



# Study to Evaluate the Effect of GBT440 in Pediatrics With Sickle Cell Disease

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## Main Information

**Primary registry identifying number**

LBCTR2019090195

**Protocol number**

GBT440-007

**MOH registration number**

1288/ص

**Study registered at the country of origin**

Yes

**Study registered at the country of origin: Specify****Type of registration**

Retrospective

**Type of registration: Justify**

Requested by Sponsor- Registry not in place upon study initiation

**Date of registration in national regulatory agency**

11/06/2014

**Primary sponsor**

Global Blood Therapeutics Inc.

**Primary sponsor: Country of origin**

United States of America

**Date of registration in primary registry**

12/10/2022

**Date of registration in national regulatory agency**

11/06/2014

**Public title**

Study to Evaluate the Effect of GBT440 in Pediatrics With Sickle Cell Disease

**Acronym****Scientific title**

A Phase 2a, Open-label, Single and Multiple Dose Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Exploratory Treatment Effect of GBT440 in Pediatric Participants With Sickle Cell Disease

**Acronym****Brief summary of the study: English**

This study consists of three parts, Parts A, B, C and D.  
- Part A is a single dose PK study in pediatric participants with Sickle Cell Disease. (Closed on 07 Aug 2017 (LPLV))  
- Part B is a multiple dose, safety, exploratory, efficacy, and PK study in adolescent Sickle Cell Disease participants who were 12-17 years of age (Closed on 04 Jan 2019 (LPLV))  
- Part C is a multiple dose, safety, tolerability, and PK study, which includes the assessment of hematological effects and the effect on TCD flow velocity of GBT440 in pediatric participants with Sickle Cell Disease who are 4 to 17 years of age.  
- Part D is a multiple dose study that will assess the safety, tolerability, and PK, as well as the hematological effects, of voxelotor in pediatric participants with SCD 6 months to < 4 years of age.

**Brief summary of the study: Arabic**

عند الأطفال المصابين بمرض الخلايا المنجلية GBT440 دراسة لتقييم تأثير

**Health conditions/problem studied: Specify**

Sickle Cell Disease





## Interventions: Specify

Drug: GBT440 administered as oral capsules, tablets, dispersible tablets or powder for oral suspension.

## Key inclusion and exclusion criteria: Inclusion criteria

1. Male or female participants with homozygous hemoglobin SS (HbSS) or hemoglobin S beta0 thalassemia (HbS  $\beta$ 0 thal).
2. Age:
  - Part A – 6 to 17 years of age (Cohort 1 [12 to 17] and Cohort 2 [6 to 11] as defined in the Study Design)
  - Part B – 12 to 17 years of age
  - Part C – 4 to 17 years of age
  - Part D – 6 months to < 4 years of age
3. Hydroxyurea (HU) therapy:
  - Parts A, B, and C – A participant taking HU may be enrolled if the dose has been stable for at least 3 months with no anticipated need for dose adjustments during the study and no sign of hematological toxicity.
  - Part D – A participant taking HU may be enrolled if the dose has been stable for at least 1 month. Titration to the maximum tolerated dose (MTD) is allowed during the study.
4. Hemoglobin (Hb):
  - Part A – No restriction
  - Part B – Hb  $\leq$  10.5 g/dL
  - Part C – Hb  $\leq$  10.5 g/dL
  - Part D – Hb  $\leq$  10.5 g/dL
5. Written informed parental/guardian consent and participant assent has been obtained per institutional review board (IRB)/Ethics Committee (EC) policy and requirements, consistent with ICH guidelines.
6. Participants in Part B (only) of the study must complete a minimum of 14 days with ePRO to be enrolled. Investigator discretion will be used to determine if a participant who has previously been screen failed due to a lack of baseline ePRO data collection can be invited back for rescreening.
7. If sexually active and female, must agree to abstain from sexual intercourse or to use a highly effective method of contraception throughout the study period and for 30 days after discontinuation of study drug. If sexually active and male, must agree to abstain from sexual intercourse or willing to use barrier methods of contraception throughout the study period and for 30 days after discontinuation of study drug.
8. Females of child-bearing potential are required to have a negative pregnancy test before the administration of study drug.
9. Sufficient venous access to permit collection of PK samples and monitoring of laboratory safety variables, in the opinion of the Investigator.
10. For Part C only, participants 12 to 17 years of age must have a TCD velocity  $\geq$  140 cm/sec by nonimaging TCD or  $\geq$  125 cm/sec by TCDi measured anytime during screening.

