# CLINICAL STUDY PROTOCOL
# VIT-2763-SCD-202

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| Title: | A Phase 2a, double-blind, randomised, placebo-controlled, efficacy, and safety study of multiple doses of VIT-2763 in subjects with sickle cell disease (ViSion Serenity) |
| Clinical Protocol Number: | VIT-2763-SCD-202 |
| Version Date: | 16 March 2023 |
| Version Number: | 4.0 |
| Prior Version/Amendments: | Version 3.0/Amendment 2, 9 March 2022<br>Version 2.0/Amendment 1, 3 March 2021<br>Version 1.0/Original, 17 December 2020 |
| Investigational Drug: | VIT-2763 (INN: Vamifeport) |
| IND Number: | 147878 |
| EudraCT Number: | 2020-005072-34 |
| Co-ordinating Investigators: | Dr Banu Kaya, MD and<br>PPD Dr Adlette Inati, MD |
| Sponsor Contact: | PPD |
| Sponsor Address: | Vifor (International) Inc.<br>Rechenstrasse 37<br>St. Gallen CH-9014<br>Switzerland<br>Phone +41 58 851 80 00 |
| Medical Monitor: | PPD |

# SIGNATURE PAGE

## Declaration of Sponsor

Title: A Phase 2a, double-blind, randomised, placebo-controlled, efficacy, and safety study of multiple doses of VIT-2763 in subjects with sickle cell disease (ViSion Serenity).

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This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Council for Harmonisation Guideline for Good Clinical Practice as amended.

PPD

Date (day month year)

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**Declaration of Co-ordinating Investigator**

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| Signature of Co-ordinating Investigator<br>Banu Kaya, Dr, Barts Health<br>NHS Trust - The Royal London Hospital<br>80 Newark Street, London, [redacted] UK<br>Phone: [redacted]<br>Email: [redacted] | Date (day month year) |

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| Signature of Co-ordinating Investigator<br>Adlette Inati, PPD<br>Hopital Nini, Rue El Maarad<br>Tripoli, Lebanon<br>Phone: [redacted]<br>Email: [redacted] | Date (day month year) |

# SIGNATURE PAGE

## Declaration of National Co-ordinating Investigator

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| Signature of National Co-ordinating Investigator<br>Name, Title, Address, Telephone Number, and Email of National Co-ordinating Investigator | Date (day month year) |

# INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

Title: A Phase 2a, double-blind, randomised, placebo-controlled, efficacy, and safety study of multiple doses of VIT-2763 in subjects with sickle cell disease (ViSion Serenity).

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I have read the attached protocol as specified on this page and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice as amended, and applicable local regulations and guidelines.

I agree to ensure that financial disclosure statements will be completed by: me (including, if applicable, my spouse (or legal partner) and dependent children) my Sub-investigators before the start of the study and to report any changes that affect my financial disclosure status for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Vifor Pharma and <<licensee's name>>.

Signature by the Investigator on this Protocol Signature Page documents review, agreement and approval of the requirements contained within this protocol.

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| Signature of Principal Investigator<br>Name, Title, Address, Telephone Number, and Email of Principal Investigator | Date (day month year) |

# SYNOPSIS

VIT-2763-SCD-202

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| Title: | A Phase 2a, double-blind, randomised, placebo-controlled, efficacy, and safety study of multiple doses of VIT-2763 in subjects with sickle cell disease (ViSion Serenity) |
| Short Title: | A Phase 2a study to assess efficacy and safety of VIT-2763 in subjects with sickle cell disease |
| Study Product(s): | VIT-2763 (vamifeport) |
| Study Population: | Adults with sickle cell disease (SCD) (sickle haemoglobin (HbS)/S or HbS/βT0 genotype) |
| Phase: | 2a |
| Sponsor: | Vifor (International) Inc. |
| Protocol Number: | VIT-2763-SCD-202 |
| Co-ordinating Investigators: | Dr Banu Kaya, MD and<br>PPD Dr Adlette Inati, MD |
| Objectives: | Primary Objective:<br>The primary objective of this study is to explore the effect of VIT-2763 on markers of haemolysis.<br>Secondary Objective:<br>The secondary objective of this study is to assess the safety and tolerability of VIT-2763 in SCD patients.<br>Exploratory Objectives:<br>• To explore the effect of VIT-2763 on haematological indices and vascular inflammation.<br>• To explore the effect of VIT-2763 on iron and erythropoiesis related blood parameters.<br>• To explore the effect of VIT-2763 on patient reported outcomes (pain and quality of life).<br>• To explore the pharmacokinetics (PK) of VIT-2763 using a population PK approach.<br>• To explore changes in abnormal red blood cells (RBCs) (sickling) assessed by peripheral blood smear.<br>• To explore the number of vaso-occlusive crises (VOC) episodes and visceral infarctions. |

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| Design: | Phase 2a, multiple dose, double-blind, randomised, placebo-controlled study in SCD subjects. VIT-2763 will be administered daily during a period of 8 weeks, according to Figure 1 and the treatment scheme below: |

**Treatment Scheme**

| | Baseline to Week 8 | | | | |
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| | **Morning Dose** | **Evening Dose** | **Morning Dose** | **Afternoon Dose** | **Evening Dose** |
| Cohort 1 (n=6) | 60 mg VIT-2763 | 60 mg VIT-2763 | | | |
| Cohort 2 (n=6) | 120 mg VIT-2763 | 120 mg VIT-2763 | | | |
| Cohort 3 (n=6) | | | 120 mg VIT-2763 | 120 mg VIT-2763 | 120 mg VIT-2763 |
| Cohort 4a (n=4) | Placebo | Placebo | | | |
| Cohort 4b (n=2) | | | Placebo | Placebo | Placebo |

Note: n=Number of subjects per cohort.

At randomisation/baseline, 24 subjects with SCD will be randomised in a 3:3:3:2:1 ratio into 3 VIT-2763 dose groups to receive either 60 mg twice daily (BID) (120 mg/day, Cohort 1), or 120 mg BID (240 mg/day, Cohort 2), or 120 mg 3 times daily (TID) (360 mg/day, Cohort 3) and 2 placebo groups (BID, Cohort 4a or TID, Cohort 4b).

All subjects will be dosed for 8 consecutive weeks.

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| Duration: | The expected duration of subject participation is a maximum of 16 weeks, including a non-treatment screening period of up to 4 weeks (28 days), an 8-week (56±4 days) treatment period, and a 4-week (28±4 days) safety follow-up period. |
| Treatment: | **Active Treatment**<br><br>VIT-2763 oral capsules of 2 dosage strengths (30 mg and 60 mg) with identical size, shape, and colour will be available. Capsules will be administered orally to achieve the specified dose and according to the administration schedule below.<br><br>**Placebo Treatment**<br><br>Matching placebo capsules to VIT-2763 will be available, administered orally, and according to the administration schedule below.<br><br>**Administration Schedule**<br><br>Randomisation to all dosage groups will be done by using a validated centralised interactive web response system (IWRS) and will be stratified by genotype (HbS/S - HbS/βT0). |

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| | **Administration Schedule**<br>**Total Daily Dose of VIT-2763** / **Number of Capsules/Day**: **VIT-2763** / **Placebo**<br>120 mg: 4 × 30 mg / N/A<br>240 mg: 4 × 60 mg / N/A<br>360 mg: 6 × 60 mg / N/A<br>0 mg: N/A / 4[1] or 6[2] × placebo<br>1 Cohort 4a.<br>2 Cohort 4b.<br>Note: N/A=Not applicable. |
| Inclusion Criteria: | 1. Subject has provided the appropriate written informed consent before any study-specific procedures are performed including screening procedures.<br>2. Ability to understand the requirements of the study and abide by the study restrictions, and agreement to return for the required assessments.<br>3. Male or female subjects with confirmed diagnosis of SCD, including only HbS/S or HbS/βT0 genotype.<br>4. Subjects who had at least 1 and no more than 10 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 opioids (excluding codeine) for moderate to severe pain.<br>5. 18 to 60 years of age inclusive at the time of screening.<br>6. Body weight ≥40 kg and ≤120 kg at screening and baseline.<br>7. Absolute reticulocyte count or percentage reticulocyte count >1.5 × upper limit of normal (ULN) during screening.<br>8. Subjects on concomitant hydroxyurea treatment 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.<br>9. Female subjects of childbearing potential must have negative pregnancy tests at screening (serum pregnancy test) and before randomisation (urine pregnancy test), 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 until at least 1 week after the last dose of investigational medicinal product (IMP) or requirements from other co-medications taken, e.g., hydroxyurea 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. |

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| | Non-childbearing potential includes being surgically sterilised at least 6 months prior to the study.<br><br>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 with spermicide or adequate and approved alternatives by the (fertile) male partner. |
| Exclusion Criteria: | 1. Subjects with confirmed SCD diagnosis other than HbS/S and HbS/βT0.<br>2. Haemoglobin (Hb) level <6.0 g/dl in any subject or >10.4 g/dl for female and >11.0 g/dl for male subjects at screening Visit V1.<br><br>Note: The Hb value at screening Visit V1 will be used for eligibility determination based on the central laboratory result. However, the baseline Hb value determined at Visit V2 (Day 1 pre-dose) also needs to be within the above specified range based on the local laboratory result.<br>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).<br>4. Subjects with a serum ferritin level of <30 µg/l at screening.<br>5. Calculated transferrin saturation (TSAT) level <25% at screening. However, in case the total iron-binding capacity (TIBC) level is within normal ranges of the central laboratory values, the subject will not be excluded.<br>6. Subjects being hospitalised for SCD-related events (including pain crisis and VOC) within 14 days before the screening visit. Note: SCD must have been the main cause for the hospitalisation to fulfil this criterion.<br>7. Chronic liver disease or history of liver cirrhosis, and/or alanine aminotransferase or aspartate aminotransferase, above 3-fold the ULN range at baseline.<br>8. Estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 $m^2$ at screening. Note: eGFR should be estimated according to Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI).<br>9. 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.<br>10. Subjects with history of partial or total splenectomy within 3 months prior to the screening visit.<br>11. 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.<br>12. A diagnosis of any form of pulmonary hypertension. |

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| | 13. 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:<br>• PR interval >0.21 seconds<br>• Evidence or history of second- or third-degree atrioventricular block<br>• QRS interval >0.12 seconds<br>14. 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.<br>15. 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.<br>16. 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.<br>17. 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.<br>18. Use of any prohibited medication(s), including (but not limited to):<br>• Prior or concomitant use of any medication that is known to prolong the QT/QTc interval or the PR/QRS interval, within 4 weeks prior to screening and until end of study (EoS).<br>• Previous oral or intravenous iron therapy or iron chelation therapy ≤4 weeks prior to screening and until EoS.<br>• Any known strong or moderate inhibitors and/or inducers of CYP 3A4 enzyme within 4 weeks prior to randomisation and during treatment period, or any known strong CYP 2D6 inhibitors or inducers as of 4 weeks prior to screening and until EoS.<br>• Receipt of HbS polymerisation inhibitors (e.g., voxelotor), L-glutamine, erythropoietin stimulating/maturation agent treatment, crizanlizumab or any other haematopoietic growth factor treatment within 5 half-lives of the respective drug prior to screening Visit V1 and until EoS, or anticipated need for such agents during the study.<br>• Any prior gene therapy. |

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| | • Use of chronic anticoagulant therapy unless treatment stopped at least 4 weeks 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 platelet aggregation inhibitors including acetylsalicylic acid are allowed.<br>• Participation in any other clinical study with an investigational product within 4 weeks prior to screening Visit V1 and until EoS.<br>19. Concomitant use of hormonal contraceptives (contraception associated with inhibition of ovulation), which are metabolised through CYP 3A4, are not allowed as the sole measure to prevent pregnancy within 4 weeks prior to screening and until 1 week after the last IMP administration (e.g., combined hormonal contraception (oral, intravaginal, transdermal)) and progesterone-only hormonal contraception (oral, injectable, implantable).<br>20. Known sensitivity to any components of the study products to be administered.<br>21. Previous participation to this study with at least 1 administration of the IMP.<br>22. History of drug or alcohol abuse within 2 years prior to screening.<br>23. Pregnant (e.g., positive serum pregnancy test) or females currently breastfeeding.<br>24. History or known concomitant solid tumours and/or haematological malignancies unless resolved in the ≥2 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).<br>25. 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.<br>26. Unable to take and absorb oral medications, unable to swallow Size 0 capsules.<br>27. 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.<br>28. Acute peptic stomach or duodenal ulcer in the previous 3 months before screening and/or not healed after 3 months of proton-pump inhibitors therapy (or adequate standard of care therapy).<br>29. Occult or evident not controlled haemorrhages (i.e., ulcerations of gastrointestinal tract or body surface).<br>30. Any employee or their close relatives of the Sponsor, or of a Contract Research Organisation (CRO), or a study site involved in the trial. |

