A Phase 2a study to assess efficacy and safety of VIT-2763 in subjects with sickle cell disease

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Main Information

Primary registry identifying number
LBCTR2021064783

Protocol number
VIT-2763-SCD-202

MOH registration number

Study registered at the country of origin
No

Study registered at the country of origin: Specify
No. Prevalence of the disease is low in the country of origin Switzerland

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency

Primary sponsor
Vifor (International) Inc.

Primary sponsor: Country of origin
Switzerland

Date of registration in primary registry
15/07/2021

Date of registration in national regulatory agency

Public title
A Phase 2a study to assess efficacy and safety of VIT-2763 in subjects with sickle cell disease

Acronym

Scientific title
A Phase 2a, double-blind, randomised, placebo-controlled, ascending dose and maintenance dose, efficacy, and safety study of multiple doses of VIT-2763 in subjects with sickle cell disease

Acronym

Brief summary of the study: English
This study is is a Phase 2a, double-blind, randomised, placebo-controlled, ascending dose and maintenance dose, efficacy, and safety study of multiple doses of VIT-2763 in subjects with sickle cell disease. The primary objective of this study is to explore the effect of VIT-2763 on markers of haemolysis.

Brief summary of the study: Arabic
أ ، مزدوجة التعمية ، عشوائية ، خاضعة للتحكم الوهمي ، جرعة تصاعدية وجرعة صيانة وفعالية ودراسة2هذه الدراسة عبارة عن مرحلة
في الأشخاص المصابين بمرض الخلايا المنجلية. الهدف الأساسي من هذه الدراسة هو استكشاف تأثير VIT-2763 سلامة لجرعات متعددة من
على علامات انحلال الدم VIT-2763.

Health conditions/problem studied: Specify
sickle cell disease (SCD) (sickle haemoglobin (HbS)/S or HbS/βT0genotype)

Interventions: Specify
Male or female Adults(18-50 years) with sickle cell disease (SCD) (sickle haemoglobin (HbS)/S or HbS/βT0genotype).
At randomisation/baseline (Part A), 25 subjects with SCD will be randomised in a 1:1:1:1:1 ratio into 4 VIT-2763 dose groups to receive either 30 mg (Cohorts 1a and 1b) or 60 mg VIT-2763 (Cohorts 2a and 2b) and 1 placebo group (Cohort 3).
During Part B, subjects in Cohort 1a (VIT-2763 30 mg) and Cohort 2a (VIT-2763 60 mg) will remain on the same VIT-2763 dose as in Part A; whereas, subjects in Cohort 1b and Cohort 2b will continue with an increased dose of VIT-2763, 60 mg and 120 mg, respectively.
Subjects randomised to placebo during Part A (Cohort 3) will continue unchanged during Part B.

Key inclusion and exclusion criteria: Inclusion criteria

Inclusion Criteria:
1. Subject has provided the appropriate written informed consent before any study-specific procedures are performed including screening procedures.
2. Ability to understand the requirements of the study and abide by the study restrictions, and agreement to return for the required assessments.
3. Male or female subjects with confirmed diagnosis of SCD, including HbS/S or HbS/βT0 genotype.
4. Subjects who had at least 1 and no more than 6 VOC episodes reported within 12 months prior to screening. Note: A VOC episode is defined as a
documented episode of acute chest syndrome or acute painful crisis for the main indication of SCD, which led to health-professional instructed prescription or use of analgesics for moderate to severe pain.
5. 18 to 50 years of age inclusive at the time of screening.
6. Body weight ≥50 kg and ≤100 kg at screening and baseline.
7. Absolute reticulocyte count and percentage reticulocyte count >1.5 × upper limit of normal (ULN) during screening.
8. Subjects on concomitant hydroxyurea must be on a stable dose (mg/kg) for ≥3 months prior to screening Visit V1. There should be no planned dose adjustments during the course of the study in the opinion of the Investigator.
9. Female subjects of childbearing potential, must have negative pregnancy tests at screening and before randomisation, must have stopped breastfeeding as of first dose, and must either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and source documented) or must be willing to use adequate contraceptive precautions, i.e., highly effective method of birth control. Abstinence should only be used as a contraceptive method if it is in line with the subjects' usual and preferred lifestyle, and periodic abstinence (calendar, symptothermal, postovulation methods) is not an acceptable method of contraception. Female subjects must agree to use adequate contraception during the study and for 1 month after the last dose of investigational medicinal product (IMP) or according to local requirements, whichever is longer. Effective contraception (highly effective method of birth control, i.e., with a failure rate of <1% per year, when used consistently and correctly) such as implants, injectables, combined oral contraceptives (see below), intrauterine devices, sexual abstinence, or vasectomised partner must be used. Non-childbearing potential includes being surgically sterilised at least 6 months prior to the study.
Note: For female subjects participating in this study, continuous use of hormonal contraception alone is not sufficient, because potential interactions
via cytochrome P450 (CYP) enzymes may alter the efficacy of hormonal contraception. The continuous use of hormonal contraception by a female
subject should be combined with the use of a condom by the male partner; the condom should then be used together with a spermicide or adequate andapproved alternatives.
10. Male subjects must practice true abstinence (abstinence should only be used as a contraceptive method if it is in line with the subjects' usual and preferred lifestyle, and it is continuous throughout the study) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, and for at least 1 month–sufficiently exceeding 5 times the mean t1/2 of VIT -2763 based on multiple dose human PK data following IMP discontinuation, even if he has undergone a successful vasectomy.