## Key inclusion and exclusion criteria: Gender

Both

## Key inclusion and exclusion criteria: Specify gender

## Key inclusion and exclusion criteria: Age minimum

0

## Key inclusion and exclusion criteria: Age maximum

17

## Key inclusion and exclusion criteria: Exclusion criteria

1. Any one of the following requiring medical attention within 14 days prior to signing the informed consent form (ICF):
    - Vaso-occlusive crisis (VOC)
    - Acute chest syndrome (ACS)
    - Splenic sequestration crisis
    - Dactylitis
  2. Requires chronic transfusion therapy.
  3. History of stroke or meeting criteria for primary stroke prophylaxis (history of two TCD measurements  $\geq$  200 cm/sec by nonimaging TCD or  $\geq$  185 cm/sec by TCDi).
    - For the potential modification, addition of approximately 20 participants enrolled in Part C, TCD  $\geq$  170 cm/sec by nonimaging TCD or  $\geq$  155 cm/sec by TCDi.
  4. Transfusion within 30 days prior to signing the ICF.
  5. Renal dysfunction requiring chronic dialysis or creatinine  $\geq$  1.5 mg/dL.
  6. Hepatic dysfunction characterized by alanine aminotransferase (ALT)  $>$  4 $\times$  upper limit of normal (ULN) for age.
  7. Clinically relevant cardiac abnormality, in the opinion of the Investigator, such as:
    - Hemodynamically significant heart disease, eg, congenital heart defect, uncompensated heart failure, or any unstable cardiac condition
    - An arrhythmic heart condition requiring medical therapy
  8. QTcF  $>$  450 msec, congenital long QT syndrome, second or third degree heart block at rest (with the exception of asymptomatic Mobitz type I second degree heart block).
  9. Received an investigational drug within 30 days or 5 half-lives, whichever is longer, of signing the ICF.
  10. Heavy smoker (defined as smoking more than 10 cigarettes/day or its nicotine equivalent including e-cigarettes).
  11. Unlikely to comply with the study procedures.
  12. Other medical, psychological, or addictive condition that, in the opinion of the Investigator, would confound or interfere with evaluation of safety and/or PK of the investigational drug, prevent compliance with the study protocol, or preclude informed consent.
  13. Participants who do not have a TCD window (Part B and C only) (ie, participants who are unable to have a TCD due to skull ossification).
  14. For Part C only, prior participation in Part B.
  15. Active symptomatic COVID-19 infection.
- In addition, for Part D only:
16. Body weight  $<$  5 kg for 1 month prior to the screening visit and at the screening visit.
  17. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable).



18. History of malignancy within the past 2 years prior to treatment Day 1 requiring chemotherapy and/or radiation (with the exception of local therapy for non-melanoma skin malignancy).

19. Clinically significant bacterial, fungal, parasitic, or viral infection currently receiving or that will require therapy.

- Participants with acute bacterial infection requiring antibiotic use should delay screening until the course of antibiotic therapy has been completed and the infection has resolved, in the opinion of the investigator.
- Known active hepatitis A, B, or C infection or human immunodeficiency virus (HIV)-positive.
- Known active malaria.

**Type of study**

Interventional

**Type of intervention**

Pharmaceutical

**Type of intervention: Specify type**

N/A

**Trial scope**

Therapy

**Trial scope: Specify scope**

N/A

**Study design: Allocation**

N/A: Single arm study

**Study design: Masking**

Open (masking not used)

**Study design: Control**

Dose comparison

**Study phase**

2

**Study design: Purpose**

Treatment

**Study design: Specify purpose**

N/A

**Study design: Assignment**

Single

**Study design: Specify assignment**

N/A

**IMP has market authorization**

Yes, Worldwide

**IMP has market authorization: Specify**

USA, UAE, EU, GB, Oman and Kuwait

**Name of IMP**

OXBRYTA

**Year of authorization**

2019

**Month of authorization**

11

**Type of IMP**

Others

**Pharmaceutical class**

Allosteric modulator of hemoglobin-oxygen affinity

**Therapeutic indication**

Sickle Cell Disease

**Therapeutic benefit**

Voxelotor is an orally bioavailable HbS polymerization inhibitor that binds specifically to HbS with a 1:1 stoichiometry, and exhibits preferential partitioning to RBCs. By increasing Hb's affinity for oxygen, voxelotor inhibits HbS polymerization in a dose dependent manner that may improve deformability, decrease the viscosity of SCD blood, and ultimately increase blood flow in the microcirculation, thus improving net O<sub>2</sub> delivery. Therefore, chronically modifying 20% to 30% of HbS with voxelotor in subjects with SCD is expected to deliver the clinical benefits of reducing HbS polymerization while improving O<sub>2</sub> delivery to peripheral tissues.

**Study model**

N/A

**Study model: Explain model**

N/A

**Study model: Specify model**

N/A

**Time perspective**

N/A

**Time perspective: Explain time perspective**

N/A

**Time perspective: Specify perspective**

N/A

**Target follow-up duration****Target follow-up duration: Unit****Number of groups/cohorts****Biospecimen retention**

None retained

**Biospecimen description**

N/A

**Target sample size**

24

**Actual enrollment target size**

38

**Date of first enrollment: Type**

Actual

**Date of first enrollment: Date**

21/07/2016

**Date of study closure: Type**

Actual

**Date of study closure: Date**

29/12/2023

**Recruitment status**

Recruiting

**Recruitment status: Specify****Date of completion****IPD sharing statement plan**

No

**IPD sharing statement description**

N/A

**Additional data URL**

<https://clinicaltrials.gov/ct2/show/NCT02850406>

**Admin comments****Trial status**

Approved



## Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
Clinicaltrials.gov	NCT02850406
EU Clinical Trials Registry	EudraCT: 2016-004209-15

