A Randomized, Double-blind, Placebo-controlled, Multicenter Study of a Single Dose of Inclacumab to Reduce Re-admission in Participants With Sickle Cell Disease and Recurrent Vaso-occlusive Crises

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Main Information

Primary registry identifying number
LBCTR2021074831

Protocol number
GBT2104-132 (C5361002)

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
15/06/2021

Primary sponsor
Global Blood Therapeutics, Inc, a wholly owned subsidiary of Pfizer, Inc

Primary sponsor: Country of origin
USA

Date of registration in primary registry
14/10/2024

Date of registration in national regulatory agency
15/06/2021

Public title
A Randomized, Double-blind, Placebo-controlled, Multicenter Study of a Single Dose of Inclacumab to Reduce Re-admission in Participants With Sickle Cell Disease and Recurrent Vaso-occlusive Crises

Acronym

Scientific title
GBT2104-132: A Randomized, Double-blind, Placebo-controlled, Multicenter Study of a Single Dose of Inclacumab to Reduce Re-admission in Participants With Sickle Cell Disease and Recurrent Vaso-occlusive Crises

Acronym

Brief summary of the study: English
This is a Phase 3, randomized, double-blind, placebo-controlled, 2-arm, multicenter, parallel-group study.

The primary objective of this study is to evaluate the safety and efficacy of a single dose of Inclacumab compared to placebo to reduce the incidence of re-admission to a healthcare facility for a vaso-occlusive crisis (VOC) after an admission for an index VOC in participants with sickle cell disease (SCD).
Additional objectives of the study are to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of Inclacumab, the presence of anti-drug antibodies (ADAs), and changes in quality of life (QOL).

Brief summary of the study: Arabic

هذه هي دراسة في المرحلة الثالثة متعددة المراكز، عشوائية التوزيع، مزدوجة التعمية، مراقبة بدواء وهمي

مقارنة بالدواء الوهمي لتقليل حدوث إعادة القبول في inclacumab الهدف الأساسي من هذه الدراسة هو تقييم سلامة وفعالية جرعة واحدة من
في المشاركين المصابين بمرض فقر الدم المنجلي .VOC بعد القبول لمؤشر (VOC) مرفق الرعاية الصحية لأزمة انسداد الأوعية الدموية
(SCD).
ووجود الأجسام المضادة ، inclacumab لـ (PD) والديناميكا الدوائية (PK) تتمثل الأهداف الإضافية للدراسة في تقييم الحرائك الدوائية
للأدوية (ADAs) ، والتغيرات في نوعية الحياة (QOL).

Health conditions/problem studied: Specify

Patients with a diagnosis of sickle cell disease (SCD) who have experienced between 2 and 10 vaso-occlusive crises in the 12 months preceding enrollment and have been hospitalized for a vaso-occlusive crisis.

Interventions: Specify

This study will be a randomized, placebo-controlled, double-blind, multicenter, parallel-group study to assess the safety and efficacy of a single dose of Inclacumab in reducing the rate of re-admission to a healthcare facility for a VOC after an index VOC. The index VOC is any VOC that required admission to a healthcare facility and treatment with parenteral pain medication where the admission includes:
• A hospital admission, or
• An admission to an emergency room, observation unit, or infusion center for ≥ 12 hours, or
• 2 visits to an emergency room, observation unit, or infusion center over a 72-hour period.
for an acute episode of pain with no other cause other than a vaso-occlusive event that includes the following:
• Uncomplicated VOC,
• Acute chest syndrome (ACS),
• Hepatic sequestration,
• Splenic sequestration, or
• Priapism.
The study will include approximately 280 adult and adolescent participants (≥ 12 years of age) with SCD. Initial enrollment will include participants ≥ 16 years of age until the Data Monitoring Committee (DMC) recommends to the Sponsor that adequate safety and PK data support the enrollment of participants 12 to 15 years of age.
Participants will be randomized with a 1:1 ratio into one of two treatment arms (140 participants per arm) as follows:
• Inclacumab 30 mg/kg administered intravenously (IV); or
• Placebo administered IV.
Randomization to occur within 5 days after the index VOC has resolved, as assessed by the Investigator (for example, hospital discharge, completion of parenteral analgesia, or transition to oral analgesics). The total duration of treatment for each participant will be 90 days with a single dose on Day 1.
At the time of randomization, participants will be stratified by Baseline hydroxyurea (HU) use (yes; no), number of VOCs (2 to 4; 5 to 10) in the preceding 12 months, and geographic region (North America; rest of world).
An independent DMC will regularly review the totality of accumulated safety data from all ongoing inclacumab studies on an ongoing, unblinded basis, with specific emphasis on adolescent participants. Details will be provided in the DMC Charter.
Participants that complete the study through Day 91 will be provided the opportunity to enroll in an open-label extension (OLE) study. The study will be conducted at up to 70 clinical sites globally.