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| Endpoints: | Primary Endpoint:<br>• Mean change from baseline in haemolysis markers as measured by reduction of indirect bilirubin after 8 weeks of treatment.<br>Secondary Endpoints:<br>• Mean change from baseline in haemolysis markers as measured by direct and total bilirubin, lactate dehydrogenase (LDH), potassium, Hb and free haptoglobin after 8 weeks of treatment.<br>• Frequency and severity of reported or observed adverse events (AEs) by system organ class (SOC) and preferred terms (PTs) using Medical Dictionary for Regulatory Activities (MedDRA) coded terms, indicating seriousness criteria and relatedness over 8 weeks of treatment.<br>Exploratory Endpoints:<br>• Changes in haemolysis markers as measured by indirect, direct, and total bilirubin, LDH, potassium, Hb, and free haptoglobin, from baseline after 2, 4, and 6 weeks of treatment and 4 weeks after end of treatment (EoT).<br>• Frequency and severity of reported or observed AEs by SOC and PTs using MedDRA coded terms, indicating seriousness criteria and relatedness up to 4 weeks after EoT<br>• Changes in clinical laboratory safety tests (serum chemistry, safety haematology, and urinalysis) from baseline, 12-lead ECG, physical examination findings, vital signs (blood pressure, pulse rate), and haematological changes due to iron-restricted erythropoiesis after 2, 4, 6 and 8 weeks of treatment and 4 weeks after EoT.<br>• Changes in haematological indices including Hb concentration, RBC count, haematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC), corpuscular haemoglobin concentration mean (CHCM), RBC distribution width, white blood cell (WBC) analyses including differential WBC counts, platelet, and reticulocyte counts, percentage reticulocytes, percentage hypochromic microcytic RBCs (RBC volume versus Hb scatterplot analysis), from baseline after 2, 4, 6 and 8 weeks of treatment and 4 weeks after EoT.<br>• Changes in blood inflammatory markers as measured by 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, from baseline after 2, 4, 6 and 8 weeks of treatment and 4 weeks after EoT.<br>• Assessment of iron-related parameters and markers of erythropoiesis: changes in total serum iron, serum ferritin, serum transferrin, TSAT, hepcidin, and erythropoietin, from baseline after 2, 4, 6 and 8 weeks of treatment and 4 weeks after EoT.<br>• VIT-2763 PK parameters ($C_{max}$, clearance, distribution volume, area under the curve (AUC)). Sparse sampling for determination of VIT-2763 plasma concentration following multiple dosing will be obtained from pre-dose to 2 hours, 4 hours and 6 hours post-morning dose at study Visit V4. A population PK approach will be applied to estimate PK parameters. |

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| | • Change in patient reported outcomes using Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me) from baseline after 2, 4, 6 and 8 weeks of treatment.<br>• Changes in abnormal RBCs (sickling) assessed by peripheral blood smear from baseline after 2, 4, 6 and 8 weeks of treatment and 4 weeks after EoT.<br>• Number of VOC episodes and visceral infarctions over 8 weeks of treatment and 4 weeks after EoT. |
| Procedures: | See Table 1 (Schedule of Events) and the applicable information in Section 8.1 to Section 8.7 of the protocol for full details of required procedures and applicable visits (and timings of each visit).<br><br><u>Screening Visit V1 (Day -28 to Day -1)</u><br><br>• The Investigator will obtain written informed consent/assent from potentially eligible subjects and/or legally acceptable guardian before any trial-related procedure is performed.<br>• Subjects who have a documented diagnosis of SCD according to inclusion criteria will be screened to determine potential eligibility.<br>• Subject demographics and baseline characteristics will be assessed according to Table 1. Events, including medical/surgical history, physical examination, body weight and height, and vital signs including seated blood pressure and pulse rate will be assessed.<br>• A single 12-lead ECG will be performed.<br>• As of the date of informed consent for each subject, the sites will document in the electronic Case Report Form (eCRF) all serious adverse events (SAEs)/AEs and changes/additions made to previous and concomitant medications. SAEs will be reported no later than 24 hours after the Investigator's awareness of the event.<br>• Blood tests using peripheral venipuncture will be drawn to determine if the subject is eligible according to the inclusion and exclusion criteria (including an optional genotyping test).<br>• During the same blood draw, a serum pregnancy test (beta human chorionic gonadotropin (hCG)) will be taken for females of childbearing potential.<br>• A urinary dipstick test will be drawn to test pH, protein, glucose, ketone, and blood.<br>• A spot urinary sample will be collected and analysed for urinary microalbumin, creatinine, and microalbumin/creatinine ratio.<br>• A quality of life questionnaire (ASCQ-Me, 6 forms) will be provided to the subject. Subjects will be asked to complete all 6 forms the day before Visit V2.<br><br><u>Visit V2 (Baseline, Day 1), before randomisation</u><br><br>If a subject did fulfil the inclusion criteria and did not meet the exclusion criteria observed from Visit V1 they will be asked to attend the baseline Visit V2. The Investigator will perform/complete the baseline procedures/assessments as shown in Table 1. |

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| | • To accommodate local hospital practice, the subject may attend the V2 visit either on the day of the first dose of study treatment (randomisation day), or on the day before the planned randomisation day. Subjects may attend Visit V4 the afternoon/evening before and stay overnight to facilitate compliance and study procedures on Visit V4. Note: A planned overnight stay prior to study treatment administration or the night before Visit V4 do not fulfil the seriousness criteria of an SAE unless there is a medical requirement.<br>• Eligibility assessment will be conducted during screening and also prior to receiving IMP. Re-screening may be considered at the discretion of the Investigator and in consultation with the Sponsor.<br>• A physical examination including body weight will be performed.<br>• Vital signs will be assessed.<br>• A single12-lead ECG will be performed.<br>• Changes/additions made to concomitant medications will be re-assessed since signing the Informed Consent Form (ICF) and all SAEs/AEs will be reported.<br>• In addition, for female subjects of childbearing potential, the urine pregnancy test sample must be taken, and the test result must be negative.<br>• The baseline Hb value will be determined using the Hb value at baseline Visit V2.<br>• All laboratory assessments as per Table 1.<br>• To determine baseline values, blood tests using peripheral venipuncture will be drawn as well as a spot urinary sample will be collected for urinary microalbumin, creatinine, and microalbumin/creatinine ratio.<br>• The subject will be asked for the number of VOC episodes that have occurred within the last 8 weeks. Visceral infarctions will be assessed as per standard of care.<br><u>Randomisation and Administration of the First Dose of Study Treatment</u><br>• Dispense subject identification card.<br>• Collect samples (pre-dose) for total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin and erythropoietin.<br>• Upon completion of the baseline visit procedures/assessments, eligible subjects will be randomised using a validated centralised IWRS to receive VIT-2763 or placebo according to the randomisation scheme.<br>• The first dose of IMP must be administered at the site and the time of administration needs to be entered in the eCRF (see ECG measurement post-morning dosing).<br>• The first dose of IMP must be administered at the site and the time of administration needs to be entered in the eCRF. The IMP total daily dose will be split into 2 or 3 doses per day. For BID: 1 in the morning and 1 in the evening. The morning dose of the IMP will be administered with water, at least 1 hour before meals between 06:00 and 10:00 a.m. The evening dose will be administered 12±1 hours after the morning dose 1 hour apart from meals. For TID: 1 in the morning, 1 in the afternoon and 1 in the evening. The |

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| | morning dose of the IMP will be administered with water, at least 1 hour before meals between 06:00 and 10:00 a.m. The afternoon dose will be administered 8±1 hours after the morning dose 1 hour apart from meals. The evening dose will be administered 16±1 hours after the morning dose after meals, 1 hour apart from any meal.<br>• A new single 12-lead ECG needs to be performed 2 hours (±30 minutes) post-morning dose.<br>• Subjects will receive IMP for home intake until the next visit.<br>• All 6 ASCQ-Me forms dispensed at screening and completed by subject will be collected. Subjects will receive 2 copies of the following forms: "Emotional Impact", "Pain Impact", "Sleep Impact", and "Stiffness Impact". Subjects will be informed to complete 1 copy of each form, 1 week after the visit, and a second copy the day before the next visit (Visit V3).<br><u>Post-randomisation Visits V3 to V6</u><br>• Dispense IMP at site (via IWRS). Note: The morning dose on the visit day needs to be taken at site.<br>• Perform IMP accountability of returned IMP.<br>• Subjects will return to the clinical site at 14-day intervals.<br>• The Investigator will perform the procedures/assessments as shown in Table 1 for the respective visit.<br>• Changes/additions made to concomitant medications will be re-assessed and all SAEs/AEs will be reported.<br>• Blood and urine samples will be collected as per Table 1.<br>• Vital signs, body weight, and physical examination assessments will be performed as per Table 1.<br>• Subjects will be asked to return to the clinical site at Visit V6, Day 56±4 days/EoT/early termination (ET) in order to complete all procedures as per Table 1.<br>• Only at Visit V6, the subject will receive the (last) IMP from the bottle received at Visit V5 (as at Visit V6 no new IMP dispensation will take place).<br>• For PK assessments (blood samples taken at pre-dose, 2 hours (±15 minutes), 4 hours (±30 minutes) and 6 hours (±30 minutes) post-dose), subjects are asked to stay in the hospital for 6 hours post-morning dose only at Visit V4.<br>• For ECG assessments, subjects are asked to stay in the hospital for 2 hours post-dose at Visits V3 to V6.<br>• Subjects who withdraw between signing informed consent and the EoT/Visit V6 will be asked to return to the clinical site to perform an ET visit, and all assessments and procedures according to Table 1 (Visit V6 EoT/ET visit) will be performed. |

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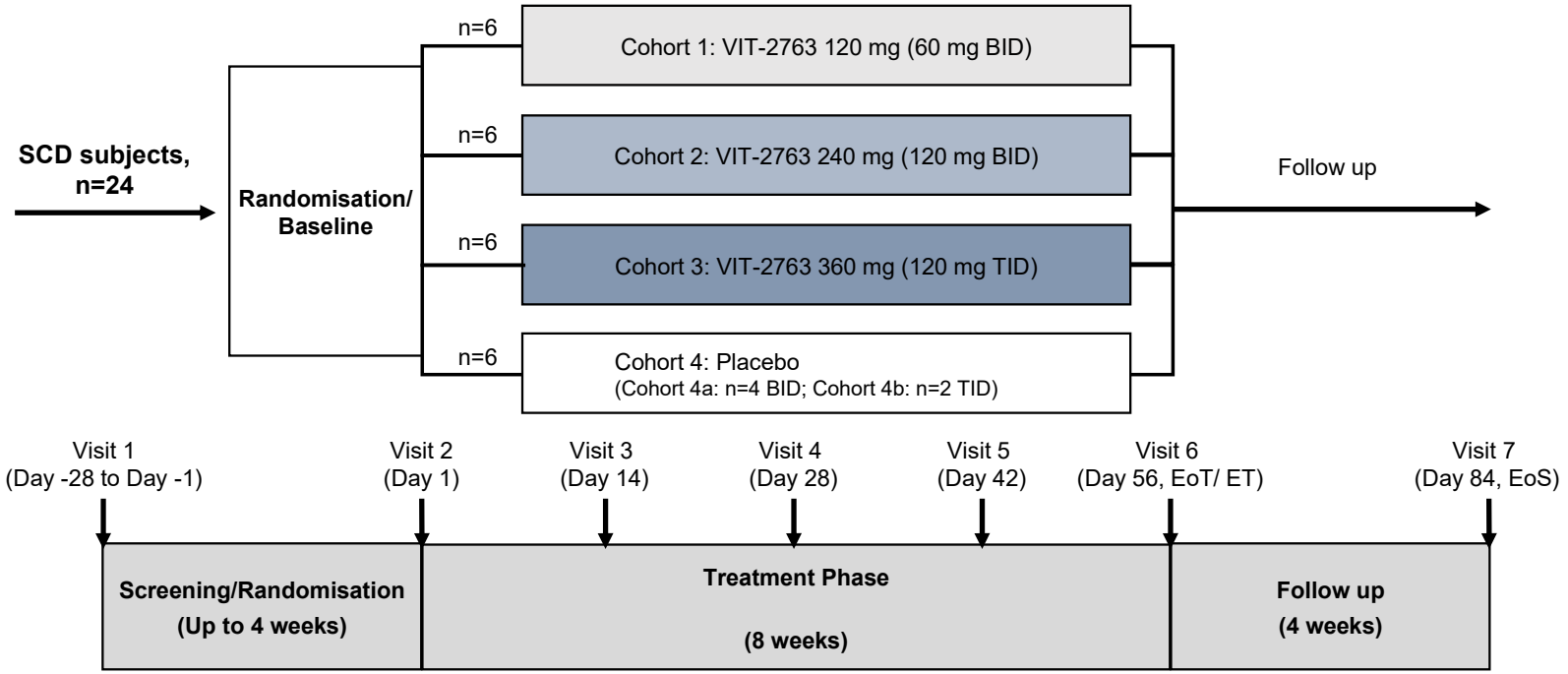
| | • At Visits V3, V4, V5, and V6 the subject will be asked for VOC episodes – number of events and pain intensity (numerical rating scale (NRS): 0-10) compared to historical VOC episodes that have occurred since previous visits. Visceral infarctions will be assessed as per standard of care.<br>• For dispensing and collecting of ASCQ-Me questionnaire forms, please refer to the respective visit in Section 8.<br><br><u>EoS/Follow-up Visit V7</u><br><br>All subjects completing the study will be asked to attend a follow-up Visit V7 (28±4 days after EoT/Visit V6) in order to complete all procedures as per Table 1.<br>• A physical examination will be performed, and vital signs will be assessed.<br>• A single 12-lead ECG will be performed.<br>• Assess change/additions of concomitant medications will be recorded.<br>• All laboratory assessments as per Table 1.<br>• SAEs/AEs will be assessed and reported.<br>• Assessment of VOC episodes and visceral infarctions.<br><br><u>Study Safety Oversight</u><br><br>An independent Data and Safety Monitoring Board (DSMB) will oversee the safety and conduct of the trial on an ongoing basis. The DSMB will include medical and statistical representatives. The DSMB will regularly, but also in an ad-hoc manner as needed, assess the safety information of the enrolled subjects, and can provide recommendations to the Sponsor regarding stopping the study, or discontinuing a treatment arm, or otherwise modifying the study design or conduct. |
| Sample Size: | This is an exploratory Phase 2a study of VIT-2763 in SCD subjects, therefore no formal sample size calculation was conducted.<br><br>A total of 24 subjects will be randomised in a 3:3:3:2:1 ratio at baseline to either VIT-2763 or to placebo.<br><br>Eligible subjects will be randomised to either VIT-2763 or placebo using a validated centralised IWRS that automates the random assignment of treatment groups to randomisation numbers. Stratified randomisation (balanced allocation across treatment groups) will be used according to genotype (HbS/S – HbS/βT0).<br><br>If more than 1 subject in any dose cohort withdraws or drops out between signing informed consent and the V6 visit, the subject will be replaced until at least 5 subjects, with no major protocol deviation impacting the primary objective of the trial, per treatment/placebo arm have passed Visit V6. |
| Study Sites: | About 20 or more sites in 5 or more countries. |
| Statistical Methods: | No formal power calculations will be performed for the sample size due to the experimental nature of this trial.<br><br>An interim analysis is not planned for this study.<br><br>Demographic data will be summarised by treatment. |