## Sources of Monetary or Material Support

Name
Global Blood Therapeutics, Inc. USA

## Secondary Sponsors

No Sponsors

## Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Dr. Adlette Inati	Tripoli	Lebanon	9613228033	adlette.inati@lau.edu.lb	Nini Hospital
Scientific	Mark Davis	181 Oyster Point Blvd., South San Francisco, CA 94080	United States of America	(925) 336- 1055	mdavis@gbt.com	Global Blood Therapeuti cs
Public	Dr. Miguel Abboud	Beirut	Lebanon	9611350000	ma56@aub.edu.lb	American University of Beirut Medical Center

## Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
American University of Beirut Medical Center	Dr. Miguel Abboud	Pediatric Hematology- Oncology	Approved
Rafik Hariri University Hospital	Dr. Adlette Inati	Pediatric Hematology- Oncology	Approved
Nini Hospital	Dr. Adlette Inati	Pediatric Hematology- Oncology	Approved



## Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
American University of Beirut Medical Center	09/07/2018	Dr. Fuad Ziyadeh	irb@aub.edu.lb	9611738025
Rafic Hariri University Hospital	31/08/2018	Dr. Iyad Issa	NA	9611830000
Nini Hospital	31/08/2018	Dr. Nabil Kabbara	NA	9616431400

## Countries of Recruitment

Name
Lebanon
United States of America
United Kingdom

## Health Conditions or Problems Studied

Condition	Code	Keyword
Sickle Cell Disease	Sickle-cell disorders (D57)	Sickle Cell, Anemia, Hemolytic, Congenital, Hematologic Diseases

## Interventions

Intervention	Description	Keyword
Drug	GBT440	Oral Capsule, Tablet, Dispersible Tablet or Powder for Oral Suspension





## Primary Outcomes

Name	Time Points	Measure
Part A: Pharmacokinetic profile of GBT440 including maximum concentration	Pre-dose to Day 15	Pharmacokinetic profile
Part A: Pharmacokinetic profile of GBT440 including the time taken to reach the maximum concentration	Pre-dose to Day 15	Pharmacokinetic profile
Part A: Pharmacokinetic profile of GBT440 including the total drug concentration over time	Pre-dose to Day 15	Pharmacokinetic profile
Part B: Change in hemoglobin	Baseline to Week 24	Hemoglobin in Blood
Part C: Change in cerebral blood flow	Baseline to Week 48	TAMM TCD velocity
Part D	During Study Duration	Incidence of TEAEs and SAEs

## Key Secondary Outcomes

Name	Time Points	Measure
Part A: Number of participants with treatment-related adverse events	Days 1 - 15	Assessed by CTCAE v4.03
Part B: Multiple Dose effect on Clinical Measures of Hemolysis	Day 1 - Week 24	Clinical Measures of Hemolysis
Part B: Pharmacokinetic profile of GBT440 including maximum concentration	Pre-dose to Week 24	Pharmacokinetic profile
Part B: Pharmacokinetic profile of GBT440 including the time taken to reach the maximum concentration	Pre-dose to Week 24	Pharmacokinetic profile
Part B: Pharmacokinetic profile of GBT440 including the total drug concentration over time	Pre-dose to Week 24	Pharmacokinetic profile
Part C: Multiple dose effect on clinical measures of hemolysis	Baseline to Week 24 and Week 48	Clinical Measures of Hemolysis
Part C: Change in cerebral blood flow	Baseline to Week 24	Measured by the TAMM TCD velocity
Part C: Pharmacokinetic profile of GBT440 including maximum concentration	Pre-Dose to Week 48	Pharmacokinetic profile
Part C: Pharmacokinetic profile of GBT440 including the time taken to reach the maximum concentration	Pre-Dose to Week 48	Pharmacokinetic profile
Part C: Pharmacokinetic profile of GBT440 including the total drug concentration over time	Pre-Dose to Week 48	Pharmacokinetic profile
Part D: Whole blood and plasma voxelotor PK (C <sub>max</sub> , AUC, t <sub>1/2</sub> , if appropriate) and occupancy	Baseline to Week 24 and Week 48	Change in Hb, LDH, indirect bilirubin, and reticulocyte count
Part D: Whole blood and plasma voxelotor PK (C <sub>max</sub> , AUC, t <sub>1/2</sub> , if appropriate) and occupancy	-	Time to initial Hb response, defined as change from baseline in Hb > 1g/dL
Part D: Whole blood and plasma voxelotor PK (C <sub>max</sub> , AUC, t <sub>1/2</sub> , if appropriate) and occupancy	During whole study duration	Incidence of stroke and VOC



## Trial Results

**Summary results**

**Study results globally**

**Date of posting of results summaries**

**Date of first journal publication of results**

**Results URL link**

**Baseline characteristics**

**Participant flow**

**Adverse events**

**Outcome measures**

**URL to protocol files**