Key inclusion and exclusion criteria: Inclusion criteria

Inclusion Criteria

1. Participant has an index VOC. The index VOC is any VOC that required admission to a healthcare facility and treatment with parenteral pain medication. An admission for the index VOC includes:
a. A hospital admission, or
b. An admission to an emergency room, observation unit, or infusion center for ≥ 12 hours, or
c. 2 visits to an emergency room, observation unit, or infusion center over a 72-hour period.
for an acute episode of pain with no other cause other than a vaso-occlusive event that includes the following:
• Uncomplicated VOC,
• Acute chest syndrome (ACS),
• Hepatic sequestration,
• Splenic sequestration, or
• Priapism.

2. Participant has a confirmed diagnosis of SCD (any genotype).
Documentation of SCD genotype is required and may be based on documented history of laboratory testing or confirmed by laboratory testing at Baseline.
3. Participant is male or female, ≥ 12 years of age at the time of informed consent.
NOTE: Initial study enrollment will include only participants ≥ 16 years of age until the DMC recommends to the Sponsor that adequate safety and PK data support the enrollment of participants 12 to 15 years of age. Sites will be informed by the Sponsor when participants 12 to 15 years of age may be enrolled.
4. Participant is able to complete screening and receive study drug within 5 days following investigator-assessed resolution of index VOC (for example, hospital discharge, discontinuation of parenteral pain medication, or transition to oral pain medication).
5. Participant has experienced between 2 and 10 VOCs (inclusive) within the 12 months prior to Screening as determined by documented medical history. The index VOC is not to be considered as one of the 2 to 10 events. A prior VOC is defined as an acute episode of pain that:
• Has no medically determined cause other than a vaso-occlusive event, and
• Results in a visit to a medical facility (hospital, emergency department, urgent care center, outpatient clinic, or infusion center) or results in a remote contact with a healthcare provider; and
• Requires parenteral narcotic agents, parenteral nonsteroidal anti-inflammatory drugs (NSAIDs), or an increase in treatment with oral narcotics.
6. Participants receiving erythropoiesis-stimulating agents (ESA, eg, erythropoietin [EPO]) must be on a stable dose for at least 90 days prior to

Screening and expected to continue with the stabilized regimen throughout the course of the study.
7. Participants receiving HU, L-glutamine, or voxelotor must be on a stable dose for at least 30 days prior to Screening and expected to continue with the stabilized regimen throughout the course of the study.
8. Participant has adequate venous access, in the opinion of the Investigator, to comply with study procedures.
9. Participant understands the study procedures and agrees to participate in the study by giving written informed consent or parental permission/written assent
10. Women of childbearing potential (WOCBP) are required to have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy tests on all subsequent clinic visits and must agree to use a highly effective method of contraception throughout the study period and for at least 165 days after dosing.
Female participants will not be considered of childbearing potential if they are pre-menarchal, surgically sterile (hysterectomy, bilateral salpingectomy, tubal ligation, or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause, confirmed by follicle-stimulating hormone test results).

