



A Phase 2/3 Randomized, Multicenter Study of GBT021601 Administered Orally to Participants with Sick Cell Disease and an Open-Label Pharmacokinetics Study in Pediatric Participants with Sick Cell Disease

11/09/2025 04:13:19

Main Information

Primary registry identifying number

LBCTR2022105089

Protocol number

GBT021601-021

MOH registration number

Study registered at the country of origin

Yes

Study registered at the country of origin: Specify

Type of registration

Prospective

Type of registration: Justify

N/A

Date of registration in national regulatory agency

Primary sponsor

Global Blood Therapeutics, Inc.

Primary sponsor: Country of origin

USA

Date of registration in primary registry

06/02/2023

Date of registration in national regulatory agency

Public title

A Phase 2/3 Randomized, Multicenter Study of GBT021601 Administered Orally to Participants with Sick Cell Disease and an Open-Label Pharmacokinetics Study in Pediatric Participants with Sick Cell Disease

Acronym

Scientific title

A Phase 2/3 Randomized, Multicenter Study of GBT021601 Administered Orally to Participants with Sick Cell Disease and an Open-Label Pharmacokinetics Study in Pediatric Participants with Sick Cell Disease

Acronym

Brief summary of the study: English

This is a three-part, multicenter, Phase 2/3 study of orally administered GBT021601 in participants with sickle cell disease (SCD). Part A will evaluate the safety, tolerability, and efficacy of GBT021601 in adult participants with SCD to determine an optimal dose. Part B will evaluate the efficacy of GBT021601 versus placebo in adult and pediatric participants with SCD for 48 weeks. Part C will evaluate the pharmacokinetics (PK) and safety of single and multiple doses (MD) of open-label single arm GBT021601 administered to pediatric participants.

Brief summary of the study: Arabic

عن طريق الفم في المشاركين المصابين بمرض الخلايا GBT021601 من 2/3 هذه دراسة من ثلاثة أجزاء ، متعددة المراكز ، المرحلة في المشاركين البالغين المصابين بفقر الدم المنجلي لتحديد الجرعة GBT021601 سيقم الجزء أ سلامة وتحمل وفعالية (SCD) المنجلية أسبوعاً. سيقوم الجزء 48 لمدة SCD مقابل الدواء الوهمي في البالغين والأطفال المشاركين مع GBT021601 المثلى. سيقم الجزء ب فعالية يُعطى للمشاركين من GBT021601 لنزاع واحد مفتوح التسمية (MD) وسلامة الجرعات الفردية والمتعددة (PK) بتقييم الحرائك الدوائية C الأطفال.





Health conditions/problem studied: Specify

Sickle Cell Disease (SCD) / Patients with SCD endure chronic hemolytic anemia and acute and recurrent clinical events that vary in frequency and severity, the most common being VOCs (vaso-occlusions). The use of curative options for SCD is currently limited to a small subgroup of patients who are deemed fit for bone marrow transplantation and have available donors. The current treatment options are not universally effective or globally available, tend to address only a single component of the disease, or are limited by their safety profile. Therefore, a significant unmet medical need exists for safe and effective therapies for the treatment of SCD that result in both an improvement in anemia and reduction in sickle cell-related crises.

Interventions: Specify

This is a three-part, multicenter, Phase 2/3 study of orally administered GBT021601 in participants with SCD.

Part A: Initially, participants will be randomized 1:1 to 100 mg and 150 mg daily. Upon review of the 150 mg safety data from at least 6 participants, there will be 1:1:1 randomization: 100 mg, 150 mg, and up to 200 mg.

Participants will then receive maintenance once daily doses through Week 12.

Part B: Following the selection of the optimal safe and effective dose from Part A of the study, Part B of the study will assess the efficacy and safety of 48 weeks of the optimal dose, compared to placebo

Part C: 100 mg dose in cohort C1, dose level for cohorts C2 to C4 to be determined based on emerging data

Key inclusion and exclusion criteria: Inclusion criteria

Key Inclusion Criteria (Part A, Part B, and Part C):

1. Male or female with SCD.

Documentation of SCD genotype homozygous for sickle cell allele (HbSS) or double heterozygote for sickle hemoglobin (HbS) and β -0 thalassemia (HbSB) may be based on history of laboratory testing or must be confirmed by laboratory testing during Screening.

2. Hb \geq 5.5 and \leq 10.5 g/dL during Screening and considered stable by the Investigator.

3. For participants taking hydroxyurea (HU) and/or L-glutamine, the dose must be stable for at least 90 days prior to signing the ICF or assent and with no anticipated need for dose adjustments during the study in the opinion of the Investigator.