| | |
|---|---|
| | The intent-to-treat (ITT) population includes all subjects randomly assigned to a treatment group. The per-protocol set (PPS) consists of all subjects who, in addition to the ITT criteria, completed the study, and had no major protocol deviations.<br><br>The ITT population will be used for the analysis of the primary and secondary endpoints related to haemolysis markers. These analyses will also be repeated on the PPS.<br><br>The secondary and exploratory safety endpoints will be calculated based on the safety population, including all randomised subjects who received at least one VIT-2763 dose or placebo.<br><br>The ITT population and the PPS will be used for the analysis of other exploratory endpoints.<br><br>Concerning the safety data, the total number of events and number (%) of subjects with an event will be presented by MedDRA SOC and PT on overall subjects receiving VIT-2763, by dose group and on all subjects receiving placebo.<br><br>Means, standard deviations, medians, ranges, and confidence intervals will be presented for continuous variables, and frequencies and percentages will be presented for categorical and ordinal variables. Further details will be specified in the Statistical Analysis Plan (SAP).<br><br>A population PK approach will be applied to estimate PK parameters ($C_{max}$, clearance, distribution volume, AUC). |

**Figure 1 Study Schema**




Notes: BID=Twice daily; EoS=End of study; EoT=End of treatment; ET=Early termination; n=Number of subjects per cohort; SCD=Sickle cell disease; TID=3 times daily.

**Table 1 Schedule of Events**

| | Visit 1 Screen | Visit 2 Baseline/ Randomisation | Visit 3 | Visit 4 | Visit 5 | Visit 6 EoT/ET | Visit 7 EoS/ Follow-up |
|---|---|---|---|---|---|---|---|
| | Day -28 to Day -1 | Day 1 | Day 14 ±2 Days | Day 28 ±4 Days | Day 42 ±4 Days | Day 56 ±4 Days | Day 84 28 Days ±4 Days After EoT |
| Informed consent | X | | | | | | |
| Eligibility criteria[1] | X | X[1] | | | | | |
| Demographics | X | | | | | | |
| Medical/surgical history | X | | | | | | |
| Physical examination[2] | X | X | | X | | X | X |
| Vital signs (seated blood pressure, pulse rate)[3] | X | X | X | X | X | X | X |
| Body weight | X | X | | X | | X | |
| Height | X | | | | | | |
| 12-lead ECG | X | X[4] | X[4] | X[4] | X[4] | X[4] | X |
| Adverse events | X | X | X | X | X | X | X |
| Prior/concomitant medications | X | X | X | X | X | X | X |
| Randomisation | | X | | | | | |
| Dispense subject identification card | | X | | | | | |
| Hb levels | C | L | L | L | L | | |
| hsCRP | C | | | | | | |
| RBC smear preparation | | L | L | L | L | L | L |
| Urine pregnancy test[5] | | L | L | L | L | L | L |
| Serum pregnancy test[6] | C | | | | | | |
| Optional SCD genotyping test[7] | L | | | | | | |

| | Visit 1 Screen | Visit 2 Baseline/ Randomisation | Visit 3 | Visit 4 | Visit 5 | Visit 6 EoT/ET | Visit 7 EoS/ Follow-up |
|---|---|---|---|---|---|---|---|
| | Day -28 to Day -1 | Day 1 | Day 14 ±2 Days | Day 28 ±4 Days | Day 42 ±4 Days | Day 56 ±4 Days | Day 84 28 Days ±4 Days After EoT |
| Serum virology (HbsAg, HBV, HCV, HIV) | C | | | | | | |
| Urinalysis[8] | C | C | C | C | C | C | C |
| Haematology panel/RBC indices[9] | C | C | C | C | C | C | C |
| Serum chemistry panel[10] | C | C | C | C | C | C | C |
| Haemolysis markers[11] | | C | C | C | C | C | C |
| Endothelial inflammation/dysfunction markers[12] | | C | C | C | C | C | C |
| Iron-related parameters/markers of erythropoiesis[13] | C | C | C | C | C | C | C |
| RBC smear assessment for sickle cells | | C | C | C | C | C | C |
| VIT-2763 pharmacokinetic[14] | | | | C | | | |
| VOC episodes/visceral infarctions[15] | | X | X | X | X | X | X |
| Dispense IMP at site (IWRS) | | X | X | X | X | | |
| Collect, dispense, and inform subjects on ASCQ-Me questionnaires[16] | X | X | X | X | X | X | |
| IMP accountability | | | X | X | X | X | |

1 Any outstanding eligibility criteria (see Section 5.2 and Section 5.3) not available during screening to be available before randomisation.
2 Body systems to be assessed include general appearance, head (eyes, ears, nose, and throat), cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymph nodes, and skin.
3 Seated systolic and diastolic blood pressure, and pulse, after subject has rested for at least 5 minutes, pre-dose (trough).
4 A single 12-lead ECG to be performed at pre-dose (trough) and 2 hours (±30 minutes) post-morning dose.
5 Only in females of childbearing potential. Positive urine pregnancy test results need to be confirmed using a serum beta-hCG test.
6 Only in females of childbearing potential.
7 Only if genetic diagnosis records do not exist or are unavailable.
8 Urinary dipstick including pH, protein, glucose, ketone, RBCs, and WBCs. Quantitative measurement only if positive dipstick. Urinalysis includes also (at Visits V1, V2, V4, and V6) urinary microalbumin, creatinine, and microalbumin/creatinine ratio (spot sample, morning void).

9 Haematology panel/RBC indices sampled at pre-dose (trough) include: Hb, reticulocytes (abs, %), RBC count, Hct, MCH, MCV, MCHC, RDW, % hypochromic RBC, CHCM, WBC, neutrophils (abs, %), lymphocytes (abs, %), monocytes (abs, %), eosinophils (abs, %), basophils (abs, %), and platelets. At screening/Visit V1, only Hb and reticulocytes will be assessed. At screening, the optional SCD genotyping test can be included.

10 Serum chemistry sampled at pre-dose (trough) includes calcium, sodium, magnesium, potassium, phosphorus, chloride, bicarbonate, blood urea nitrogen, uric acid, creatinine kinase, creatinine, folic acid, albumin, total protein, globulin (calculated), alanine transaminase, aspartate transaminase, alkaline phosphatase, glucose, triglycerides, and cholesterol.

11 Haemolysis markers sampled at pre-dose (trough) include LDH, free haptoglobin, and direct/total bilirubin (indirectly calculated).

12 Endothelial inflammation/dysfunction markers sampled at pre-dose (trough) include hsCRP, IL-1, IL-6, TNF-alpha, sP-selectin, sVCAM-1, xanthine oxidase, and endothelin-1.

13 Iron-related parameters/markers of erythropoiesis sampled at pre-dose and 2 hours post-morning dose include total serum iron, serum ferritin, transferrin, TSAT, hepcidin, and erythropoietin. At Visit V1, serum ferritin, and TSAT will be sampled for exclusion criteria only.

14 PK samples are collected on Visit V4 at pre-dose, and 2 hours (±15 minutes), 4 hours (±30 minutes), and 6 hours (±30 minutes) post-dose.

15 At Visit V2, the subject will be asked for VOC episodes within the last 8 weeks. At Visits V3, V4, V5, and V6, the subject will be asked for VOC episodes (number of events and pain intensity (NRS: 0-10) compared to historical VOC episodes) since previous visits. Visceral infarctions will be assessed as per standard of care.

16 For more details see the respective visit in Section 8.

Notes: abs=Absolute; ASCQ-Me=Adult Sickle Cell Quality of Life Measurement System; C=Central laboratory assessment; CHCM=Corpuscular Hb concentration mean; ECG=Electrocardiogram; EoS=End of study; EoT=End of treatment; ET=Early termination; Hb=Haemoglobin; HbsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; hCG=Human chorionic gonadotropin; Hct=Haematocrit; HCV=Hepatitis C virus; hsCRP=High sensitivity C-reactive protein; IL=Interleukin; IMP=Investigational medicinal product; IWRS=Interactive web response system; L=Local laboratory assessment; LDH=Lactate dehydrogenase; MCH=Mean corpuscular Hb; MCHC=Mean corpuscular Hb concentration; MCV=Mean corpuscular volume; NRS=Numerical rating scale; PK=Pharmacokinetic; RBC=Red blood cell; RDW=Red blood cell distribution width; SCD=Sickle cell disease; sP=Soluble platelet; sVCAM=Soluble vascular cell adhesion molecule; TNF=tumour necrosis factor; TSAT=Transferrin saturation; V=Visit; VOC=Vaso-occlusive crises; WBC=White blood cell.

# TABLE OF CONTENTS

Page

# LIST OF TABLES

Page

# LIST OF FIGURES

Page

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| ASCQ-Me | Adult Sickle Cell Quality of Life Measurement System |
| AUC | area under the curve |
| BID | twice daily |
| CHCM | corpuscular haemoglobin concentration mean |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| $C_{max}$ | maximum concentration |
| CRO | Contract Research Organisation |
| CYP | cytochrome P450 |
| DSMB | Data and Safety Monitoring Board |
| EC | Ethics Committee |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| eGFR | estimated glomerular filtration rate |
| EoS | end of study |
| EoT | end of treatment |
| ET | early termination |
| EU | European Union |
| FPN | ferroportin |
| Hb | haemoglobin |
| HbS | sickle haemoglobin |
| hCG | human chorionic gonadotropin |
| Hct | haematocrit |
| HDPE | high-density polyethylene |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IMP | investigational medicinal product |
| IND | Investigational New Drug |

| | |
|---|---|
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| IWRS | interactive web response system |
| LDH | lactate dehydrogenase |
| MATE | multidrug and toxin extrusion transporter |
| MCH | mean corpuscular haemoglobin |
| MCHC | mean corpuscular haemoglobin concentration |
| MCV | mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NOAEL | no observed adverse effect level |
| NRS | numerical rating scale |
| NTD | non-transfusion dependent |
| OCT | organic cation transporter |
| PD | pharmacodynamic |
| PK | pharmacokinetic |
| PPS | per-protocol set |
| PT | preferred term |
| QD | once daily |
| RBC | red blood cell |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SCD | sickle cell disease |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TIBC | total iron-binding capacity |
| TID | 3 times daily |
| TSAT | transferrin saturation |
| ULN | upper limit of normal |
| VOC | vaso-occlusive crises |
| WBC | white blood cell |

# 1. INTRODUCTION AND BACKGROUND

VIT-2763 (2-(2-{[2-(1H-benzimidazol-2-yl) ethyl] amino} ethyl)-N-[(3-fluoropyridin-2-yl) methyl]-1,3-oxazole-4-carboxamide trihydrochloride) is a small molecule, which has been identified by Vifor Pharma as a ferroportin (FPN) inhibitor acting similar to hepcidin.

