The Pharmacokinetics (PK) of GBT440 are Similar in Adolescents and Adults with Sickle Cell Disease (SCD)

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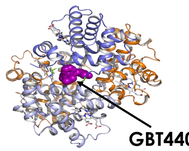
INTRODUCTION

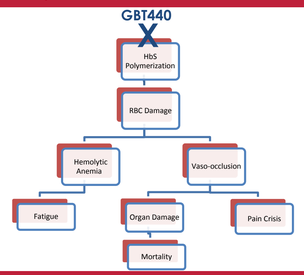
- Sickle cell disease (SCD) is a genetic disorder resulting in the production of mutated hemoglobin S (HbS) that upon deoxygenation, polymerizes and distorts red blood cells (RBCs) resulting in sickled RBCs, hemolysis and vaso-occlusion
- SCD is a congenital hemoglobinopathy with disease beginning in childhood; approximately 50% of SCD prevalence is in the pediatric population
- GBT440 is an oral, once-daily therapy that modulates hemoglobin (Hb) affinity for oxygen, thereby inhibiting polymerization in SCD (Figures 1 and 2)
- GBT440-007 is an ongoing Phase 2a study in pediatrics (6 to 17 years). The data presented are a summary of the analysis of the single dose adolescent cohort (12 to 17 years) and represents the first evaluation of GBT440 in a pediatric population

Figure 1. GBT440: Designed to Bind Hemoglobin with High Selectivity



- Reversible covalent binding to N-terminus of hemoglobin α chain → stabilizes oxy-Hb conformation
- Profile confirms properties with high selectivity for hemoglobin
  - 1:1 stoichiometry of GBT440 to Hb tetramer binding
  - Preferential partitioning into RBCs
  - Potent, dose-dependent increase in Hb-O_2 affinity

Figure 2. GBT440 Inhibits HbS Polymerization, the Fundamental Cause of SCD Pathophysiology



GBT440-007 PART A STUDY OBJECTIVES

PRIMARY OBJECTIVE

To characterize the pharmacokinetics (PK) of GBT440 in whole blood and plasma following a single dose in pediatrics with SCD

SECONDARY OBJECTIVE

To evaluate the safety and tolerability of GBT440 following a single dose in pediatrics with SCD

PK OBJECTIVES

- To compare GBT440 PK properties in adults to those observed in the pediatric population
- To support dose selection in ongoing studies evaluating safety and efficacy of GBT440 in pediatric patients
- To select doses for pediatrics (6 to 17 years) based on PK data and population PK (PPK) modeling to achieve similar exposures to the two doses (900 mg and 1500 mg) which are currently being investigated in the pivotal Phase 3 HOPE study

METHODS

Figure 3. GBT440-007 Study Design

Part A – Single Dose

- Adolescents (12 to 17 years) GBT440 600 mg
- Children (6 to 11 years) GBT440 600 mg

Part B – Multiple Doses

- Adolescents (12 to 17 years) 900 mg daily for 24 weeks
- Adolescents (12 to 17 years) 1500 mg daily for 24 weeks

Key Inclusion Criteria

- Male or female age 6 to 17 with HbSS or HbS β^0 thal
- Participants taking hydroxyurea (HU)/hydroxycarbamide needed to be on a stable regimen (at least 3 months)
- Written informed parental/guardian consent and subject assent

Key Exclusion Criteria

- Any of the following requiring medical attention within 14 days of signing the informed consent:
  - Vaso-occlusive crisis (VOC)
  - Acute chest syndrome (ACS)
  - Splenic sequestration crisis
  - Dactylitis
- Requires chronic transfusion therapy or within 30 days prior to consent
- History of stroke or two TCD measurements ≥200 cm/sec

PK Methods

- Samples for PK analysis of GBT440 were collected at pre-dose and at 2, 8, 24 hours (Day 2), 48 hours (Day 3), 96 hours (Day 5), 168 hours (Day 8) and 336 hours (Day 15)
- Concentrations of GBT440 were determined in whole blood and plasma using validated liquid chromatography with tandem mass spectrometry (LC-MS-MS) assays

METHODS (CONTINUED)

- A noncompartmental PK analysis using Phoenix® WinNonlin® Version 6.4.0 was performed using all available samples collected
- PPK models for whole blood and plasma were developed for adolescents using the same model structure (2-compartment model with1st order absorption) as the adult PPK models (Figure 4) using NONMEM v. 7.3
- A large number of virtual individuals (14,000) simulated from the adult PPK model (2.5th and 97.5th percentile of simulated data) were created and the adolescent's PK data from the single dose study were overlaid for comparison
- Allometric scaling of central clearance and volumes were used to estimate doses expected to provide GBT440 exposures similar to those observed in adults

RESULTS

To date, adolescents have completed Part A of GBT440-007 and data are summarized below.