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

50

Key inclusion and exclusion criteria: Exclusion criteria

Exclusion Criteria:
1. Subjects with confirmed diagnosis of HbS/βT+ genotype or HbSC disease.
2. Hb level <6.0 g/dl or >10.4 g/dl at screening Visit V1 (based on local laboratory value).
Note: The Hb value at screening Visit V1 will be used for eligibility determination. However, the baseline Hb value determined at Visit V2 (Day 1 pre-dose) also needs to be within the above specified range.
3. Having received RBC transfusion therapy within 4 weeks prior to screening, or ongoing or planned RBC transfusion therapy during the course of the study (including chronic, prophylactic, or preventive transfusion to treat SCD).
4. Ferritin level <30 µg/l or calculated transferrin saturation (TSAT) level <25% or total iron-binding capacity (TIBC) level <250 µg/dl at screening.
5. Subjects being hospitalised for SCD-related events (including pain crisis and VOC) within 30 days before the screening visit. Note: SCD must have been the main cause for the hospitalisation to fulfil this criterion.
6. Chronic liver disease or history of liver cirrhosis, and/or alanine aminotransferase or aspartate aminotransferase, above 3-fold the ULN range at
baseline.
7. Estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m2, and/or significant urinary albumin/creatinine ratio >30 mg/g (>3.39 mg/mmol) at
screening or on chronic dialysis. Note: eGFR should be estimated according to Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI).
8. Newly diagnosed folate deficiency anaemia (i.e., folic acid <2 ng/ml), which is considered clinically relevant by the Investigator at screening. Subjects with known folate deficiency anaemia who are on ≥12 weeks stable replacement therapy at screening are eligible. Note: A subject fulfilling this criterion will be excluded but can be re-screened at a later time point.
9. Subjects with history of partial or total splenectomy within 6 months prior tothe screening visit.
10. Any history or clinically important finding of cardiac or pulmonary disorders, including (but not limited to) clinically relevant or uncontrolled cardiac
arrhythmia, cardiomyopathy, coronary disease (unstable angina pectoris or myocardial infarction or elective coronary intervention), valve disorder, or