4. Female participants of child-bearing potential, must agree to use highly effective methods of contraception or practice abstinence from study start to 120 days after the last dose of study drug. Males who are not surgically sterile with partners of childbearing potential must agree to use a highly effective method of birth control during the study and for 120 days after the last dose of study drug. In addition, males who are not surgically sterile with a partner who is pregnant must agree to condom use or maintain sexual abstinence during the study and for 120 days after the last dose of study drug.

5. Female participants of child-bearing potential must have a negative pregnancy test before administration of study drug.

6. Participant has provided documented informed consent (Part A and Part B for adult participants) or written informed parental/guardian consent and participant assent has been obtained per institutional review board (IRB)/Ethics Committee (EC) policy and requirements, consistent with International Council for Harmonisation (ICH) guidelines (Part B for pediatric participants and Part C).

Additional Key Inclusion Criteria (Part A):

1. Age 18 to \leq 65 years, inclusive at Screening.

2. Males must agree to not donate sperm from study start through 120 days after the final dose.

Additional Key Inclusion Criteria (Part B):

1. Age 12 to \leq 65 years, inclusive at Screening. Participants 12 to $<$ 18 years will only be enrolled in Part B after evaluation of safety in Part C Cohort C1.

2. Males must agree to not donate sperm from study start through 120 days after the final dose.

Additional Key Inclusion Criteria (Part B only):

1. More than or equal to 2 and \leq 10 VOCs within 12 months of Screening.

Additional Key Inclusion Criteria (Part C only):

1. Age by cohort at Screening:

☐ Cohort C1: 12 to $<$ 18 years

☐ Cohort C2: 6 to $<$ 12 years

☐ Cohort C3: 2 to $<$ 6 years

☐ Cohort C4: 6 months to $<$ 2 years

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

1

Key inclusion and exclusion criteria: Age maximum

65

Key inclusion and exclusion criteria: Exclusion criteria

Key Exclusion Criteria (Part A, Part B, and Part C):

1. More than 10 VOCs within 12 months of Screening.

2. Female participant who is breastfeeding or pregnant.

3. Receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) or has received an RBC or exchange transfusion for any reason within 90 days of Day 1.

4. Hospitalized for sickle cell crisis or other vaso-occlusive event within 14 days of signing the ICF.

5. Screening laboratory test of alanine aminotransferase (ALT) $>$ 4 \times upper limit of normal (ULN) for age.

6. Acute illness or clinically significant bacterial, fungal, parasitic, or viral infection which requires therapy, including acute bacterial infection requiring antibiotics within 14 days prior to the study drug administration.

7. Participants known to have active hepatitis A, B, or C or human immunodeficiency virus (HIV).

8. Participants with active, symptomatic coronavirus disease 2019 (COVID-19) infection.

9. Estimated glomerular filtration rate (eGFR) $<$ 60 mL/min/1.73 m² at the Screening Visit, calculated by the central laboratory, or is on chronic dialysis.



10. 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).
 11. History of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent.
 12. Has received COVID-19 vaccine (first dose, second dose, or booster dose), authorized by regional regulatory authority, within 7 days prior to Day 1.
 13. Received EPO or other hematopoietic growth factor treatment within 28 days of signing ICF or is anticipated to require such agents during the study.
 14. Current or recent use of voxelotor. Recent use is defined as within 10 days prior to Day 1.
 15. Current or recent use of crizanlizumab. Recent use is defined as within 90 days prior to Day 1.
 16. Ongoing or recent use of strong or moderate inducers of cytochrome P450 (CYP) or CYP3A4/CYP3A5. Recent is defined as within 5 elimination half-lives or 14 days, whichever is longer prior to Day 1.
 17. Ongoing or recent use of strong or moderate inhibitors of CYP3A4/CYP3A5. Recent is defined as within 5 elimination half-lives prior to Day 1.
 18. Ongoing or recent use of the P-glycoprotein substrates digoxin or dabigatran. Recent is defined as within 5 elimination half-lives prior to Day 1.
 19. Use of prohibited prescription or nonprescription drugs and dietary supplements (including herbal and alternative medications). Marijuana use is allowed, except for 24 hours prior to neurocognitive assessments as outlined in the Schedule of Assessments.
 20. Known allergy to GBT021601 or other Hb polymerization inhibitors.
 21. History of severe allergic reaction (including anaphylaxis) to any substance, or previous status asthmaticus.
 22. Unlikely to comply with the study procedures.
- Key Exclusion Criteria (Part C only):
1. History of stroke or meeting criteria for primary stroke prophylaxis (history of two transcranial doppler [TCD] measurements ≥ 200 cm/sec by nonimaging TCD or ≥ 185 cm/sec by TCDi).

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

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

N/A

Study phase

2 to 3

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

GBT021601

Year of authorization

Month of authorization

Type of IMP

Cell therapy

Pharmaceutical class



GBT021601 drug product and placebo formulations are manufactured in accordance with Good Manufacturing Practices and are available as capsule and tablet dosage forms.