FPN is the only known iron transporter in mammals mediating iron transfer into the blood stream. FPN is mainly expressed on intestinal enterocytes, spleen and liver macrophages, and hepatocytes. On the basolateral membrane of intestinal enterocytes, FPN exports the dietary iron into the plasma. On spleen and liver macrophages and hepatocytes, FPN exports endogenous iron recycled from the Hb of senescent RBCs and released from the liver stores, respectively [1]. The action of FPN is antagonised by hepcidin, a 25-amino acid peptide, which is mainly produced in hepatocytes. Its transcription is downregulated by erythropoiesis, anaemia, and hypoxia, and it is upregulated by inflammation and high systemic iron levels. Hepcidin binds to and triggers internalisation and degradation of FPN, and by this causes a rapid drop in serum iron levels [2,3].

## 1.1 Background of the Disease and Treatment Options

Iron is essential for cell survival. It is a key component of Hb, cytochromes, myoglobin, and of many enzymes. It is involved not only in the transport, storage, and use of oxygen, but also in major metabolic pathways. Consequently, iron homeostasis in the body is closely regulated, and imbalances may become pathogenic. Iron deficiency may result in anaemia; iron overload syndromes in siderosis, i.e., the iron deposition in organs, which may lead to multiple organ dysfunction and damage [4]. Primary iron overload syndromes arise from mutations, e.g., in genes of human haemochromatosis protein, haemojuvelin, hepcidin, transferrin receptor 2, and FPN. Secondary causes for iron overload are SCD, other inherited, or acquired anaemias, myelodysplastic syndrome, chronic liver diseases, and transfusions [5].

SCD is a multisystem disease and is one of the most common severe monogenic disorders worldwide. This often-devastating disease is associated with episodes of acute illness and progressive organ damage [6,7]. The pathophysiology of SCD arises from a single amino acid alteration in adult Hb, the expression of which is primarily limited to RBCs. The pathological single amino acid substitution (Glu to Val) at the sixth position of the β-chain of HbS results in HbS instability and polymerisation [8]. Following deoxygenation of HbS, and aggregating into polymers, the RBC changes shape (‘sickles’) owing to this polymer induced distortion. This distortion is the fundamental basis for the haemolytic anaemia, vaso-occlusion associated with painful events, organ dysfunction and shortened lifespan in patients with SCD [9].

The consequences of haemolysis include the immediate effects of RBC loss, such as anaemia and expansion of erythropoiesis with increased reticulocytosis. Oxidative changes in the sickle RBC promote haemolysis, depletion of nitric oxide, excess reactive oxygen species and endothelial activation. It is estimated that about one-third of haemolysis in SCD

is intravascular, owing to mechanical destruction of deformed and inelastic sickle RBCs, whereas two-thirds is extravascular, resulting from removal of abnormal sickle RBCs by the reticuloendothelial system [10].

Erythrocyte transfusion has an established role in the management of both acute and chronic complications in SCD. Transfusion corrects anaemia, decreases the percentage of HbS, suppresses HbS synthesis, and reduces haemolysis, all of which are of potential benefit. Chronic blood transfusion is inevitably associated with iron overload, although the pattern of haemosiderosis seems different to that described in thalassaemia; in particular, most iron loading occurs in the liver, with little cardiac iron deposition [11].

Curative therapies, such as haematopoietic stem cell transplantation or gene therapy are limited to a small patient population or are not yet available. Chronic transfusion is generally used for primary or secondary stroke prevention [9].

Acute pain crisis may be managed with pain medications, including opioids and may require additional in-patient or outpatient treatments, including hydration, transfusion, supplemental oxygen, and a variety of other treatments. Currently approved therapies such as hydroxyurea address some of the pathologies in SCD. Hydroxyurea is used to reduce the number of acute pain crises in those with frequent or severe crises and in those with a history of acute chest syndrome or severe anaemia. Within the past several years, a few new treatment options, such as L-glutamine, crizanlizumab, and voxelotor, have gained regulatory approval in the United States; however, the evidence for the clinical effectiveness of these treatments has been controversial [12].

Drugs that target the broader sequelae of SCD are needed, and prevention of haemolysis might provide a novel therapeutic option. Overt iron deficiency in patients with SCD has been associated with reduction of HbS in sickle RBCs and decreased markers of haemolysis [13,14].

VIT-2763 is developed by Vifor Pharma 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 [15].

Since no FPN inhibitors or hepcidin-mimetic drugs are yet available for the treatment of iron loading anaemias including SCD, VIT-2763 would be considered as a first-in-class drug.

## 1.2 Summary of Nonclinical and Clinical Data

### 1.2.1 Nonclinical Pharmacology and Pharmacological Activity

VIT-2763 is an inhibitor of the iron exporter FPN and acts similarly to hepcidin. Through its action on FPN, hepcidin controls the major iron flows into the plasma. Similar to hepcidin, VIT-2763 induces FPN internalisation, ubiquitination, and degradation. As a consequence, VIT-2763 blocks iron export into plasma. Nonclinical pharmacology studies demonstrated that VIT-2763 prevents dietary iron absorption presumably by blocking intestinal FPN. In hereditary haemochromatosis, inappropriately low hepcidin expression leads to increased dietary iron absorption and organ overload. Accordingly, prevention of iron absorption by VIT-2763 decreased liver iron concentration in 2 haemochromatosis mouse models.

In vitro studies in cells expressing FPN have demonstrated that VIT-2763 was similar in potency to hepcidin in a hepcidin-FPN binding and internalisation assay (half maximal inhibitory concentration: 9±5 versus 13±4 nM). VIT-2763 decreased serum iron levels in a dose-dependent manner in mice comparable to hepcidin and inhibited intestinal iron absorption in rats. Further studies in disease-specific animal models have demonstrated expected effects based on the pharmacology of VIT-2763. Importantly, iron restriction by the oral FPN inhibitor VIT-2763 has shown to improve haemolysis, systemic and vascular inflammation, to reduce apoptosis of RBCs and thereby improve blood flow in the Townes' mouse model of SCD.

#### 1.2.1.1 Absorption, Distribution, Biotransformation, and Elimination

The oral bioavailability depends on species and dose; it ranged from 16 to 51% in rats and up to 85% in dogs. Higher than proportional plasma concentrations with increasing dose could be due to nonlinear excretion, resulting from saturation of clearance.

Distribution in rats was widespread, with the highest measured tissue radioactivity at 1 hour post-dose. Rapid accumulation was observed in particular in the kidney pyramid, but also in the adrenal medulla and mammary glands (females). Twenty-four hours post-dose, radioactivity was not detectable or at very low levels with the exception of adrenal medulla, preputial gland, and mammary tissues.

In vitro, VIT-2763 was shown to be a substrate of P-glycoprotein, organic anion transporter 3, multidrug and toxin extrusion transporter 1 (MATE1) and MATE-2K, and likely also of the organic cation transporter 1 (OCT1) and OCT2. In vitro studies in human hepatocytes have shown that VIT-2763 is mainly metabolised by CYP 3A4 and to some extent by CYP 2D6. VIT-2763 showed high clearance in rats and moderate clearance in dogs, both in vitro and in vivo. In human hepatocytes and liver microsomes, low levels of metabolism have been observed. The abundance of individual metabolites was different across species, whereby the metabolites in the human in vitro samples (one of them being unique to human) were all detected with low quantities.

Mass balance data in rats revealed primary excretion in urine (53.7% of total radioactive dose) and bile (20.6% of total radioactive dose). No parent VIT-2763 was detected in another bile duct cannulated rat study indicating that VIT-2763 metabolites or conjugation products are excreted in bile. The majority of the radioactivity in urine and bile accumulated within 8 hours and the vast majority of the radioactivity was eliminated within 24 hours of dose administration. The second peak observed in rat plasma was less pronounced in bile duct cannulated compared to non-bile duct cannulated animals, suggesting that enterohepatic circulation occurs.

CYP 2B6, CYP 3A4 and CYP 1A2 were not induced by VIT-2763. A weak inhibitory potential for CYP 1A2 at a targeted dose of 240 mg and for CYP 2D6 and CYP 3A4 at a 60 to 240 mg dose was concluded in vitro. In vitro transporter inhibition indicated a weak inhibitory potential for OCT2, OCT1, MATE1, and MATE2-K. Clinical studies of VIT-2763 with concomitant medications have not been performed.

## 1.3 Nonclinical Safety Data

### 1.3.1 Long-term Toxicity

VIT-2763 was tested in studies up to 26 weeks in the rat and 39 weeks in the dog. In addition, two 28-day studies were conducted in juvenile rats.

Findings in the rat mainly resulted from the pharmacology of VIT-2763 and included iron deficiency anaemia due to decreased circulating iron concentrations and consequences thereof (e.g., cardiomegaly). The no observed adverse effect level (NOAEL) was 600 mg/kg/day, the highest dose tested, in the 14-day study, 100 mg/kg/day in the 13-week study (due to significant anaemia at 200 mg/kg/day after 8 weeks) and 150 mg/kg/day, the highest dose tested, in the 26-week study.

Findings emanating from the pharmacology of VIT-2763 were also noted in the dog. The NOAEL was 30 mg/kg/day in the 14-day study (due to the severity of the observed clinical signs, i.e., vomiting, decreased activity and tremors and other findings at 100 mg/kg/day), 75 mg/kg/day, the highest dose tested, in the 13-week study and 30 mg/kg/day (due to significant anaemia at 75 mg/kg/day after 13 weeks) in the 39-week study. The ECG changes identified in the safety pharmacology study were confirmed in all studies, i.e., increases in PR, QRS and/or heart rate at ≥30 mg/kg 1 hour after administration.

### 1.3.2 Safety Pharmacology

VIT-2763 demonstrated no impact on the central nervous and respiratory system in rats and the NOAEL was 600 mg/kg. The half maximal inhibitory concentration in the human ether-à-go-go related gene assay was 27 µM. The no observed effect level in the dog cardiovascular safety study was 10 mg/kg, based on an increase in QRS at 30 and 75 mg/kg. Additionally, an increase of PR for 75 mg/kg was observed. There were also sporadic increases in heart rate. The magnitude of the PR and QRS increases followed the PK of VIT-2763 with most significant increases occurring around 1 hour post-dose. Statistically significant QRS increases from baseline were observed 0.5 to 4 hours after 75 mg/kg and

1 to 2 hours after 30 mg/kg. No impact on ECG waveform morphology or on cardiac function was observed.

### 1.3.3 Mutagenicity

VIT-2763 is not genotoxic based on the available weight of evidence. VIT-2763 was negative in the Ames test. The mouse lymphoma assay was negative after short-term incubation but positive after long-term incubation. The in vivo micronucleus assay and comet assay were negative.

### 1.3.4 Carcinogenicity

Carcinogenicity studies have not been performed.

### 1.3.5 Paediatric Use

Clinical studies in paediatric patients have not yet been performed.

Two 28-day studies were conducted in juvenile rats. In 1 study, iron deficiency anaemia was induced by feeding 3-week-old male Wistar rats a low iron diet for 9 days, by which time all animals had developed anaemia, and which was compared with repeat administration of VIT-2763. VIT-2763 and a low iron diet similarly induced iron deficiency anaemia in juvenile rats. This effect could only be reversed with administration of intravenous iron in animals on a low iron diet. In those administered VIT-2763, intravenous iron treatment resulted in iron sequestration in spleen and liver. The second study treated 3-week-old juvenile rats for 7 days (5 days on drug; 2 days off) and 4 days (3 days on drug and 1 day off) with 300 mg/kg VIT-2763 and was well tolerated. Expected pharmacological effects on RBC parameters were observed, with no differences between the dosing regimens.

The consequences of iron deficiency in human are well understood and there is extensive knowledge of the effects of iron deficiency in developing children. In addition, parameters associated with iron metabolism and RBC parameters can be monitored during the clinical studies, ensuring that patients on VIT-2763 will not become iron deficient. Both EMA and FDA have confirmed that no further studies in juvenile animals are required to include adolescents or children as young as 6 months in clinical trials with VIT-2763.

### 1.3.6 Reproductive Toxicity

There are no data from the use of VIT-2763 in pregnant women. Studies in animals have shown reproductive toxicity.

Data of nonclinical studies of the effect of VIT-2763 on pregnancy and fertility indicate that women of childbearing potential should use highly effective methods of contraception whilst taking VIT-2763 and until at least 1 week after the last dose. No data on breastfeeding has been generated yet, so breastfeeding must be discontinued during treatment with VIT-2763 and for at least 1 week after the last dose.

## 1.4 Summary of Completed Clinical Studies

### 1.4.1 Study VIT-2763-101

A Phase 1 study in healthy volunteers with the title "A Phase 1, Double-blind, Randomised, Placebo-controlled Study on the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple Ascending Doses of VIT-2763 in Healthy Subjects", Protocol No. VIT-2763-101, EudraCT No. 2017-003395-31, has been performed [16].

The study consisted of a single ascending dose part (Part A) and a multiple ascending dose part (Part B) to assess the safety, tolerability, PK, and pharmacodynamics (PD) of ascending single and multiple oral doses of VIT-2763. The primary endpoint in this first-in-human study was to collect the incidence of AEs and SAEs by changes in vital signs, clinical laboratory, 12-lead ECG and cardiac telemetry examinations and physical examination findings following single and multiple oral doses compared to baseline.