heart failure according to New York Heart Association classification 3-4.
11. Known pulmonary hypertension, defined as a tricuspid regurgitant velocity (TRV) ≥2.5 m/s, NT-proBNP ≥160 pg/ml or confirmed by right heart
catheterisation.
12. Any clinically relevant abnormal 12-lead electrocardiogram (ECG) finding during screening or prior to randomisation (as deemed by the Investigator)including (but not limited to) any of the following:
• PR interval >0.21 seconds
• Evidence or history of second- or third-degree atrioventricular block
• QRS interval >0.12 seconds
13. Family history of long-QT syndrome or sudden death without a preceding diagnosis of a condition that could be causative of sudden death (such as known coronary artery disease, congestive heart failure, or terminal cancer), or subjects with QT interval corrected (QTcF) >450 msec.
14. Clinically significant bacterial, fungal, parasitic, or viral infection which requires therapy. Note: A subject meeting this criterion should delay screening and/or enrolment for a minimum of 2 weeks, or if excluded can be re-screened at maximum 2 times at a later time point.
• Known history, and/or positive result on screening for hepatitis B surface antigen, hepatitis B virus, hepatitis C virus, or HIV infection. Note: Subjects with known hepatitis B surface antigen positivity and/or hepatitis C virus antibody positivity will be allowed to participate only if the disease has been treated efficiently/is not active.
• Known active COVID-19 infection (positive result of a SARS-Cov-2 virus test (nucleic acid or antigen detection) within 2 weeks preceding screening), or any other active infection. Note: A subject who tested positive within 2 weeks preceding screening or during screening will be excluded but can be re-screened at a later time point as per Investigator's judgement and if confirmation of a negative SARS-CoV-2 test is available based on standard of care.
15. Use of any prohibited medication(s), including (but not limited to):
• Prior or concomitant use of any medication that is known to prolong the QT/QTc interval or the PR/QRS interval, within 3 weeks prior to screening and until end of study (EoS).
• Previous oral or intravenous iron therapy ≤4 weeks prior to screening and until EoS.
• Any drug that is metabolised mainly via CYP 3A4 and/or CYP 2D6 (except hormonal contraceptives that have been used by females at constant doses at minimum for 4 weeks prior to screening), or any known strong CYP 3A4 or CYP 2D6 inhibitor or inducer, or known P-glycoprotein (P-gp) inhibitors as of 4 weeks prior to screening and until EoS.
• Receipt of HbS polymerisation inhibitors (e.g., voxelotor), l-glutamine, erythropoietin stimulating/maturation agent treatment, crizanlizumab or any other haematopoietic growth factor treatment within 8 weeks prior to screening Visit V1 and until EoS, or anticipated need for such agents during the study.
• Any prior gene therapy.
• Use of chronic anticoagulant therapy unless treatment stopped at least 28 days prior to randomisation. Anticoagulant therapies used for prophylaxis for surgery or high-risk procedures as well as low molecular weight heparin for superficial venous thrombosis and chronic aspirin are allowed.
• Participation in any other clinical study with an investigational product <30 days prior to screening Visit V1 and until EoS.
16. Known sensitivity to any components of the study products to be administered.
17. Previous participation to this study with at least one administration of the IMP.
18. History of drug or alcohol abuse within 2 years prior to screening.
19. Pregnant (e.g., positive pregnancy test) or females currently breastfeeding.
20. History or known concomitant solid tumours and/or haematological malignancies unless resolved in the ≥5 past years, except for basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, incidental histologic finding of prostate cancer (T1a or T1b according to the Classification of Malignant Tumours clinical staging system).
21. Vulnerable subjects (e.g., subjects kept in detention, protected adults under guardianship, trusteeship, and soldiers) or subjects committed to an institution by governmental or juridical order, and any other vulnerable subjects.
22. Unable to take and absorb oral medications, unable to swallow Size 0 capsules.
23. Known significant medical condition(s), anticipated need for major surgery during the study, or any other kind of disorder that may be associated with increased risk to the subject, or may interfere with study assessments, outcomes, or the ability to provide written informed consent or comply with study procedures, in the Investigator's opinion.
24. Acute peptic stomach or duodenal ulcer in the previous 6 months before screening.
25. Any employee or their close relatives of the Sponsor, or of a Contract Research Organisation (CRO), or a study site involved in the trial.

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Other

Trial scope: Specify scope

Study design: Allocation

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

Placebo

Study phase

2

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

VIT-2763

Year of authorization

Month of authorization

Type of IMP

Cell therapy

Pharmaceutical class

VIT-2763 is a Ferroportin (FPN) inhibitor and hepcidin-mimetic.

Therapeutic indication

Sickle cell disease.

Therapeutic benefit

VIT-2763 is developed as a novel oral drug targeting FPN, and as such for the treatment of secondary iron overload and conditions in which iron metabolism is involved: ineffective or otherwise disturbed erythropoiesis, including (but not limited to) hereditary haemochromatosis, haemoglobinopathies (e.g., thalassaemia and SCD), or myeloproliferative/dysplastic disorders (e.g., polycythaemia vera and myelodysplastic
syndrome, respectively). Furthermore, the oral FPN inhibitor VIT-2763 has shown positive results on haemolysis, haemodynamics, and prevention of vaso-occlusion in a model of 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 without DNA

Biospecimen description

Blood and urine samples will be collected for routine clinical safety laboratory assessments according to the schedule of assessments

Target sample size

Actual enrollment target size

25

Date of first enrollment: Type
Anticipated

Date of first enrollment: Date
30/09/2021

Date of study closure: Type
Anticipated

Date of study closure: Date
30/09/2022

Recruitment status
Pending

Recruitment status: Specify

Date of completion

IPD sharing statement plan
No

IPD sharing statement description
NA

Additional data URL

Admin comments

Trial status
Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
EMA	2020-005072-34
FDA US IND	147878

Sources of Monetary or Material Support

Name
Vifor (International) Inc.