GBT021601 Drug Product:

□ GBT021601 Capsules: GBT021601 is available as a capsule dosage form of 5 mg and 25 mg that are packaged in high-density polyethylene (HDPE) bottles with child-resistant caps and induction seal. The drug product is an immediate release, oral dosage form in white, opaque, hydroxypropyl methylcellulose capsules, containing an appropriate amount of GBT021601 drug substance for the active capsules or microcrystalline cellulose for the matching placebo capsules. □ GBT021601 Tablets: GBT021601 is available as a tablet dosage form of 25 mg and 100 mg strengths that are packaged in HDPE bottles with child-resistant caps and induction seal. The drug product is an immediate release, oral dosage form containing an appropriate amount of the blend prepared with GBT021601 drug substance and excipients for the active tablets or with just excipients for the matching placebo tablets. All the excipients used for the formulations are listed in the FDA Inactive Ingredient Guide (IID) or are pharmaceutical excipient mixtures entirely composed of FDA IID listed components. All the excipients used for the formulations are either compendial per European Pharmacopoeia (Ph. Eur.) or are composed of mixtures that are compendial per Ph. Eur. or accepted by E number (E number Purity Criteria according to Commission Regulation (EU) No. 231/2012 for Food Additives).

Therapeutic indication

sickle cell disease (SCD)

Therapeutic benefit

Given its drug exposure, GBT021601 has the capacity to achieve a targeted % Hb occupancy and attain the desired hematological effect at low doses, therefore reducing pill burden and improving clinical outcomes for patients living with SCD. Forthcoming multiple-dose data will help to evaluate GBT021601's potential as an oral and disease-modifying therapy for SCD

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

480

Actual enrollment target size

**Date of first enrollment: Type**

Anticipated

Date of first enrollment: Date

06/07/2022

Date of study closure: Type

Anticipated

Date of study closure: Date

30/04/2027

Recruitment status

Pending

Recruitment status: Specify**Date of completion**

31/10/2026

IPD sharing statement plan

No

IPD sharing statement description

N/A

Additional data URL**Admin comments****Trial status**

Approved

Secondary Identifying Numbers

No Numbers

Sources of Monetary or Material Support

Name

Global Blood Therapeutics, Inc.

Secondary Sponsors

Name

N.A



Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
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Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Nini Hospital	Adlette Inati	Professor of Pediatric Hematology and Oncology	Pending
American University of Beirut Medical Center	Miguel Abboud	Professor of Pediatric Hematology and Oncology	Pending

Ethics Review

No Reviews

Countries of Recruitment

Name
Lebanon

Health Conditions or Problems Studied

Condition	Code	Keyword
Sickle Cell Disease	Sickle-cell disorders (D57)	SCD



Interventions

Intervention	Description	Keyword
GBT021601	Sickle Cell Disease	SCD

Primary Outcomes

Name	Time Points	Measure
Part A	Through week 12	Number of adult participants with change from baseline in hemoglobin (Hb) through week 12 as measured by change in GBT021601 concentrations from baseline or percentage change from baseline of clinical measures of anemia (hemoglobin) and hemolysis (including indirect bilirubin, reticulocytes and lactate dehydrogenase).
Part B	Through week 48	Proportion of participants with an increase from baseline of >1 g/dL in Hb at week 48 as measured by change in GBT021601 concentrations from baseline or percentage change from baseline of clinical measures of anemia (hemoglobin) and hemolysis (including indirect bilirubin, reticulocytes and lactate dehydrogenase).
Part C	Through Week 6	Assess the pharmacokinetics, while observing maximum concentration (C _{max}) after a single dose as measured by a noncompartmental PK analysis or population PK analysis using nonlinear mixed-effect modeling.
Part C	Through Week 2	Assess the pharmacokinetics, while observing minimum concentration (C _{min}) and maximum concentration after multiple dose administration as measured by a noncompartmental PK analysis or population PK analysis using nonlinear mixed-effect modeling will be performed to characterize GBT021601 PK in plasma and whole blood following multiple doses

Key Secondary Outcomes

Name	Time Points	Measure
Part A	Through Week 12	To evaluate the effects of GBT021601 on total hemoglobin and clinical measures of hemolysis. To evaluate the safety and tolerability as well as the PK and pharmacodynamic (PD) properties of multiple dose GBT021601 administration.
Part B	Through end of Week 48	To evaluate the effects of GBT021601 compared to placebo on total hemoglobin, clinical measures of hemolysis, and relevant clinical outcomes. To evaluate the safety and tolerability of 48 weeks of daily GBT021601 administration.
Part C	Through Week 2	To evaluate the safety and change in total hemoglobin and clinical measures of hemolysis after multiple doses of GBT021601.



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