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

12

Key inclusion and exclusion criteria: Age maximum

90

Key inclusion and exclusion criteria: Exclusion criteria

Exclusion Criteria
Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening or Baseline visits or at the timepoint specified in the individual criterion listed.
1. Participant is receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventative transfusion).
2. Participant is taking or has received crizanlizumab (ADAKVEO®) within 90 days prior to Screening.
3. Participant weighs > 133 kg (292 lbs).
4. Participant has a significant active and poorly controlled (unstable) hepatic disorder clearly unrelated to SCD.
5. Participant has any of the following laboratory values at Screening:
a. Absolute neutrophil count (ANC) < 1.0 × 109/L
b. Platelet count < 80 × 10^9/L
c. Hemoglobin < 4.0 g/dL for adults and < 5.0 g/dL for participants ages 12 to < 18 years of age
d. Estimated glomerular filtration rate (eGFR) < 30 mL/min using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula in adults, and Schwartz formula in adolescents.
NOTE: Laboratory assessments conducted during Screening must be done by the local laboratory and must include CBC with total and differential leukocyte count, platelet count, hemoglobin, and chemistry panel with blood urea nitrogen, bilirubin (total, direct and indirect), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, serum albumin, sodium, potassium, calcium, chloride, glucose, bicarbonate, serum, creatinine, and total protein to assess participant eligibility. Laboratory assessments conducted during the index VOC admission that are obtained within 7 days prior to screening may be used for Screening assessments if done as part of standard medical care.
6. Participant has known active (symptomatic) COVID infection or tests positive for COVID-19 at any time during their index admission.
7. Participant has a history of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to Screening including severe or unstable pulmonary hypertension.
8. Participant has had treatment for a malignancy within the 12 months prior to Screening (except non-melanoma skin cancer and in situ cervical cancers).
9. Participant has had a stroke within the 2 years prior to the Screening Visit.
10. Participant has a positive test indicative of active malaria infection at Screening. Testing to be conducted at local laboratories in malaria-endemic regions at the discretion of the Investigator.
11. Participant has any confirmed clinically significant drug allergy and/or known hypersensitivity to monoclonal antibody therapeutics or formulation components of the study drug or a related drug.
12. Participant has been treated with another investigational agent within 30 days or 5 half-lives of the investigational agent (whichever is greater) prior to Screening.
13. Participant has had a major surgery within 8 weeks prior to the Screening Visit.
14. Participant is pregnant, breastfeeding, or planning to become pregnant during the 90-day treatment period.
15. Participant, parent, or legal guardian are unlikely to comply with the study procedures.
16. Participant has other medical, or psychological, or behavioral conditions that, in the opinion of the Investigator, would: confound or interfere with evaluation of safety, efficacy, and/or PK of the investigational drug; prevent compliance with the study protocol; preclude informed consent; or render the participant, parent, or caretaker unable/unlikely to comply with the study procedures.

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Safety

Trial scope: Specify scope

N/A

Study design: Allocation

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

Placebo

Study phase

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

Inclacumab

Year of authorization

Month of authorization

Type of IMP

Immunological

Pharmaceutical class

Inclacumab is a recombinant human monoclonal antibody (huMAb) of the immunoglobulin (Ig)G4 subclass directed against human P-selectin, which is being developed by Global Blood Therapeutics, Inc. (GBT), for the treatment of sickle cell disease (SCD). Inclacumab binds to P-selectin, which is a cell adhesion molecule produced by endothelial cells and platelets. Upon activation of these cells (e.g., by thrombin, cytokines, complement components, hypoxia, and heme), P-selectin is translocated to the cell surface where it binds to its primary ligand P-selectin glycoprotein ligand-1 (PSGL-1) and mediates leukocytes recruitment by platelets or endothelial cells. The same mechanism is also responsible for abnormal rolling and adhesion of sickle red blood cells (RBC) to the endothelium, initiating acute vascular occlusion and chronically impairing microvascular blood flow in patients with SCD.
Inclacumab binding of P-selectin and prevention of P-selectin binding to its ligands is the putative mechanism by which Inclacumab prevents the binding of sickle RBCs or leukocytes to endothelium

Therapeutic indication

Sickle Cell Disease (SCD)

Therapeutic benefit

Inclacumab is a recombinant huMAb of the IgG4 subclass directed against human P-selectin. The molecule is composed of two heterodimers, each composed of a heavy and a light polypeptide chain. The four polypeptide chains are linked together by disulfide bonds.
To avoid antibody-dependent cell-mediated cytotoxicity and to improve structural stability, two single point mutations (L235E, S228P) were introduced into the Fc part of the molecule. The Inclacumab drug substance is manufactured by fermentation cell culture using Chinese hamster ovary (CHO) cells followed by purification. The drug substance, drug product, and placebo are manufactured in accordance with Good Manufacturing Practices (GMP).
Results from the SUSTAIN trial in patients with SCD showed that treatment with crizanlizumab, a humanized antibody to P-selectin, resulted in a significantly lower rate of sickle cell-related pain crises (i.e., VOC) than placebo. These data validated P-selectin as a therapeutic target for SCD disease. Inclacumab is currently not approved by any health authority for the treatment of patients with any disease. Inclacumab is being developed to reduce the risk of vaso-occlusive crises in patients with 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

Time perspective: Specify perspective

N/A

N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention

Samples with DNA**

Biospecimen description

Optional genomic samples will be retained beyond study completion.

Target sample size

280

Actual enrollment target size

72

Date of first enrollment: Type

Actual

Date of first enrollment: Date

13/12/2021

Date of study closure: Type

Actual

Date of study closure: Date

29/06/2023

Recruitment status

Other

Recruitment status: Specify

GBT/Pfizer has elected to discontinue Study GBT2104-132 (C5361002) due to poor accrual and associated recruitment challenges. This decision is not due to any specific safety concerns or requests from any regulatory authorities.