Secondary Sponsors

Name
Not Applicable

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
Chronic Care Center	Dr. Suzanne Koussa	Hematology and Oncology	Pending
American University of Beirut Medical Center	Dr. Ali Taher	Hematology and Oncology	Pending
Nini Hospital	Dr. Adlette Inati	Hematology and Oncology	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Nini Hospital	20/04/2021	Kamleh Ibrahim	kamleh.ibrahim@hopitalnini.com	00961 6 431400 ext 1062

Countries of Recruitment

Name
Lebanon
United States of America
United Kingdom
Greece

Health Conditions or Problems Studied

Condition	Code	Keyword
sickle cell disease	Sickle-cell disorders (D57)	sickle cell disease

Interventions

Intervention	Description	Keyword
VIT-2763 oral capsules of 2 dosage strengths (30 mg and 60 mg)	□ Treatment Group 1a: 1 capsule of 30 mg VIT-2763 in the morning and 1 capsule of placebo in the evening for 8 weeks □ Treatment Group 1b: 1 capsule of 30 mg VIT-2763 in the morning and 1 capsule of placebo in the evening for 4 weeks followed by 1 capsule of 30 mg VIT-2763 in the morning and 1 capsule of 30mg VIT-2763 in the evening for 4 weeks □ Treatment Group 2a: 1 capsule of 30 mg VIT-2763 in the morning and 1 capsule of 30mg VIT-2763 in the evening for 8 weeks □ Treatment Group 2b: 1 capsule of 30 mg VIT-2763 in the morning and 1 capsule of 30mg VIT-2763 in the evening for 4 weeks followed by 1 capsule of 60 mg VIT-2763 in the morning and 1 capsule of 60 mg VIT-2763 in the evening for 4 weeks □ Treatment Group 3: 1 capsule of placebo in the morning and 1 capsule of placebo in the evening for 8 weeks.	VIT-2763

Primary Outcomes

Name	Time Points	Measure
Mean change in heamolysis marker	from baseline to after 8 weeks treatment	reduction of indirect bilirubin

Key Secondary Outcomes

Name	Time Points	Measure
Frequency and severity of reported or observed AEs by SOC and PTs	up to 4 weeks after EoT	All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA)
Changes in clinical laboratory safety tests	After 2, 4, 6, and 8 weeks of treatment and 4 weeks after EoT	serum biochemistry, safety haematology, and urinalysis
Changes in 12-Lead ECG	after 2, 4, 6, and 8 weeks of treatment and 4 weeks after EoT.	ventricular rate, PR interval, QRS duration, QT interval and QTcF
Changes in blood inflammatory markers	from baseline after 2, 4, 6, and 8 weeks of treatment and 4 weeks after EoT	high sensitivity C-reactive protein, interleukin 1 and interleukin 6, tumour necrosis factor alpha, soluble vascular cell adhesion molecule 1, endothelin-1, soluble platelet-selectin, and xanthine oxidase
Assessment of iron-related parameters and markers of erythropoiesis	from baseline after 2, 4, 6, and 8 weeks of treatment and 4 weeks after EoT	total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin
Change in patient reported outcomes	from baseline after 2, 4, 6 and 8 weeks of treatment.	using ASCQ-Me
Changes in abnormal RBCs (sickling)	baseline after 2, 4, 6 and 8 weeks of treatment and 4 weeks after EoT.	peripheral blood smear
Number of VOC episodes and visceral infarctions	over 8 weeks of treatment and 4 weeks after EoT.	VOC episodes
PK parameters	from pre-dose trough to 1 hour and 3 hours post-morning dose at selected study visits.	Cmax, clearance, distribution volume, AUC
Changes in haematological indices	from baseline after 2, 4, 6, and 8 weeks of treatment and 4 weeks after EoT.	Hb concentration, RBC count, Hct, MCV, MCH, MCHC, CHCM, RDW, WBC analyses including differential WBC counts, platelet and reticulocyte counts, percentage reticulocytes, percentage hypochromic microcytic RBCs (RBC volume versus Hb scatterplot analysis),
Physical examination findings	screening/Visit V1 (i.e., Day -14 to Day -1) and on Visits V2 (Day 1), V4 (Day 28), V6 (Day 56), and V7 (Day 84). Facultative physical examinations can be performed on indication, i.e., symptom-directed, on all other visits.	general appearance, head (eyes, ears, nose, and throat), cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymph nodes, and skin.
Vital signs	Vital signs should be performed before IMP administration (trough), after a resting period of at least 5 minutes in all visits	(blood pressure, pulse rate)
Mean change from baseline in haemolysis markers	after 8 weeks of treatment.	measured by direct and total bilirubin, lactate dehydrogenase (LDH), potassium, Hb and free haptoglobin

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