Secondary endpoints were to characterise the PK of VIT-2763 and to measure PD parameters to identify potential surrogate markers of VIT-2763 mechanism of action after single or multiple oral dosing.

Treatment with single oral doses ranging from 5 mg to 240 mg and a 7-day treatment with oral doses of 60 mg once daily (QD), 120 mg QD, 60 mg every 12 hours, and 120 mg every 12 hours were well tolerated by healthy male and female volunteers. Following single dose all treatment-emergent adverse events (TEAEs) were of mild severity. There were no SAEs reported and no discontinuations due to AEs. Following 7-day repeated treatment, all TEAEs were mild or moderate. There were no SAEs reported and no discontinuations due to AEs. There were no findings of clinical relevance with respect to vital signs, 12-lead ECG, telemetry, or physical examination.

The PK analyses revealed that the initial oral absorption of VIT-2763 was relatively fast, most subjects had detectable levels already at 15 to 30 minutes post-dose, and $T_{max}$ for VIT-2763 ranged from 0.50 to 3 hours post-dose. A second peak or shoulder in the concentration-time profile was observed around 3 to 4 hours post-dose (from 15 mg dose). The exposure over the dose range of 5 mg to 240 mg was slightly more than dose proportional for $C_{max}$, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$.

Following multiple oral dose for 7 days up to 120 mg every 12 hours there was no apparent change in absorption and accumulation was minimal. The apparent volume of distribution following single oral administration was moderate ranging from 64.3 to 145 l indicating moderate distribution to tissues. The geometric mean $t_{1/2}$ ranged from 1.9 to 5.3 hours following single oral dosing and from 2.07 to 3.80 hours on Day 1 and from 2.61 to 5.26 hours on Day 7 following repeated dosing.

Following both single and multiple dosing, a temporary decrease in mean serum iron levels and a temporary decrease in mean calculated % TSAT was seen at all VIT-2763 dose levels

between 4-hours and 12-hours post-dose. Following both single and multiple dosing, a temporary increase in mean serum hepcidin levels was seen at doses of 60/120/240 mg for single dosing and at all VIT-2763 multiple dose levels. Maximum mean serum hepcidin levels were observed between 1-hour and 4-hours post-dose for the highest single dose levels of 60 mg, 120 mg, and 240 mg, and for all 4 multiple dose levels. No dose related effects were observed with respect to serum ferritin, serum transferrin, serum erythropoietin and serum soluble transferrin receptor levels on both Day 1 and Day 7.

### 1.4.2 Study VIT-2763-THAL-201

A Phase 2a trial has recently been completed (Q4, 2021), with study sites in the EU, Thailand, Israel, and Lebanon. Study VIT-2763-THAL-201 was a double-blind, randomised, placebo-controlled, parallel group trial evaluating the safety, tolerability, PK, PD, and preliminary efficacy of multiple doses of VIT-2763 in 25 adult subjects with non-transfusion dependent (NTD) thalassaemia. After database lock, topline results were generated January 2022.

The primary safety endpoints were reported or observed AEs and SAEs, changes in vital signs (blood pressure and pulse rate and respiratory rate), clinical laboratory safety tests (haematology, serum biochemistry, coagulation, and urinalysis), 12-lead ECG, and physical examination findings.

The first subject in Study VIT-2763-THAL-201 was enrolled in June 2020 (in Lebanon). Blinded interim results in 10 adult subjects were obtained in Q1/2021 and revealed no safety concerns as judged by the Safety Review Committee; topline results of all subjects have been analysed (Q1/2022) (Investigational New Drug (IND), Section 1.11.4), demonstrating that VIT-2763 was safe and well tolerated. The interim analysis also showed that VIT-2763 had significant target engagement with FPN, lowering consistently and throughout the treatment period serum iron and TSAT. The study could not show significant changes from baseline in clinically relevant blood biomarkers such as Hb, RBC count, MCHC, MCV, reticulocyte counts and reticulocyte Hb content. Learnings from Study VIT-2763-THAL-201 suggest that TID dosing may be required to achieve the full efficacy of vamifeport, and PK and PD samples will needed to be collected at additional time points to fully understand the effects of vamifeport. These results led to the amendment of this study protocol (see Section 2.3).

# 2. RATIONALE

## 2.1 Rationale to Investigate the Effects of VIT-2763 in SCD

While there is good evidence that overt iron deficiency is associated with a decrease in the severity of haemolysis, evidence of a clinical benefit is limited because studies are few and assessment of the severity of the disease is difficult. It has been shown that overt iron deficiency induced by repeated erythrocytapheresis in 2 patients with sickle cell anaemia was associated with a decrease in reticulocytes, with only a slight decrease in the blood Hb concentration. The lower red cell production from lack of iron appeared to have been compensated by the improvement in red cell survival. Following the induction of overt iron deficiency, a remarkable decrease in the number of pain crises over 30 months of observation was seen in 1 patient and the healing of recalcitrant leg ulcers was seen in the other. Iron deficiency did not appear to have any apparent deleterious effects [13]. Other authors described 2 patients in whom overt iron deficiency induced by repeated phlebotomies was associated with a remarkable decrease in the number of pain crises during 4 years of observation [14].

In the Townes mouse model of SCD, VIT-2763 showed reduced intravascular haemolysis markers, such as plasma LDH, haeme, and bilirubin [17]. Furthermore, VIT-2763 lowered markers of vascular inflammation and oxidative stress, for instance soluble vascular cell adhesion molecule 1, soluble platelet-selectin, and xanthine oxidase. The RBC indices of Townes mice treated with VIT-2763 showed changes attributable to iron-restricted erythropoiesis: decrease in RBC counts, Hct, MCV, MCH, reticulocyte Hb content, and CHCM. Small changes in CHCM are expected to have a large impact on HbS polymerisation rate, which is proportional to HbS concentration in RBCs with a factor of about $10^{30}$ and therefore on all the ensuing sequelae such as haemolysis and vaso-occlusion [18]. Accordingly, VIT-2763 reduced blood cell adhesion in venules, restored blood flow and prevented vaso-occlusion in the Townes model of SCD as demonstrated by intravital fluorescence video microscopy. In addition, VIT-2763 significantly lowered the relative spleen weight of Townes mice, suggesting improved extramedullary erythropoiesis and decreased clearance of RBCs.

Hence, iron restriction by the oral FPN inhibitor VIT-2763 lowers the concentration of HbS and has the potential to alleviate VOC and thereby to improve haemodynamics in SCD, presumably by reducing haemolysis and vascular inflammation.

## 2.2 Study Design Rationale

This is a randomised, double-blind, placebo-controlled, parallel group trial that explores 3 different dosing regimens of VIT-2763: 60 mg BID, 120 mg BID and 120 mg TID.

The treatment duration of 8 weeks is considered sufficiently long enough to explore the effects of VIT-2763 on markers of haemolysis, haematological indices, and vascular inflammation, safety and tolerability, iron and erythropoiesis related blood parameters, pain

and quality of life, and at the same time to discern possible negative effects on iron restriction over time.

Subjects in this study will be required to have experienced at least 1 and no more than 10 VOC episodes reported within 12 months prior to screening, in order to define a symptomatic disease status, but to exclude the most severely impacted subjects, e.g., those who suffer from additional comorbidities. There is no commonly agreed threshold in the number of VOC episodes experienced in patients with SCD. A study including more than 8,500 patients with a follow-up period of 2.7 years evaluated the prevalence rate of VOC episodes (uncomplicated and complicated VOC episodes), and the primary reasons for emergency room visits and in-patient admissions for SCD patients [19]. During the first-year follow-up period, an average of 2.79 VOC episodes were identified per SCD patients, with 1.06 VOC episodes treated in the in-patient setting and 0.90 VOC episodes treated in the emergency room without admission. The defined baseline characteristic of having experienced at least 1 to no more than 10 VOC episodes ensures that subjects are sufficiently stable, while this threshold is in line with the overall prevalence of VOC episodes in the target population and compares well with the baseline characteristics of SCD patients in similar early clinical trials conducted in the past [20]. Hence, the likelihood that subjects will suffer from VOC episodes during the 8-week treatment schedule while participating in the main trial is considered low.

Patients with homozygous HbS/S and the compound heterozygous condition HbS/βT0 thalassaemia present amongst the most prevalent SCD genotypes and are clinically very similar [21].

A required Hb threshold between 6.0 g/dl and 10.4 g/dl for female and >11.0 g/dl for male subjects at the time of screening is considered appropriate, as it typically covers most patients with HbS/βT0 thalassaemia and HbS/S genotype. In addition, ineffective erythropoiesis is expected to be more pronounced in HbS/βT0 because of the beta-thalassaemia genotype.

Subjects with absolute reticulocyte count or % reticulocyte count >1.5 × ULN during screening are eligible. The reticulocyte count is useful as a marker to estimate the degree of erythropoiesis and the appropriateness of the bone marrow response to anaemia. Absence of reticulocytosis in anaemia usually signals a problem with the bone marrow such as an aplastic anaemia, and points to a lower impact on ineffective erythropoiesis. The reticulocyte count is reported to be elevated between 4 to 15% in samples from SCD patients [11,22-24]; however, a threshold of 1.5 × ULN seems plausible in this trial to target those patients who might respond best following VIT-2763 administration.

VIT-2763 lowered serum iron in rodents, dogs, and humans (healthy volunteers and non-transfusion dependent beta-thalassaemia patients) suggesting similar mechanism of action of VIT-2763 in these species [15,16] (see IND, Section 1.11.4). The PD effect of VIT-2763 in humans can be monitored by determination of plasma iron levels (acute effect) and haematological RBC indices (chronic effect). In addition, biomarkers for haemolysis,

inflammation and haemopoietic/erythropoietic activity in SCD patients will be assessed as preliminary efficacy readouts. Data from the completed first-in-human study [16] revealed that oral administration of VIT-2763 to healthy male and female volunteers for up to 7 consecutive days, QD or BID dosing, and at up to 240 mg total daily dose was well tolerated with no safety findings of clinical relevance. Short-term treatment in adult subjects was well tolerated with no difference between active dose groups and placebo both in terms of frequency and intensity of AEs following single and multiple doses. The human PK profile exhibited dose linearity and only slight dose super-proportionality for $C_{max}$ and AUC at steady-state PK.

Topline results from the first patient study (IND, Section 1.11.4) revealed that oral administration of 120 mg QD or 120 mg BID of VIT-2763 to male and female NTD beta-thalassaemia patients for 12 weeks was well tolerated with no safety findings of clinical relevance. Both treatment regimens were well tolerated with no difference between active dose groups and placebo both in terms of frequency and intensity of TEAEs. Furthermore, VIT-2763 showed a comparable PK profile, as previously observed in healthy volunteers (IND, Section 1.11.4). The Sponsor assumes that the PK profile in the target patient population of this study will not differ from previous results in humans.

Placebo treatment will be used in a minority of adult SCD subjects in order to discriminate potential side-effects of active treatment from non-active treatment, and to explore the natural variability of haemolysis markers and iron-related markers and biomarkers for haemopoietic/erythropoietic activity. Placebo treatment in this study does not bear an additional risk for the study participants and will allow subjects to keep their standard of care.

In order to maintain the subjects' usual medical treatment, subjects will be allowed to be concomitantly treated with hydroxyurea and must be on a stable dose for ≥3 months prior to screening. Hence, the use of a placebo arm is considered ethically justified. In case there is a need for a hospitalisation or further medical care during the course of the trial, based on the judgement of the treating physician, subjects may need to be withdrawn from IMP intake. In order to assess changes in the laboratory parameters, and changes of the well-being of subjects randomised into the study, a DSMB will be established to protect the safety of study participants.

## 2.3 Dose Selection

### 2.3.1 Summary

This protocol was amended on the basis of results from Study VIT-2763-THAL-201, where β-thalassaemia patients were treated with either QD or BID doses of 60 or 120 mg of VIT-2763 for 12 weeks. VIT-2763-treated patients experienced dose-dependent reductions of total serum iron and TSAT from Week 1 to EoS. However, no changes in relevant haematological biomarkers such as Hb could be detected. The Sponsor wants to explore at its best the PD range of VIT-2763 in this Phase 2a study, therefore changes in dose and dosing frequency have been implemented to ensure a more sustained iron restriction. The

proposed dose levels and dosing frequencies are considered to be safe after an analysis of all currently available nonclinical, clinical and simulation data of VIT-2763.

### 2.3.2 Justification of Safety

The nonclinical risk assessment for the first-in-human study (VIT-2763-101) focused on minimising the risk for increase in QRS duration and PR interval, on the basis of observations made in dog studies [16]. As this effect was transient and followed the PK profile of VIT-2763, $C_{max}$ is considered the most relevant parameter for monitoring the risk of changes in QRS duration and increased PR-interval. In the current study at each study visit pre-dose and 2 hours post-dose (approximately at $T_{max}$) ECG assessments will be performed to monitor this risk.

