A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of Inclacumab in Participants with Sickle Cell Disease Experiencing Vaso-occlusive Crises

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Main Information

Primary registry identifying number
LBCTR2021064791

Protocol number
GBT2104-131

MOH registration number

Study registered at the country of origin
No

Study registered at the country of origin: Specify
Study is currently under registration in the US

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency
18/06/2021

Primary sponsor
Global Blood Therapeutics, Inc.

Primary sponsor: Country of origin
USA

Date of registration in primary registry
23/05/2022

Date of registration in national regulatory agency
18/06/2021

Public title
A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of Inclacumab in Participants with Sickle Cell Disease Experiencing Vaso-occlusive Crises

Acronym

Scientific title
A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of Inclacumab in Participants with Sickle Cell Disease Experiencing Vaso-occlusive Crises

Acronym

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

The primary objective of this study is to evaluate the safety and efficacy of treatment every 12 weeks with inclacumab, a P-selectin inhibitor, to reduce the incidence of vaso-occlusive crises (VOCs) 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

أسبو ًعا باستعمال عقار إنكالكوماب لتقليل حدوث نوبات انسداد االوعية الدموية12الهدف الرئيس لهذه الدراسة هو تقييم أمان وفعالية العالج كل
(PD) والديناميكا الدوائية (PK) لدى المشاركين المصابين بمرض فقر الدم المنجلي. تتمثل االهداف االضافية للدراسة في تقييم الحرائك الدوائية
(QOL). والتغيرات في نوعية الحياة (ADA) لعقارإنكالكوماب، ووجود االجسام المضادة ضد العقاقير

Health conditions/problem studied: Specify

Patients with a diagnosis of sickle cell disease who have experienced between 2 and 10 vaso-occlusive crises in the 12 months preceding enrollment in this study.

Interventions: Specify

This study will assess the safety and efficacy of inclacumab in reducing the frequency of VOCs in approximately 240 adult and adolescent participants (≥ 12 years of age) with SCD. Initial enrollment will include participants ≥ 16 years of age until the independent Data Monitoring Committee (DMC) determines that adequate safety and PK data support the enrollment of participants 12 to 15 years of age.
Eligible participants will be randomized with a 1:1 ratio into one of two treatment arms as follows:
- Inclacumab 30 mg/kg administered IV Q12W; or
- Placebo administered IV Q12W.
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; sub-Saharan Africa; Europe/rest of world).
The total duration of treatment for each participant will be 48 weeks. Doses will be administered at Day 1 and Weeks 12, 24, and 36 with blood levels expected to be in the target range through at least Week 48.

Key inclusion and exclusion criteria: Inclusion criteria

Inclusion Criteria:
1. Participant has a confirmed diagnosis of SCD (HbSS, HbSC, HbSβ0 thalassemia, or HbSβ+ thalassemia genotype).
Documentation of SCD genotype is required and may be based on documented history of laboratory testing or confirmed by laboratory testing during Screening.
2. Participant is male or female, ≥ 12 years of age at the time of informed consent.
NOTE: Initial study enrollment will include participants ≥ 16 years of age until the DMC determines 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.
3. Participant has experienced between 2 and 10 VOCs within the 12 months prior to the Screening Visit as determined by documented medical history.
A prior VOC is defined as an acute episode of pain which:
- 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.
4. Participants receiving erythropoiesis-stimulating agents (ESA, erythropoietin [EPO]) must be on a stable dose for at least 90 days prior to the Screening Visit and expected to continue with the stabilized regimen throughout the course of the study.
5. Participants receiving HU, L-glutamine, or voxelotor (Oxbryta) must be on a stable dose for at least 30 days prior to the Screening Visit and expected to continue with the stabilized regimen throughout the course of the study.
6. Participant has adequate venous access, in the opinion of the Investigator, to comply with study procedures.
7. Participant understands the study procedures and agrees to participate in the study by giving written informed consent or parental permission/written assent.
8. Women of childbearing potential (WOCBP) are required to have a negative serum pregnancy test at the Screening visit and negative urine pregnancy test 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 red blood cell (RBC) transfusion therapy (also termed chronic, prophylactic, or preventative transfusion).
2. Participant is taking or has received crizanlizumab (ADAKVEO) within 90 days prior to the Screening Visit.
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 × 109/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
6. Participant has known active (symptomatic) COVID infection or tests positive for COVID-19 during Screening.
7. Participant has a history of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including severe or unstable pulmonary hypertension.
8. Participant has had treatment for a malignancy within the 12 months prior to the Screening Visit (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 an 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 in another investigational trial within 30 days or 5 half-lives of the investigational agent (whichever is greater) prior to the Screening Visit.
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 48-week treatment period.
15. Participant, parent, or legal guardian are unlikely to comply with the study procedures.
16. Participant has other medical, psychological, or addictive condition 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