Date of completion

29/06/2023

IPD sharing statement plan

Yes

IPD sharing statement description

Patient's full identity will not be on any of the study documents or sample collected and kept by the sponsor for their studies. Only the partial date of birth will be only collected. Only a unique participant number for the study will link the data or samples to the patients.

Additional data URL

https://clinicaltrials.gov/ct2/show/NCT04927247

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
National Institute of Health (NIH)	NCT04927247
European Medicines Agency (EMA)	2020-005287-60

Sources of Monetary or Material Support

Name
Global Blood Therapeutics, Inc, a wholly owned subsidiary of Pfizer, Inc.

Secondary Sponsors

Name
N/A

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Aziz Zoghbi	MCT-CRO, Berytech Technology and Health, 5th Floor Damascus Road, Beirut, Lebanon	Lebanon	+9617100 8269	aziz.zoghbi@mct-cro.com	Director of Country Oversight and Management MENA, Gulf and Africa
Scientific	Miguel Abboud	American University of Beirut Medical Center, Cairo Street, Hamra, Beirut, Lebanon	Lebanon	+9613534 213	ma56@aub.edu.lb	PI
Scientific	Adlette Inati	Nini Hospital, el Maarad Street, Triploli, Lebanon	Lebanon	+9613228 033	adlette.inati@lau.edu.lb	PI
Scientific	Carolyn Hoppe	181 Oyster Point Blvd. South San Francisco, CA 94080, USA	United States of America	+1 510.289.9097	Carolyn.hoppe@pfizer.com	Medical Monitor

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	Approved
American University of Beirut Medical Center	Miguel Abboud	Professor of Pediatric Hematology and Oncology	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
American University of Beirut Medical Center	10/01/2022	Miguel Abboud	ma56@aub.edu.lb	+9613534213
Nini Hospital	23/06/2021	Elias Bitar	elias.bitar@hopitalnini.com	+961 (0) 6 431 400 ext 3165

Countries of Recruitment

Name
Brazil
Colombia
Germany
Italy
Kenya
Lebanon
Nigeria
Oman
Saudi Arabia
Turkey
United States of America

Health Conditions or Problems Studied

Condition	Code	Keyword
Sickle Cell Disease (SCD)	Sickle-cell disorders (D57)	SCD, vaso-occlusive crisis, blood disorders, hemoglobin, red blood cells, sickle-like shape, mutation in hemoglobin gene, sickle-cell trait, sickle-cell crisis, Sickle Cell Disease SCD, Hydroxyurea/ Hydroxycarbamide Therapy, SCA

Interventions

Intervention	Description	Keyword
Inclacumab	Participants will be randomized with a 1:1 ratio into one of two treatment arms (140 participants per arm) as follows: • Inclacumab 30 mg/kg administered intravenously (IV); or • Placebo administered IV. Randomization may occur up to 5 days after the index VOC has resolved, as assessed by the Investigator (for example, hospital discharge, completion of parenteral analgesia, or transition to oral analgesics).	Treatment

Primary Outcomes

Name	Time Points	Measure
Re-admission for a VOC within 90 days of randomization	Within 90 days of randomization	Following an index VOC, the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication.

Key Secondary Outcomes

Name	Time Points	Measure
Time to first re-admission for a VOC	Within 90 days of randomization	Time to first VOC that required admission to a healthcare facility and treatment with parenteral pain medication.
Readmission for a VOC within 30 days	Within 30 days of randomization	Proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication.
Rate of VOCs leading to a healthcare visit	Within 90 days following randomization	Rate of VOCs leading to a healthcare visit (hospital, emergency room, clinic visit, or remote contact with a healthcare provider) that requires parenteral pain medication (eg, parenteral narcotic agents or parenteral nonsteroidal anti-inflammatory drugs [NSAIDs]), or an increase in treatment with oral narcotics.
Incidence of treatment-emergent adverse events (TEAEs).	Through Day 91	Treatment-emergent adverse events (TEAEs).
PD parameter (P-selectin inhibition)	Through Day 91	To characterize the pharmacodynamics (PD) (P-selectin inhibition) of Inclacumab at 30 mg/kg.
PD parameter (Platelet Leukocyte Aggregation)	Through Day 91	To characterize the pharmacodynamics (PD) (PLA) of Inclacumab at 30 mg/kg

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