A Phase 3 Double-blind, Randomized, Placebo-controlled, Multicenter Study of Voxelotor Administered Orally to Patients With Sickle Cell Disease

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Primary ObjectiveThe primary objective is to assess the effect of vexelotor compared to placebo on improvement in hemoglobinSecondary ObjectivesThe secondary objectives are t o evaluate the effects of voxelotor compared to placebo on : - Clinical...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Blood and lymphatic system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON49079

Source
ToetsingOnline

Brief title
GBT440-031, Voxelotor, GBT-HOPE

Condition

- Blood and lymphatic system disorders congenital

Synonym
Anemia, sickel cell disease

Research involving
Human

Sponsors and support

Primary sponsor: Global Blood Therapeutics, Inc.

Source(s) of monetary or material Support: Industry;Global Blood Therapeutics

Intervention

Keyword: Anemia, GBT440, Genetic, Sickle Cell Disease

Outcome measures

Primary outcome

The primary efficacy measure is Hb response., defined as increase of Hb

from baseline by > 1 g/dL at 24 weeks. Hb at 24 weeks is determined by

the average value of Hb levels at Week 20 and Week 24.

Secondary outcome

The secondary efficacy endpoints are as follows:

· Change from baseline in hemoglobin at Week 24

· Change and percent change from baseline in hemolysis measures,

including unconjugated bilirubin, absolute reticulocyte, reticulocytes %,

and LDH at Week 24

· Incidence of severe anemic episodes (Hb < 5.5 g/dL)

· Annualized incidence rate of VOC

Study description

Background summary

Sickle cell disease (SCD) is an inherited disorder caused by a point mutation in the
*-globin gene leading to formation of sickle hemoglobin (HbS). SCD predominantly occurs in
individuals whose ancestors originated from sub-Saharan Africa, Spanish speaking regions of the
Western Hemisphere (South America, Caribbean, and Central America); Saudi Arabia; India; and Mediterranean countries including Turkey, Greece, and Italy.

SCD is the most common single gene disorder in African Americans. A primary and obligatory event in the molecular pathogenesis of SCD is the polymerisation of deoxygenated HbS and the resultant sickling of red blood cells (RBCs). SCD is characterized by hemolytic anemia and vaso-occlusion leading to progressive end-organ damage with a clinical course of life-long pain, disability, and early death.

Management strategies for SCD have evolved very slowly, and treatment of SCD remains a serious unmet medical need. Hydroxyurea (HU) is the only approved therapy for SCD and is indicated to reduce the frequency of painful crisis requiring visiting a medical facility, although it has a minimal effect on the severe burden of daily pain. HU is limited by its side effect profile, poor patient adherence, variable patient responses, and concerns of long-term toxicity. In addition to HU treatment, blood transfusions are used in this patient population to alleviate symptomatic anemia and to prevent certain SCD complications (especially cerebrovascular complications). Attaining anti-sickling activity by blood transfusions has its own limitations: the treatments are expensive, not uniformly accessible and accompanied by risks. The only curative
treatment is bone marrow transplantation from a histocompatible donor, an option that has been available since the 1990s , but bone marrow transplantation carries significant risks and is associated with a ~5% mortality rate. Despite the current standard of care, including HU, blood transfusion, and palliative therapy for acute attacks, patients with SCD continue to suffer serious morbidity and premature mortality.

To date, no drugs have been approved that specifically and directly target HbS polymerization, the underlying mechanism of SCD. There is a significant unmet need in SCD for new mechanism based, preventive, and potentially disease-modifying therapies.

Because oxyhemoglobin is a potent inhibitor of HbS, allosteric modification of Hb to increase the proportion of oxyhemoglobin is a promising strategy to achieve inhibition of HbS in all RBCs. Prior experimental drugs and approaches (discontinued due to poor pharmaceutical
properties or off-target toxicity) have provided proof of concept for the Hb modification approach by demonstrating an increase in oxyhemoglobin, a decrease in clinical biomarkers of hemolysis, and an improvement in incidence of vaso-occlusive crisis (VOC). Global Blood Therapeutics (GBT) has developed GBT440, a small molecule allosteric modulator of Hb oxygen affinity, for the treatment of SCD. GBT440 is administered orally. Data from the GBT440-001 Phase 1/2 study has confirmed that GBT440 treatment in SCD subjects for up to 90 days results in increased Hb oxygen affinity, rapid and sustained improvement in clinical measures of hemolysis consistent with an inhibition of HbS polymerization, and acceptable safety and tolerability when dosed in the target range of 20 to 30% Hb modification. Analysis and modeling of the exposure response relationship from Study GBT440-001 allows for the selection of doses of GBT440 to be studied in Phase 3, which will maintain approximately 20% to 30% Hb modification (with a higher dose achieving this target in a greater

proportion of subjects).

