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 clinical complications (pain, fatigue, and vaso-occlusive crises) that are under-recognized and undertreated.

OBJECTIVES AND STUDY DESIGN

- To evaluate safety, pharmacokinetics and pharmacodynamics of GBT440, a novel HbS polymerization inhibitor
- To determine the dosage and timing of GBT440 in sickle cell disease (SCD) patients
- To evaluate the effect of GBT440 on clinical markers of hemolysis and anemia

RESULTS

- All SCD patients (N = 41) receiving GBT440 for up to 6 months have shown hematologic response (Hb, reticulocytes, and/or bilirubin; see Table 2)
- Profound and durable reduction in hemolysis and peripheral blood sickle cells (see Table 3)
- 40% of patients demonstrated a clinically significant increase in Hb-O2 affinity, increased O2 delivery to the tissues of peripheral blood sickle cells (P < 0.001)
- Greater than a 70% median decrease in irreversibly sickled cells
- The treatment response data are consistent with a selective inhibition of Hb polymerization

Efficacy

- All SCD patients (N = 41) receiving GBT440 for up to 6 months have shown hematologic response (Hb, reticulocytes, and/or bilirubin; see Table 2)
- Profound and durable reduction in hemolysis and peripheral blood sickle cells (see Table 3)
- 40% of patients demonstrated a clinically significant increase in Hb-O2 affinity, increased O2 delivery to the tissues of peripheral blood sickle cells (P < 0.001)
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- The treatment response data are consistent with a selective inhibition of Hb polymerization

SAFETY AND TOLERABILITY

- No sickle cell crises events while on study drug
- All treatment-related AEs were Grade 1 or 2 in severity (see Table 4)
- No evidence of tissue hypoxia
- No increase in exposure to sickle cell crisis
- No treatment-related AEs have occurred with dosing beyond 90 days

CONCLUSION

- Long-term dosing up to 6 months continues to show favorable safety profile
- GBT440 treatment leads to a rapid, profound, and durable reduction in hemolysis and sickled cells in all SCD patients dosed to date
- Supports in vivo inhibition of polymerization
- Significant proportion of patients achieve large Hb response (> 1 g/dL)
- Results support Phase 3a trial design study
- Supports primary endpoint of hemoglobin response (1 g/dL)
- Key secondary objective is to demonstrate translation to clinical benefit towards SCD symptom exacerbations (refer to Poster #K507)

Acknowledgments

- The authors wish to thank all the healthy volunteers and the sickle cell patients, families, caregivers, and healthcare providers
- The authors wish to thank the following contributors:
  - Global Blood Therapeutics: Allison Intondi, Theresa Thuener, Brian Metcalf
  - Attali: Michel, Brian, Magee, Paul
  - Kings’ College Hospital: Timothy Mant, Kenneth Bridges, Claire Hemmaway, Jonal Lohrer-Grauer, Jonathan Dufu
  - Global Blood Therapeutics: Allison Intondi, Theresa Thuener, Brian Metcalf

Disclosure

- Jo Howard, Claire Jane Hemmaway, Paul Telfer, Mark Layton, Moji Awogbade, and Jake Potter have no conflict of interest.
- Timothy Mant is currently employed by Quintiles. Sandeele Warren, Kobina Dufu, Athlith Hutcheechelaha, Margaret Tonda, Kenneth Bridges, Chooneram, and Joshua Lohrer-Grauer are currently employed by and have equity ownership of Global Blood Therapeutics.