The Sponsor expects that VIT-2763 will have similar PK characteristics in patients with SCD as previously reported for both healthy volunteers [16] and patients with NTD beta-thalassaemia (IND, Section 1.11.4). VIT-2763 is quickly eliminated in humans (elimination half-life 2-5 hours) and no relevant accumulation has been detected in any of the studies where PK measurements have been performed. Therefore, the VIT-2763 $C_{max}$ values for the proposed dose levels are expected not to exceed the plasma concentrations observed previously in humans even with a 120 mg TID dosing regimen. For further analysis please refer to the IND, Section 1.11.4.

Our estimated cumulative 24-hour AUC exposure (20,250.00 ng/ml; IND, Section 1.11.4) of 120 mg TID VIT-2763 plasma concentrations at steady-state leaves a safety margin to the AUC at NOAEL doses of the rat repeat-dose toxicity studies of 2-12 times [25,26,27] and 1-4 times to the AUC at NOAEL doses of the dog repeat-dose toxicity studies [28,29,30]. We consider the safety margins for the 120 mg TID VIT-2763 dose level to be adequate for this Phase 2a exploratory study in patients. Signs of chronic excessive PD effects (i.e., iron deficiency or anaemia) that may occur, can be detected early on with the current study setup as haematological safety parameters will be monitored throughout the study (every 2 weeks). For a more detailed analysis please refer to the IND, Section 1.11.4.

### 2.3.3 Justification of Dose

The PD effects after approximately 2 hours of VIT-2763 administration in the VIT-2763-THAL-201 study clearly demonstrated that VIT-2763 acted as an FPN inhibitor, at both dosing regimens and induced a mean baseline-corrected change in TSAT of -26.2% (±18.6%) and -46.8% (±23.6%) for the QD and BID regimens, respectively, after 12 weeks of treatment. The placebo group achieved a mean baseline-corrected change in TSAT of -1.3% (±2.3%) after 12 weeks of treatment. On the other hand, the PD effects did not translate into effects on the ineffective erythropoiesis of treated patients; Hb levels, as well as RBC counts, MCHC, MCV, reticulocyte counts and reticulocyte Hb content did not change after 12 weeks of treatment (IND, Section 1.11.4). Several hypotheses may explain these results; however, the Sponsor believes that an insufficient sustained serum iron restriction in between drug administrations may be the cause for such disconnect. VIT-2763 has a short elimination half-life (2-5 hours) after repeat-dose administration that leads to

insufficient drug concentrations to maintain constant low serum iron levels, in particular when VIT-2763 is applied only QD.

Consequently, in this exploratory Phase 2a study adult subjects will receive for 8 weeks either 60 mg BID VIT-2763 (Cohort 1), 120 mg BID VIT-2763 (Cohort 2), 120 mg TID VIT-2763 (Cohort 3) or placebo (Cohort 4a and 4b) (see Figure 1 and Table 2).

Animal models of SCD with 2 administrations of VIT-2763 during the day, showed significant clinical benefit. However, data obtained from the VIT-2763-THAL-201 study indicate that higher doses or more frequent dosing is required to sustain iron restriction throughout the whole dosing period. Signs of chronic excessive PD effects (i.e., anaemia) can be detected early on; haematological safety parameters will be monitored throughout the study (every 2 weeks). The selected VIT-2763 dose levels and dosing frequencies in this Phase 2a exploratory study are considered to be safe and are intended to explore at its best the potential therapeutic PD range of VIT-2763 in this patient population. Different levels of serum iron restriction (doses of 120 mg, 240 mg and 360 mg) and different fluctuations of induced peak and trough serum iron throughout a 24-hour period (BID and TID) are explored. It is still unknown if a more sustained serum iron restriction (TID) or more fluctuating (BID) serum iron levels translate into better clinical outcomes in SCD. That is the reason why in the current protocol a broad range of doses and dosing regimens is explored.

# 3. STUDY OBJECTIVES AND ENDPOINTS

## 3.1 Primary Objective

The primary objective of this study is to explore the effect of VIT-2763 on markers of haemolysis.

## 3.2 Secondary Objective

The secondary objective of this study is to assess the safety and tolerability of VIT-2763 in SCD patients.

## 3.3 Exploratory Objectives

- To explore the effect of VIT-2763 on haematological indices and vascular inflammation.
- To explore the effect of VIT-2763 on iron and erythropoiesis related blood parameters.
- To explore the effect of VIT-2763 on patient reported outcomes (pain and quality of life).
- To explore the PK of VIT-2763 using a population PK approach.
- To explore the changes in abnormal RBCs (sickling) assessed by peripheral blood smear.
- To explore the number of VOC episodes and visceral infarctions.

## 3.4 Primary Endpoint

- Mean change from baseline in haemolysis markers as measured by reduction of indirect bilirubin after 8 weeks of treatment.

## 3.5 Secondary Endpoints

- Mean change from baseline in haemolysis markers as measured by direct and total bilirubin, LDH, potassium, Hb and free haptoglobin after 8 weeks of treatment.
- Frequency and severity of reported or observed AEs by SOC and PTs using MedDRA coded terms, indicating seriousness criteria and relatedness over 8 weeks of treatment.

## 3.6 Exploratory Endpoints

- Changes in haemolysis markers as measured by indirect, direct, and total bilirubin, LDH, potassium, Hb, and free haptoglobin, from baseline after 2, 4, and 6 weeks of treatment and 4 weeks after EoT.
- Frequency and severity of reported or observed AEs by SOC and PTs using MedDRA coded terms, indicating seriousness criteria and relatedness up to 4 weeks after EoT.

- Changes in clinical laboratory safety tests (serum biochemistry, safety haematology, and urinalysis) from baseline, 12-lead ECG, physical examination findings, vital signs (blood pressure, pulse rate), and haematological changes due to iron-restricted erythropoiesis after 2, 4, 6, and 8 weeks of treatment and 4 weeks after EoT.

- Changes in haematological indices, including Hb concentration, RBC count, Hct, MCV, MCH, MCHC, CHCM, RBC distribution width, WBC analyses including differential WBC counts, platelet and reticulocyte counts, percentage reticulocytes, percentage hypochromic microcytic RBCs (RBC volume versus Hb scatterplot analysis), from baseline after 2, 4, 6, and 8 weeks of treatment and 4 weeks after EoT.

- Changes in blood inflammatory markers as measured by 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, from baseline after 2, 4, 6, and 8 weeks of treatment and 4 weeks after EoT.

- Assessment of iron-related parameters and markers of erythropoiesis: changes in total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin, from baseline after 2, 4, 6, and 8 weeks of treatment and 4 weeks after EoT.

- VIT-2763 PK parameters ($C_{max}$, clearance, distribution volume, AUC). Sparse sampling for determination of VIT-2763 plasma concentration following multiple dosing will be obtained from pre-dose to 2 hours, 4 hours and 6 hours post-morning dose at study Visit V4. A population PK approach will be applied to estimate PK parameters.

- Change in patient reported outcomes using ASCQ-Me from baseline after 2, 4, 6 and 8 weeks of treatment.

- Changes in abnormal RBCs (sickling) assessed by peripheral blood smear from baseline after 2, 4, 6 and 8 weeks of treatment and 4 weeks after EoT.

- Number of VOC episodes and visceral infarctions over 8 weeks of treatment and 4 weeks after EoT.

# 4. INVESTIGATIONAL PLAN

## 4.1 Overall Study Design

This is a Phase 2a, randomised, double-blind, placebo-controlled, parallel group trial in SCD subjects. Multiple doses of VIT-2763 will be administered at 3 dose levels and with 2 different dosing frequencies (60 mg BID, 120 mg BID, 120 mg TID).

A total of 24 subjects with confirmed diagnosis of SCD will be randomised into 4 cohorts (either VIT-2763 or corresponding placebo) (see Figure 1 and Table 2) through a secure and validated centralised IWRS that automates the random assignment of treatment groups to randomisation numbers. Stratified randomisation (balanced allocation across treatment groups) will be used according to genotype (HbS/S - HbS/βT0).

At baseline, subjects will be assigned to 60 mg BID VIT-2763 (Cohort 1), 120 mg BID VIT-2763 (Cohort 2), 120 mg TID (Cohort 3) and placebo (Cohort 4a and 4b). If more than 1 subject in any dose cohort withdraws or drops out between signing informed consent and the V6 visit, the subject will be replaced until at least 5 subjects, with no major protocol deviation impacting the primary objective of the trial, per treatment/placebo (Cohorts 4a and 4b) arm have passed Visit V6.

Subjects eligible for randomisation will receive a randomisation number. Randomised subjects who terminate their study participation for any reason, regardless of whether the IMP was taken or not, will retain their randomisation number. The next subject will be given the next randomisation number.

An independent DSMB will oversee the safety and conduct of the trial on an ongoing basis. The DSMB will be comprised of medical and statistical representatives. The DSMB can provide recommendations to the Sponsor regarding stopping the study or discontinuing a treatment arm or otherwise modifying the study design or conduct. The DSMB will review safety data on a periodic, but also as needed on an ad-hoc manner, basis as defined in the DSMB Charter.

Treatment stopping rules for individual subjects are defined in Section 5.4.2.

The expected duration of subject participation is a maximum of 16 weeks: a non-treatment screening period of a maximum of 4 weeks (28 days), an 8-week treatment period and a 4-week safety follow-up period. The schedule of assessments is provided in Table 1.

## 4.2 Duration of Subject Participation and Study

The expected duration of subject participation is a maximum of 16 weeks, including a non-treatment screening period of up to 4 weeks (28 days), an 8-week (56±4 days) treatment period and a 4-week (28±4 days) safety follow-up period.

The overall end of trial is defined as the date of the last visit of the last patient participating in the trial and the end of patient data collection.

# 5. SELECTION AND WITHDRAWAL OF SUBJECTS

## 5.1 Number of Subjects

No specific sample size calculations have been performed for this study.

It is planned to randomise 24 subjects in a 3:3:3:2:1 ratio into 3 VIT-2763 dose groups and 2 placebo groups (Cohorts 4a and 4b).

## 5.2 Inclusion Criteria

The following inclusion criteria must be met for each subject:

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 only HbS/S or HbS/βT0 genotype.

4. Subjects who had at least 1 and no more than 10 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 opioids (excluding codeine) for moderate to severe pain.

5. 18 to 60 years of age inclusive at the time of screening.

6. Body weight ≥40 kg and ≤120 kg at screening and baseline.

7. Absolute reticulocyte count or percentage reticulocyte count >1.5 × ULN during screening.

8. Subjects on concomitant hydroxyurea treatment 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 (serum pregnancy test) and before randomisation (urine pregnancy test), 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 until at least 1 week after the last dose of IMP or requirements from other co-medications taken, e.g., hydroxyurea 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 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 with spermicide or adequate and approved alternatives by the (fertile) male partner.

## 5.3 Exclusion Criteria

The following criteria exclude a subject from participating in this trial:

1. Subjects with confirmed SCD diagnosis other than HbS/S and HbS/βT0.

2. Hb level <6.0 g/dl or >10.4 g/dl for female and >11.0 g/dl for male subjects at screening Visit V1.

   Note: The Hb value at screening Visit V1 will be used for eligibility determination based on the central laboratory result. However, the baseline Hb value determined at Visit V2 (Day 1 pre-dose) also needs to be within the above specified range, based on the local laboratory result.

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. Subjects with a serum ferritin level of <30 µg/l at screening.

5. Calculated TSAT level <25% at screening. However, in case the TIBC is within normal ranges of the central laboratory values, the subject will not be excluded.

6. Subjects being hospitalised for SCD-related events (including pain crisis and VOC) within 14 days before the screening visit. Note: SCD must have been the main cause for the hospitalisation to fulfil this criterion.

7. Chronic liver disease or history of liver cirrhosis, and/or alanine aminotransferase or aspartate aminotransferase, above 3-fold the ULN range at baseline.

8. eGFR <45 ml/min/1.73 $m^2$ at screening. Note: eGFR should be estimated according to CKD-EPI formula.

9. 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.

10. Subjects with history of partial or total splenectomy within 3 months prior to the screening visit.

11. 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.

12. A diagnosis of any form of pulmonary hypertension.

13. Any clinically relevant abnormal 12-lead 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

14. 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 QTcF >450 msec.

15. 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.

16. 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.

17. 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.

18. 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 4 weeks prior to screening and until EoS.

    - Previous oral or intravenous iron therapy or iron chelation therapy ≤4 weeks prior to screening and until EoS.

    - Any known strong or moderate inhibitors and/or inducers of CYP 3A4 enzyme within 4 weeks prior to randomisation and during treatment, or any known strong CYP 2D6 inhibitors or inducers 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 5 half-lives of the respective drug 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 4 weeks 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 platelet aggregation inhibitors including acetylsalicylic acid are allowed.

    - Participation in any other clinical study with an investigational product within 4 weeks prior to screening Visit V1 and until EoS.