Study objective

Primary Objective
The primary objective is to assess the effect of vexelotor compared to placebo on improvement in hemoglobin

Secondary Objectives
The secondary objectives are t o evaluate the effects of voxelotor compared to placebo on :
- Clinical measures of hemolysis
- Long term VOC incidence

Exploratory objectives
The exploratory objectives are to evaluate the effects of voxelotor compared to placebo on:
- Sickle Cell Disease Severity Measure (SCDSM)
- EuroQol EQ-5D-5L health questionnaire (EQ-5D-DLTM)
- Clinical Global Impression of Change (CGIC)- Groups 1 and 2 only
- Incidence and time to first RBC transfusion and post baseline onset of VOC
- School and/or work attendance and the use of opiod during the treatment period as recorded via eDiary
- Measures related to SCD pathophysiology and their utility as pharmacodynamic markers to evaluate including inflammatory biomarkers (Part1 only), kidney function and RBC rheology
- Measures predictive of response to voxelotor

Safety Objectives
The safety objectives are to assess the safety of voxelotor compared to placebo based on AEs, clinical laboratory tests, physical examinations, and other clinical measures (eg, discontinuations due to AEs, dose reductions).

Pharmacokinetic Objective
The PK objective is to assess the PK of voxelotor as evaluated by population PK analysis.

Study design

This study is a randomized, placebo-controlled, double blind, parallel group, multicenter study of participants, age 12 to 65 years, with SCD (HbSS or HbS*0 thal)
conducted in three groups of study participants, Groups 1, 2, and 3. The key purposes
for each group are:
Group 1:

* Dose selection: different GBT440 doses for further study.
* Final definition of endpoints for patient reported outcomes measure for the Main Population Analysis
* Electronic patient reported outcomes (ePRO) qualification for the Main Population Analysis
Group 2:
* To allow for a seamless transition from Group 1 to Group 3 by continuing enrollment and data collection in the study during the Group 1 treatment period and data analysis (referred to as Group 1 Analysis).
Group 3:
* Establish efficacy and safety of GBT440 at the selected dose. The final data analysis set (referred to as the Main Population) will include
* Group 2 participants
* Assigned to placebo
* Assigned to the selected dose and
* All Group 3 participants.

Intervention

Participants receiving 1500 mg GBT440 will receive five 300 mg capsules or tablets, administered orally, once daily; participants receiving 900 mg GBT440 will receive three 300 mg capsules or tablets, and 2 placebo capsules or tablets administered orally, once daily. Participants randomized to placebo will receive 5 placebo capsules or tablets administered orally, once daily. Study drug may be taken with or without
food. Participants in Group 1 must take their study drug in the mornings and must avoid high fat meals for 4 hours before and 4 hours after taking study drug. Group 2 and Group 3 participants may take study drug in the morning or evening, preferably at same time each day throughout the study (Group 2 and Group 3 participants have no food restrictions/requirements).

Study burden and risks

The emerging clinical experience indicates that GBT440 is safe and well tolerated over a wide range of doses and is anticipated to have favorable benefit-to-risk profile in this proposed study in subjects with SCD. This experience is derived from 11 clinical studies: Phase 1/2 study in healthy subjects and subjects with SCD (GBT440-001), Phase 2a study in pediatrics (GBT440-007), the extension study (GBT440-024) and 8 clinical pharmacology studies (GBT440-002, GBT440-003, GBT440-004, GBT440-005, GBT440-008, GBT440-017, GBT440-018, and GBT440-019). As of 30 September 2016, a total of 205 healthy subjects 47 adult subjects with SCD and 7 pediatric subjects with SCD had been treated with single and multiple doses of GBT440 across all 11 studies. In the multiple dose studies, the most common AEs have been headache, back pain, pain, diarrhea, fatigue, cough, rash, and sickle cell anemia with crisis, which were mainly Grade 1 or Grade 2 in severity, and most of which

