subjects
- Because the T 1/2 of GBT440 was much shorter than RBC HbA (120 days), this supports the hypothesis that the binding between GBT440 to hemoglobin is a reversible process
- After an oral administration, approximately one third of the dose was excreted as the unchanged drug into the plasma (unabsorbed and/or via biliary excretion)
- Two thirds of the administered dose was metabolized and excreted into urine and feces
- The major metabolic pathway was via phase 1 and phase 2 metabolism
- Because GBT440 was not excreted directly into the urine, the pharmacokinetics are unlikely to be affected in patients with renal disorders

Disclosure

All authors are employed by and have equity ownership in Global Blood Therapeutics.

Figure 2. Proposed pharmacokinetic model of GBT440

Figure 3. Mass balance study

Table 1. Mean (NCV) pharmacokinetic parameters of GBT440 in healthy male subjects after oral dosing of 400 mg (100 µCi) [14C]GBT440 at steady state

Figure 4. Representative radio-choratograms of pooled blood (A), plasma (B), urine (C), and feces (D)

Figure 5. Proposed Metabolic Pathways of GBT440