19. Concomitant use of hormonal contraceptives (contraception associated with inhibition of ovulation), which are metabolised through CYP 3A4, are not allowed as the sole measure to prevent pregnancy within 4 weeks prior to screening and until 1 week after the last IMP administration (e.g., combined hormonal contraception (oral, intravaginal, transdermal)) and progesterone-only hormonal contraception (oral, injectable, implantable).

20. Known sensitivity to any components of the study products to be administered.

21. Previous participation to this study with at least 1 administration of the IMP.

22. History of drug or alcohol abuse within 2 years prior to screening.

23. Pregnant (e.g., positive serum pregnancy test) or females currently breastfeeding.

24. History or known concomitant solid tumours and/or haematological malignancies unless resolved in the ≥2 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).

25. 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.

26. Unable to take and absorb oral medications, unable to swallow Size 0 capsules.

27. 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.

28. Acute peptic stomach or duodenal ulcer in the previous 3 months before screening and/or not healed after 3 months of proton-pump inhibitors therapy (or adequate standard of care therapy).

29. Occult or evident not controlled haemorrhages (i.e., ulcerations of gastrointestinal tract or body surface)

30. Any employee or their close relatives of the Sponsor, or of a CRO, or a study site involved in the trial.

## 5.4 Withdrawal of Subjects

### 5.4.1 Withdrawal of Subjects from Study

Subjects may voluntarily withdraw from study participation at any time without having to provide a reason. Subjects may be withdrawn because of the appearance of a new health condition requiring care or medications prohibited by the protocol, unacceptable AE, refusal to continue treatment, or at the Investigator's discretion if it is in the subject's best interest.

If a subject withdraws from the study at any time either at his or her request or at the Investigator's discretion, the reason(s) for withdrawal must be recorded on the relevant page of the subject's eCRF and source documentation. Subjects who withdraw from the study prematurely (with the exceptions of "withdrawal by subject" and "lost to follow-up") should undergo all study assessments as per Visit V6, if possible.

It is vital to obtain follow-up data on any subject withdrawn because of an AE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures (see Section 8.7). If a subject is discontinued due to an AE, the event should be followed by the Investigator through contact with the subject until resolution or stabilisation has occurred. All AEs should be followed until resolution, stabilisation, or the subject is lost to follow-up and cannot be contacted.

If a subject refuses to continue study procedures, the reason for refusal should be fully documented in the subject's source document and recorded in the study-specific eCRF. Although subjects are not obliged to give a reason for withdrawing consent, the Investigator will make every effort to obtain the reason, while fully respecting the subject's rights. If the subject withdraws from the trial without providing a reason, the source documents and the eCRF should document the reason for discontinuation as "withdrawal by subject".

### 5.4.2 Withdrawal of Subjects from Study Drug

IMP must be stopped if any of the below criteria may apply:

- Serum transaminases (alanine aminotransferase or aspartate aminotransferase) >3 × ULN range and total bilirubin >2 × ULN (confirmed by subsequent repeat ≥24 hours apart).
- Hb level <5.7 g/dl or an Hb decrease of >1.5 g/dl from last visit.
- Ferritin level <15 µg/l.
- Increase of QTcF interval of 60 ms over baseline on 2 consecutive 12-lead ECG measurements, and/or any QTcF ≥500 ms. Note: Occurrence of this condition would qualify the subject for permanent discontinuation from the study (see last paragraph in Section 5.4.2).
- Atrioventricular conduction delays on 2 consecutive 12-lead ECG measurements:
  - Absolute PR interval prolongation >240 ms.
  - Relative PR interval change >25% from baseline or previous visit.
  - Second-degree atrioventricular block or higher.
  - Symptoms and signs of decreased cardiac output.
- Unexpected clinically relevant worsening of complications related to SCD, as per Principal Investigator assessment.
- Major protocol deviations, including noncompliance or lost to follow-up.
- Participation in any other clinical study during the duration of this clinical study.

- Loss of ability to freely provide consent through imprisonment or involuntary.
- Incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Inability to comply with the protocol or study procedures.

Any permanent subject withdrawal from study medication needs to be discussed and agreed with the Medical Monitor. Withdrawing a subject from study drug can be temporary, and the study medication might be reinitiated upon resolution of withdrawal reason and consultation and agreement with Medical Monitor.

### 5.4.3 Study Stopping Rules

A DSMB will regularly, and as needed on an ad-hoc manner, assess the safety information of the enrolled subjects, and can provide recommendations to the Sponsor regarding stopping the study or discontinuing a treatment arm or otherwise modifying the study design or conduct.

## 5.5 Re-screening of Subjects

A subject can only be randomised once in the trial. If a randomised subject withdraws consent for further follow-up, the subject cannot be re-screened. However, a subject who fails to meet the protocol inclusion/exclusion criteria (e.g., clinically significant bacterial, fungal, parasitic, or viral infections which require therapy, folate deficiency anaemia) can be re-screened at a later time point. Before randomisation (Visit V2), re-screening may be considered at the discretion of the Investigator and in consultation with the Sponsor. The subject must sign a new written informed consent and will be allocated a new screening number.

# 6. STUDY TREATMENTS

## 6.1 Treatment Blinding

This study is conducted in a double-blind fashion[1]. The IMPs (VIT-2763 30 mg, 60 mg, or placebo) are provided as identical white opaque hypromellose Size 0 hard capsules in white high-density polyethylene (HDPE) bottles with identical labels. The appearance of the placebo capsules is identical to the VIT-2763 dosage strengths (30 mg and 60 mg) expressed as drug substance base. To minimise the potential for bias, treatment randomisation information will be kept confidential by the unblinded biostatistician and will not be released to the Investigator or site personnel until the study database has been locked. The blind will be maintained for subjects and site personnel. The Sponsor (except a defined study independent team and clinical trial supply manager), all CRO staff (except staff required for the development of the randomisation schedule and outputs for the DSMB) are blinded. The DSMB members will be unblinded.

The Sponsor/CRO staff who may be unblinded will be identified prior to final breaking of the blind. If the Investigator or site personnel becomes aware of a subject's study treatment assignment, efforts should be made to not disclose treatment assignments to other study staff, subjects, or their caregivers.

Subjects should refrain from discussion of their IMP with the site staff or other subjects, and any questions regarding the physical properties or appearance of the IMP should be directed to the dispensing Investigational Pharmacist only.

During the study, the blind will only be broken under particular conditions that are specified in Section 6.1.1.

### 6.1.1 Unblinding

The study blind will only be broken for an individual subject in the following situations: In case of a medical emergency, when knowledge of the treatment arm that was administrated is relevant for the treatment of the subject.

- When reporting of the treatment arm to the Health Authorities is required, e.g., for reporting a suspected unexpected serious adverse reaction (SUSAR) (see Section 10.7.2).

- If a subject becomes pregnant during the study, the knowledge of the treatment arm is therefore necessary (see Section 10.8.3).

[1]This study is a double-blind study, although subjects receiving oral treatment TID will know that they are not in the BID treatment cohorts, subjects will still be blinded for verum and placebo. Similarly, subjects randomised into the BID treatment cohorts will know that they are not in the TID treatment cohorts, nevertheless all subjects are blinded within their cohort.

If breaking of the blind is required, the unblinded information should be, wherever possible accessible only to those clinical site staff who need to be involved in the diagnostic workup, treatment, or medical follow-up of the subject (e.g., in case of a medical emergency or a pregnancy), or those involved in the safety reporting to external regulatory bodies (e.g., in case of a SUSAR or a pregnancy). The responsibility to break the treatment code in emergency situations resides solely with the Investigator. However, if in the opinion of the Investigator, the situation allows, the study Medical Monitor may be contacted for discussion in advance. The Investigator may inform the subject and/or his/her treating physician of the treatment assignment. Unblinding by IWRS must always be performed according to the procedures that are specified in applicable Standard Operating Procedures.

## 6.2 Dosage Forms/Formulation

All IMPs used in this study have been manufactured in accordance with current Good Manufacturing Practice.

### 6.2.1 VIT-2763

VIT-2763 will be provided by the Sponsor for this study.

| | |
|---|---|
| Active Ingredient: | VIT-2763 |
| Chemical Name: | 2-(2-{[2-(1H-benzimidazol-2-yl) ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl) methyl]-1,3-oxazole-4-carboxamide trihydrochloride |
| Strength: | Two dosage strengths of VIT-2763 (30 mg, 60 mg) are used |
| Excipients: | Capsule: hypromellose 94.1 mg, titanium dioxide (E171) 1.92 mg |
| Appearance: | Size 0 hard capsules with a white opaque body and cap |
| Dosage Form: | Capsules |
| Manufacturer: | Aptuit S.r.l., Via A. Fleming 4, 37135 Verona, Italy |
| Storage: | VIT-2763 capsules are packed in 60-ml HDPE bottles with desiccant and should be stored according to the instructions on the label |

### 6.2.2 Placebo

Placebo will be provided by the Sponsor for this study.

| | |
|---|---|
| Excipients: | Capsule: hypromellose 94.1 mg, titanium dioxide (E171) 1.92 mg |
| Filling: | Microcrystalline cellulose 49.5 mg, magnesium stearate 0.5 mg |
| Appearance: | Identical to VIT-2763. Size 0 hard capsules with a white opaque body and cap |

Dosage Form: Capsules

Manufacturer: Aptuit S.r.l., Via A. Fleming 4, 37135 Verona, Italy

Storage: Placebo capsules are packed in 60 ml HDPE bottles with desiccant and should be stored according to the instructions on the label

## 6.3 Drug Dosage and Administration

### 6.3.1 Treatment Arms

IMPs will be administered during 8 weeks each according to Figure 1 and Table 2.

**Table 2 Treatment Scheme**

| | **Treatment Scheme** | | | | |
|---|---|---|---|---|---|
| | **Baseline to Week 8** | | | | |
| | **Morning Dose** | **Evening Dose** | **Morning Dose** | **Afternoon Dose** | **Evening Dose** |
| Cohort 1 (n=6) | 60 mg VIT-2763 | 60 mg VIT-2763 | | | |
| Cohort 2 (n=6) | 120 mg VIT-2763 | 120 mg VIT-2763 | | | |
| Cohort 3 (n=6) | | | 120 mg VIT-2763 | 120 mg VIT-2763 | 120 mg VIT-2763 |
| Cohort 4a (n=4) | Placebo | Placebo | | | |
| Cohort 4b (n=2) | | | Placebo | Placebo | Placebo |

Note: n=Number of subjects per cohort.

At randomisation/baseline, 24 subjects with SCD will be randomised in a 3:3:3:2:1 ratio into 3 VIT-2763 dose groups to receive either 60 mg BID (120 mg/day, Cohort 1), or 120 mg BID (240 mg/day, Cohort 2), or 120 mg TID (360 mg/day, Cohort 3) and 2 placebo groups (BID, Cohort 4a or TID, Cohort 4b).

All subjects will be dosed for 8 consecutive weeks. Compliance will be documented in the eCRF as detailed in the eCRF completion guidelines. The first dose of IMP will be administered in-hospital at the V2 visit (Day 1). The compliance and exact timing of the treatment will be ensured by the study personnel. Subjects will receive IMP for home intake until the next visit. The subject should return all IMP to site at the following visit where accountability is done and receives new IMP according to randomisation and Table 1 to ensure compliance. Compliance for the take-home IMP will be assessed on the basis of the prescribed number of IMP capsules, the duration of treatment, and the quantity of dispensed and returned IMP capsules.

The Investigational Pharmacist or dedicated site staff will inform the study personnel if any compliance issues (e.g., <80% of expected usage) are identified so that the subject can be retrained on proper dosing and administration.

### 6.3.2 Dosing and Administration Guidelines

At randomisation/baseline (Visit V2/Day 1) IMP will be assigned by IWRS as per the randomisation scheme (see Figure 1) and administration schedule (see Table 3). For Cohorts 1, 2, and 4a, the IMP total daily dose will be split into 2 doses per day, 1 in the morning and 1 in the evening. The first dose of IMP will be administered at site from the assigned IMP kits. A single dose out of the assigned kits of 30 mg or 60 mg VIT-2763 or placebo capsules will be administered orally in the morning with about 240 ml water at least 1 hour before meals between 06:00 and 10:00 am. The evening dose will be administered 12 hours (±1 hour) after the morning dose with water 1 hour apart from meals. The evening dose may be administered outside the clinic.

For Cohorts 3 and 4b, the IMP total daily dose will be split into 3 doses per day, 1 in the morning, 1 in the afternoon and 1 in the evening. The first dose of IMP will be administered at site from the assigned IMP kits. A single dose out of the assigned kits of 60 mg VIT-2763 or placebo capsules will be administered orally in the morning with about 240 ml water at least 1 hour before meals between 06:00 and 10:00 am. The afternoon dose will be administered 8 hours (±1 hour) after the morning dose with water 1 hour apart from a meal. The evening dose will be administered 16 hours (±1 hour) after the morning dose with water 1 hour apart from any meal. The afternoon and evening dose may be administered outside the clinical site.