Table 1. Baseline Characteristics

	Part A n=7
Female (n) Male (n)	4 3
Age (years, median, range)	16 (14 to 16)
Body Weight (kg, median, range)	52.8 (45 – 66)
Genotype (%)	HbSS (100%)
Concurrent Hydroxyurea/Hydroxycarbamide Use, n (%)	5 (71%)
Baseline Hb (g/dL, median, range)	8.2 (7.5 – 10.2)
Hospitalizations due to painful crisis in prior year: n (%)	
0	5
≥ 1	2

Safety Results

- GBT440 was well tolerated following a single dose of GBT440 600 mg
- No serious or severe adverse events related to study drug were observed
- Two treatment-related Grade 1 adverse events (flatulence and nausea) were reported

PK Results

- Following a single oral dose of GBT440, maximum concentrations (C_{max}) in whole blood and plasma were reached at 24 hours and 2 hours, respectively (Table 2)
- GBT440 concentrations decreased in a monophasic manner, with a half-life ($T_{1/2}$) in whole blood of 32 hours and plasma of 43.5 hours (Figure 5 and Table 2)
- In adolescents, high RBC:plasma partitioning was observed which is consistent with high specificity for binding to hemoglobin and data observed in adults
- Based on dose normalization and simulations, the PK of GBT440 in adolescents following a single dose of 600 mg were similar to those expected in adults (Figure 6)
- The same model structure used to describe the adult GBT440 concentration profiles in whole blood and in plasma was used to describe the concentration profiles in adolescents (a 2-compartment model with first order absorption and elimination). Overall, the model predictions are aligned with the observed concentration profiles (Figure 7)
- Daily doses of 900 mg and 1500 mg, which are currently being evaluated in the pivotal Phase 3 HOPE study were selected to be evaluated in adolescents in Part B of this study and exposures are expected to be similar to those observed in adults (Figure 8)

Figure 4. Goodness of Fit Plot and Visual Predictive Check (VPC) for the Adult PPK Model

Figure 4a

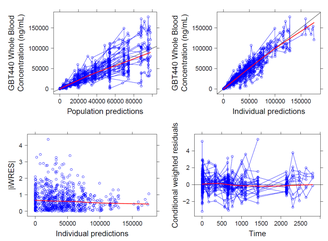
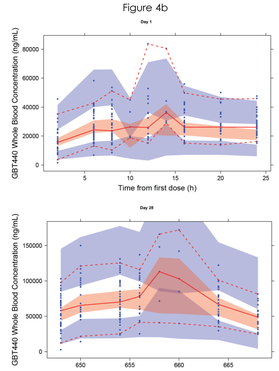


Figure 4b



Goodness of fit plots (Figure 4a) indicate that the adult PPK model describes the data adequately with little model bias. The prediction corrected VPC (Figure 4b) shows the model fit and observed data on Day 1 and after 28 days of dosing.

Note: In Figure 4a, each symbol represents a single observation connected by lines for each patient. The red line is a local regression smooth.
In Figure 4b, the shaded regions encompass 90% of the simulated values of the predicted medians (coral), 5th (blue) and 95th (blue) percentiles.

GBT440 Adult Population PK (PPK) Model Description

- The PPK of GBT440 in adults with SCD was best described by a two-compartment model with first-order absorption and first-order elimination. Key model parameters are summarized in Table 3
- The PPK model included estimates of between-subject variability on apparent clearance (CL/F) and apparent volume (V/F). A combined proportional plus additive residual error model was used
- The prediction-corrected visual predictive check (VPC) and goodness of fit diagnostic plots for the whole blood model indicate that the model describes the data adequately (Figure 4)

Table 2. GBT440 Whole Blood and Plasma Noncompartmental PK Parameters Following A Single Dose of GBT440 600 mg in Adolescents

PK Parameters	GBT440 in Whole Blood	GBT440 in Plasma
C_{max} (µg/mL)[a]	24.2 (47.7%)	2.08 (30.7%)
T_{max} (hour)[b]	24.0	2.00
AUC_t (hr•µg /mL)[a]	1671.6 (38.2%)	114.8 (17.6%)
$T_{1/2}$ (hour)[c]	32.4 ± 5.79	43.5 ± 5.07

AUC_t = area under to the time of the last quantifiable concentration ; C_{max} = maximum observed blood concentration; T_{max} = time-average maximum; $T_{1/2}$ = time needed for concentration to reduce by half (half-life)
[a]Values reported as geometric means (percent %CV) [b] Median [c]Values reported as arithmetic means ± SD

Figure 5. GBT440 Whole Blood and Plasma Concentration-Time Profiles Following A Single Dose of GBT440 600 mg in Adolescents