resolved without treatment and are easily monitored. The most common treatment-related AE (as assessed by the Investigator) that occurred in subjects with SCD was Grade 1 or 2 headache (28% GBT440 and 36% placebo). In SCD subjects, all serious and severe (Grade 3) AEs have been deemed not related to study drug and are consistent with common clinical events in this patient population. There has been no evidence of mechanism-related toxicity (tissue hypoxia) as indicated by clinical observations, vital signs, ECGs, hematologic changes or cardiopulmonary exercise testing. The PK are dose proportional, with evidence of high GBT440 selectivity for Hb, as evidenced by a high RBC: plasma drug ratio. GBT440 resulted in a large and sustained reduction in clinical measures of hemolysis and an improvement in anemia.
The treatment response result from GBT440-001 are consistent with inhibition of HbS polymerization leading to decreased RBC damage, improved RBC lifespan, and improvement in inflammation and tissue oxygen delivery.
Overall, the safety and treatment response data to date support further investigation of GBT440 as a potential disease-modifying therapy for SCD.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female study participants with Sickle Cell Disease:
* Documentation of SCD genotype (HbSS, HbSC, HbS* thalassemia or
other sickle cell syndrome variants) may be based on history of laboratory testing or must be confirmed by laboratory testing during screening
2. Participants have had at least 1 episode of VOC in the past 12 months.
For study eligibility, VOC is defined as a previously documented episode of ACS or acute painful crisis (for which there was no explanation other than VOC) which required prescription or healthcare professionalinstructed use of analgesics for moderate to severe pain (documentation
must exist in the patient medical record prior to Screening)
3. Age 12 to 65 years
4. Hemoglobin (Hb) *6.0 and *10.5 g/dL during screening
5. Absolute reticulocyte count and % reticulocyte count must be >1.5 × ULN during Screening
6. For participants taking hydroxyurea (HU), the dose of HU (mg/kg) must be stable for at least 3 months prior to signing the ICF and with no anticipated need for dose adjustments during the study, in the opinion of the Investigator
7. Participants must demonstrate 75% compliance with ePRO measure completion to be enrolled (participants will be given an ePRO device for at least 28 days during Screening; participants who are 60 to 74% compliant can re-screen once with Investigator approval; re-screening is
not allowed for participants who are <60% compliant) 8. Participants, who if female and of child bearing potential, are using highly effective methods of contraception from study start to 3 months
after the last dose of study drug, and who if male are willing to use barrier methods of contraception, from study start to 3 months after the last dose of study drug
9. Participant has provided documented informed consent or assent (the informed consent form [ICF] must be reviewed and signed by each participant; in the case of pediatric participants, both the consent of the participant's legal representative or legal guardian, and the participant's
assent must be obtained)

Exclusion criteria

1. More than 10 VOCs within the past 12 months that required a hospital,
emergency room or clinic visit

2. Female who is breast feeding or pregnant
3. Patients who are receiving regularly scheduled blood (RBC)
transfusion therapy (also termed chronic, prophylactic, or preventive
transfusion) or have received a RBC transfusion for any reason within 28
days of signing the ICF 4. Hospitalized for sickle cell crisis or other vaso-occlusive event
within
14 days of signing the ICF (i.e., a vaso-occlusive event cannot be within 14 days prior to ICF)
5. Hepatic dysfunction characterized by alanine aminotransferase (ALT) >4 × ULN
6. Participants with clinically significant bacterial, fungal, parasitic or viral infection which
require therapy:
* Participants with acute bacterial infection requiring antibiotic use
should delay screening/enrollment until the course of antibiotic therapy has been completed.
* Participants with known active hepatitis A, B, or C or who are known to be human
immunodeficiency virus (HIV) positive 7. Severe renal dysfunction (estimated glomerular
filtration rate at the Screening visit; calculated by the central laboratory) <30mL/min/1.732
or on chronic dialysis
8. 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)
9. History of unstable or deteriorating cardiac or pulmonary disease
within 6 months prior to consent including but not limited to the following:
* Unstable angina pectoris or myocardial infarction or elective coronary intervention
* Congestive heart failure requiring hospitalization
* Uncontrolled clinically significant arrhythmias
10. Any condition affecting drug absorption, such as major surgery involving the stomach or
small intestine (prior cholecystectomy is acceptable)
11. Participated in another clinical trial of an investigational agent (or medical device) within
30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently
participating in another trial of an investigational agent (or medical device)
12. Inadequate venous access as determined by the Investigator/site staff
13. Medical, psychological, or behavioral conditions, which, in the opinion of the Investigator,
may confound study interpretation, interfere with compliance, or preclude informed consent

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-02-2018
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GBT440
Generic name:	Voxelotor

Ethics review

Approved WMO Date:	28-03-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-08-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-12-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-003370-40-NL
ClinicalTrials.gov	NCT03036813
CCMO	NL60453.018.17