N/A

Time perspective: Specify perspective

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
240

Actual enrollment target size

Date of first enrollment: Type
Actual

Date of first enrollment: Date
26/10/2021

Date of study closure: Type
Actual

Date of study closure: Date
31/10/2023

Recruitment status
Recruiting

Recruitment status: Specify

Date of completion
31/01/2024

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

Admin comments

Trial status
Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
N.A	N.A

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
Public	Aziz Zoghbi	MCT-CRO, Berytech Technology and Health, 5th Floor Damascus Road, Beirut, Lebanon	Lebanon	009617100 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	009613534 213	ma56@aub.edu.lb	PI
Scientific	Adlette Inati	Nini Hospital, el Maarad Street, Triploli, Lebanon	Lebanon	009613228 033	adlette.inati@lau.edu.lb	PI
Scientific	Carolyn Hoppe	181 Oyster Point Blvd. South San Francisco, CA 94080, USA	United States of America	+1 510.289.90 97	choppe@gbt.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	Pending

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Nini Hospital	20/04/2021	Nabil Kabbara	Nabil.kabbara@hopitalnini.com	+961 (0) 6 431 400 ext 1062

Countries of Recruitment

Name
Lebanon

Health Conditions or Problems Studied

Condition	Code	Keyword
Sickle Cell Disease	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	Eligible participants will be randomized with a 1:1 ratio into one of two treatment arms as follows: Inclacumab 30 mg/kg administered IV every 12 weeks (Day 1, Week 12, Week 24, and Week 36); or Placebo administered IV every 12 weeks (Day 1, Week 12, Week 24, and Week 36).	Treatment

Primary Outcomes

Name	Time Points	Measure
Rate of VOCs.	the rate of VOCs during the 48-week treatment period will be compared between the inclacumab and placebo arms with the use of negative binomial regression model.	The incidence of VOC events will be collected every 4 weeks. Each month on non-treatment visit days, participants will be contacted by phone to determine if a VOC event or a pain crisis leading to contact with a healthcare provider without a visit to a medical facility has occurred, to collect AEs, and to record changes to concomitant medications. A VOC is defined as an acute episode of pain that: 1) Has no medically determined cause other than a vaso-occlusive event, and 2) Results in a visit to a medical facility (hospitalization, emergency department, urgent care center, outpatient clinic, or infusion center), or results in a remote contact with a healthcare provider; and 3) Requires parenteral narcotic agents, parenteral nonsteroidal anti-inflammatory drugs (NSAIDs), or an increase in treatment with oral narcotics.
Change in Laboratory assessments.	at each visit	Complete blood count, chemistry and coagulation

Key Secondary Outcomes

Name	Time Points	Measure
Time to first VOC during the 48-week treatment period.	48-week treatment period	The secondary efficacy endpoints are based on collection of the incidence and timing of VOCs (per the definition in the primary endpoint) after randomization, QOL assessments and on hospital durations.
Time to second VOC during the 48-week treatment period.	48-week treatment period	The secondary efficacy endpoints are based on collection of the incidence and timing of VOCs (per the definition in the primary endpoint) after randomization, QOL assessments and on hospital durations.
Proportion of participants with no VOCs during the 48-week treatment period.	48-week treatment period	The secondary efficacy endpoints are based on collection of the incidence and timing of VOCs (per the definition in the primary endpoint) after randomization, QOL assessments and on hospital durations.
Rate of VOCs that required admission to a healthcare facility and treatment with parenteral pain medication during the 48-week treatment.	48-week treatment period	The secondary efficacy endpoints are based on collection of the incidence and timing of VOCs (per the definition in the primary endpoint) after randomization, QOL assessments and on hospital durations.
Number of days of inpatient hospitalization for a VOC during the 48-week treatment period.	48-week treatment period	The secondary efficacy endpoints are based on collection of the incidence and timing of VOCs (per the definition in the primary endpoint) after randomization, QOL assessments and on hospital durations.
Incidence of treatment-emergent adverse events.	At each visit	Treatment-emergent adverse events (TEAEs).

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