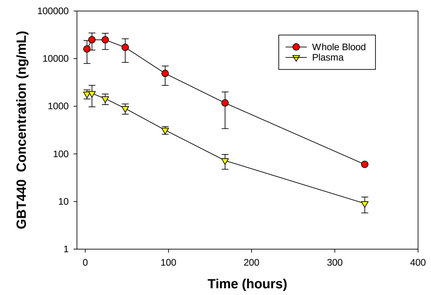
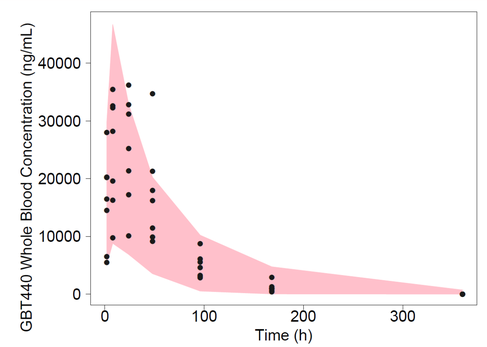


Table 3. PPK Model Parameter Estimates for GBT440 in Adults and Adolescents with SCD

PK Parameters	GBT440 in Whole Blood Adults (RSE %)	GBT440 in Whole Blood Adolescents (RSE %)
CL/F (L/h)	0.43 (5)	0.37 (13)
V/F (L)	21.4 (6)	15 (17)
Ka (1/h)	0.34 (13)	0.19 (30)
$T_{1/2}$ (h)	34.5	28.1
	GBT440 in Plasma Adults (RSE %)	**GBT440 in Plasma Adolescents (RSE %)**
CL/F (L/h)	7.63 (5)	5.4 (6)
V/F (L)	373 (5)	329 (7)
Ka (1/h)	2.83 (14)	1.37
$T_{1/2}$	33.9	42.2

CL /F = apparent clearance, Ka = absorption rate constant, RSE = relative standard error, V/F = apparent volume of distribution; $T_{1/2}$ = half-life; L= liters; h= hours

Figure 6. Comparison of Adult (95% Simulated Prediction Intervals, in pink) and Adolescent (Observed, black circles) GBT440 Whole Blood Exposures Following a Single Dose of GBT440 600mg



The external model validations shown above indicate good agreement between observed adolescent PK data and simulated adult PK profiles following a single dose of GBT440 600 mg.

RESULTS (CONTINUED)

Figure 7. Individual GBT440 Whole Blood Concentration-Time Profiles (black circles) overlaid with Individual (red line) and Population Predictions (blue line) for the Adolescent PPK Model

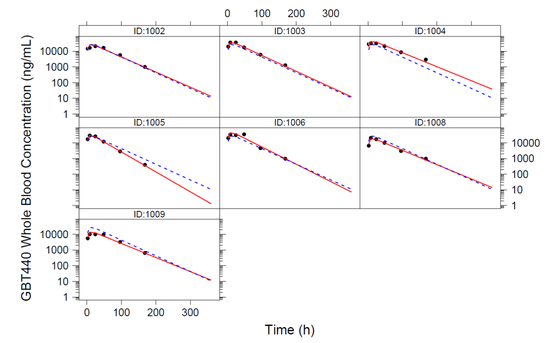
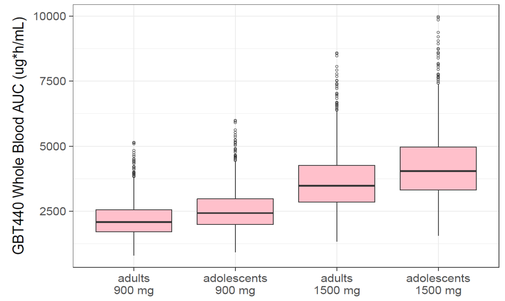


Figure 8. Simulations of Whole Blood GBT440 Exposures Following 900 mg and 1500 mg in Adults and Adolescents



CONCLUSIONS

- GBT440 was well tolerated following a single dose (600 mg) in adolescents
- PK exposures and half-life for GBT440 were similar in adults and adolescents and continue to demonstrate excellent PK properties with half-life supporting once daily dosing and a high RBC partitioning which is consistent with a high specificity for hemoglobin
- Based on the PK and safety data, daily doses of 900 mg and 1500 mg were selected to be evaluated in adolescents in Part B of this ongoing study which are the same doses currently being investigated in the pivotal Phase 3 HOPE study
- Single dose PK results from this study support:
  - Ongoing multiple dosing in adolescents in this current study exploring treatment effects on hematologic, transcranial doppler (TCD) and other parameters
  - Adolescent enrollment in the pivotal Phase 3 HOPE study
- This PPK model will be used to simulate PK parameters to support future GBT440 dose selection for evaluation in the younger pediatric population (9 months to < 12 years)

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