**Table 3 Administration Schedule**

| Administration Schedule | | |
|---|---|---|
| **Total Daily Dose of VIT-2763** | **Number of Capsules/Day** | |
| | **VIT-2763** | **Placebo** |
| 120 mg | 4 × 30 mg | N/A |
| 240 mg | 4 × 60 mg | N/A |
| 360 mg | 6 × 60 mg | N/A |
| 0 mg | N/A | 4[1] or 6[2] × placebo |

1 Cohort 4a.
2 Cohort 4b.
Note: N/A=Not applicable.

Subjects will take the assigned IMP for home intake until the next visit. At each visit, the IMP for that day will be administered at site (subjects need to be informed that they will be receiving the IMP at site for the next visit).

Two VIT-2763 dosage strengths (30 mg, 60 mg) and placebo are available and will be used accordingly to achieve the specified doses and to maintain the blind.

Subjects randomised to placebo will be administered orally 2 or 3 single doses of placebo matching to VIT-2763 as per randomisation scheme and administration schedule. The placebo will match the VIT-2763 capsules used in the respective cohort.

If a subject forgets to take an IMP dose (independent of BID or TID dosing), this forgotten dose can be safely taken when realised that there are at least 4 hours left to the next planned dose. Conversely, if less than 4 hours remain until the next scheduled dose, the recommendation is to wait and only take the next dose.

## 6.4 Package and Labelling

VIT-2763 (30 mg and 60 mg) and placebo capsules in HDPE bottles will be supplied to the investigational site as double-blind IMP with identical appearance.

IMP labels will comply with local requirements.

## 6.5 Study Treatment Allocation

Each eligible subject will be assigned to 1 of 5 groups through a secure and validated IWRS as described in Section 6.3.2. Stratified randomisation (balanced allocation across treatment groups) will be used according to genotype (HbS/S - HbS/βT0).

Subjects will be assigned to VIT-2763 120 mg (Cohort 1), VIT-2763 240 mg (Cohort 2), VIT-2763 360 mg (Cohort 3) and placebo (Cohort 4a and 4b).

All subjects randomised to each cohort will remain on their respective treatment schedules until EoT.

## 6.6 Site Supply, Storage, Accountability

### 6.6.1 Site Supply

Once a site has been approved to receive IMP, the site will be supplied with an initial stock of VIT-2763 (dosage strengths of 30 mg and 60 mg) and placebo. The need for IMP resupply will be assessed on a regular basis taking into account the number of subjects enrolled, and the number of subjects in screening at the site.

If a subject is not able to visit the site for IMP resupply in case of extraordinary events (e.g., COVID-19 pandemic), a direct shipment of the study drug to the subject home/place of stay can be implemented, if allowed by the local regulations. The shipment will be performed by a logistics provider in a traceable and preferably temperature-controlled manner, after agreement with the Investigator and on the basis of an Investigator's prescription. The process will be documented adequately. Written information on the dose regimen will be provided to the subject along with contact information to site for any questions subject may have. The subject will return any unused IMP and empty IMP packages by a logistics provider or during the next on-site visit as instructed by the Investigator. For further details refer to Section 8.8.

### 6.6.2 Storage

Upon receipt, all IMPs should be stored according to the instructions specified on the drug labels and accessible to authorised personnel only.

Each site should have a calibrated thermometer that records minimum and maximum temperatures daily or the temperature should be monitored continuously using a temperature monitoring system. Maintenance of a temperature log is mandatory. The log should be updated by site personnel at least every workday. This log must be available for review by the Monitor/Clinical Research Associate during on-site monitoring visits. Should the storage temperature be outside the range, the IMP must be quarantined immediately, and the Sponsor contacted for guidance.

### 6.6.3 Accountability

The Investigator at each site is responsible for the storage and accountability of the IMP supplies. The Investigator will ensure that adequate records of the receipt, dispensation, administration, and return of the IMP are kept and that the IMP is used only for subjects enrolled in the study. All data regarding the IMP (including kit and/or batch numbers) must be recorded in the eCRF and on any other relevant forms provided.

Each study site will maintain a drug inventory/dispensing record for all IMPs dispensed and returned. At the end of the study, 1 copy of the drug inventory/dispensing record should be sent to the Sponsor for the central study file. The original will be kept in the site files.

After completion of the study, or if it is prematurely terminated, all unused materials will be returned to the Sponsor. All used IMP containers will be retained at the site by the Investigator/qualified designee for the Study Monitor's verification. The decision to destroy IMPs at the site must first be made by the Sponsor. If IMP is destroyed at the site, the Investigator will forward the certificate of destruction to the Sponsor.

## 6.7 Drug Dose Modification

### 6.7.1 Procedures for Overdose

Excessive doses of VIT-2763 could cause severe and transient hypoferraemia. Based on nonclinical data, ECG monitoring is recommended, and standard emergency treatment should be applied. In addition, it theoretically may warrant acute medical management following transient changes in serum iron parameters, e.g., if concurrent (additional) blood loss or haemolysis is suspected or if Hb measurements are low enough to cause symptoms of decreased oxygen delivery. While it is unlikely that this may occur under the controlled environment of this study and based on dose-response relationship examinations obtained from the first-in-human trial in healthy volunteers, further dosing in any affected subjects must be stopped immediately and depending on the observed or reported signs or symptoms of the subject, standard medical care should be provided. When VIT-2763 overdose may lead to very unlikely cardiac dysrhythmias or widened PR interval or increased QRS duration due to block of sodium channel, further VIT-2763 dosing will be stopped, and it

may warrant administration of sodium bicarbonate in particular in case these subjects are hypotensive and/or comatose. Additional emergency and intensive care must be provided in case deemed necessary at the discretion of the Investigator.

## 6.8 Prohibited Therapy and Concomitant Treatment

Prohibited therapies in this study will include the following treatments:

- Prior or concomitant use of any medication that is known to prolong the QT/QTc interval or the PR/QRS interval, within 4 weeks prior to screening and until EoS.
- Previous oral or intravenous iron therapy ≤4 weeks prior to screening and until EoS.
- Any known strong or moderate inhibitors and/or inducers of CYP 3A4 enzyme within 4 weeks prior to randomisation and during treatment period, or any known strong CYP 2D6 inhibitors or inducers, 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 5 half-lives of the respective drug prior to screening/Visit V1, or anticipated need for such agents during the study.
- Any prior gene therapy.
- Use of chronic anticoagulant therapy unless treatment stopped at least 4 weeks 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 platelet aggregation inhibitors including acetylsalicylic acid are allowed.
- Iron chelation therapy and RBC transfusion.
- Current treatment or participation in any other investigational drug study within 4 weeks prior to screening/Visit V1 and until EoS.

In case any subject warrants medical care during the course of the study, the Investigator will be permitted to prescribe treatment(s) at their discretion, in order to protect the subject's safety and well-being and according to acceptable standards of medical care.

Any concomitant treatment given for any reason during the course of the study must be recorded on the eCRF and in the subject's medical records, including dosage, start and stop dates and reason for use.

# 7. RISKS/PRECAUTIONS

## 7.1 Special Warnings and Precautions for Use

The safety, tolerability, and preliminary efficacy of multiple doses of VIT-2763 in adult subjects with SCD will be investigated in this Phase 2a clinical trial.

The results of a Phase 1 clinical trial in 72 healthy volunteers showed that treatment with single oral doses of VIT-2763 ranging from 5 mg to 240 mg and 7-day treatment with VIT-2763 oral doses of 60 mg QD, 120 mg QD, 60 mg BID, and 120 mg BID was well tolerated and no SAEs or discontinuations due to AEs were reported. Safety and tolerability data from a Phase 2a clinical study in 25 NTD beta-thalassaemia subjects showed that treatment with multiple oral doses of VIT-2763 ranging from 60 mg QD to 120 mg BID was well tolerated with a few safety findings of clinical relevance. No SAEs were reported, and all AEs were mild to moderate. Treatment regimens showed no differences between active and placebo dose groups, both in terms of frequencies and intensity of TEAEs.

In both studies, there were no findings of clinical relevance with respect to vital signs, 12-lead ECG, or physical examination throughout the trials. With limited clinical data about previously observed adverse reactions from human studies being available, no serious adverse drug reactions (ADRs) are considered expected by the Sponsor for the purpose of expedited safety reporting of SUSAR and annual/aggregate safety reporting.

Excessive doses of VIT-2763 could cause severe and transient hypoferraemia. Based on nonclinical data, ECG monitoring is recommended, and standard emergency treatment should be applied.

Caution should be exercised in subjects with:

- Iron deficiency
- Clinically relevant deviations in RBC or WBC counts

Based on the nonclinical safety findings, caution should be exercised in subjects with:

- History or clinical finding of cardiac disorders such as clinically relevant cardiac arrhythmia, cardiomyopathy, coronary disease, valve disorder, or heart failure
- Prior or concomitant use of any medication slowing cardiac conduction (PR and QRS interval prolongation), or that prolongs the QT/QTc interval

## 7.2 Fertility, Contraception and Lactation

### 7.2.1 Fertility

There are no data on the effects of VIT-2763 on human fertility. VIT-2763 produced no effects on male or female fertility or early embryonic development at oral doses up to 200 mg/kg/day in rats.

### 7.2.2 Pregnancy

Data of nonclinical studies of the effect of VIT-2763 on pregnancy and fertility indicate that women of childbearing potential should use highly effective methods of contraception whilst taking VIT-2763 and until at least 1 week after the last dose. No data on breastfeeding has been generated yet, so breastfeeding must be discontinued during treatment with VIT-2763 and for at least 1 week after the last dose.

Highly effective methods of contraception for female subjects participating in this trial are:

- Intrauterine device, implants
- Injectables, and combined oral contraceptives
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence
- Subject has been surgically sterilised at least 6 months prior to the study

For female subjects participating in this study, continuous use of hormonal contraception alone is not sufficient, because potential interactions via 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 and approved alternatives.

For men participating in this study no contraceptive measures are needed.

# 8. STUDY PROCEDURES

For a detailed schedule of assessments (including all protocol required assessments, visits and visit windows) please refer to Table 1.

## 8.1 Screening Visit/Visit 1 (Day -28 to Day -1)

Before any study-specific procedures are performed, the subject will receive an explanation of all study procedures and must sign and date a written ICF approved by an Institutional Review Board (IRB) or equivalent Ethics Committee (EC) (see Section 13.2 for additional requirements).

The following activities will be performed at Visit V1:

- The Investigator will obtain written informed consent/assent from potentially eligible subjects and/or legally acceptable guardian before any trial-related procedure is performed
- Review of inclusion and exclusion criteria. Any outstanding eligibility criteria (see Section 5.2 and Section 5.3) not available during screening needs to be available before randomisation, including genotyping (local laboratory haemoglobinopathy evaluation/Hb electrophoresis; see Inclusion Criterion 3), in case not available previously
- Collect demographic information
- Review medical/surgical history
- Perform physical examination. Body systems to be assessed include general appearance, head (eyes, ears, nose, and throat), cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymph nodes, and skin
- Assess vital signs, e.g., systolic blood pressure, diastolic blood pressure, and pulse, after subject has rested for at least 5 minutes
- Record body weight and height
- Perform a single 12-lead ECG
- As of the date of informed consent for each subject, document in the eCRF all SAEs/AEs and changes/additions made to previous and concomitant medications. SAEs will be reported as they occur, but no later than 24 hours after the Investigator's awareness of the event

- Draw blood tests using peripheral venipuncture to determine if the subject is eligible according to the inclusion and exclusion criteria:
  - Blood sample for optional genotyping for SCD in case no genotype diagnosis exists (local laboratory)
  - Blood sample for assessment of high sensitivity C-reactive protein (central laboratory)
  - Serum ferritin, and TSAT (for exclusion criteria only) (central laboratory)
  - Serum pregnancy test (only in females of childbearing potential) for central laboratory assessment
  - Serum virology (hepatitis B surface antigen, hepatitis B virus, hepatitis C virus, HIV) for central laboratory assessment
- Collect sample for central laboratory assessment of Hb and reticulocytes
- Collect sample for central laboratory assessment of serum chemistry
- Collect urinalysis samples for central laboratory assessment of:
  - pH, protein, glucose, ketone, RBCs, and WBCs (urinary dipstick test); quantitative measurement only if positive dipstick
  - Urinary microalbumin, creatinine, and microalbumin/creatinine ratio (spot urinary sample, morning void)
- Dispense 1 copy of all 6 ASCQ-Me forms
- Inform subject to complete all ASCQ-Me forms the day before the next visit (baseline visit/V2)

## 8.2 Baseline/Randomisation/Visit 2 (Day 1)

To accommodate local hospital practice, the subject may attend the V2 visit either on the day of the first dose of study treatment (randomisation day), or on the day before the planned randomisation day. Note: A planned overnight stay prior to study treatment administration does not fulfil the seriousness criteria of an SAE unless there is a medical requirement.

If a subject cannot return to the site post-randomisation for a study visit in case of extraordinary events (e.g., COVID-19 pandemic), the Investigator will conduct a remote visit (e.g., telemedicine, phone call), a visit at the subject home, or in facilities near to the subject's home to evaluate subject safety and eligibility to continue the study therapy, if applicable and as per local country guidance (see Section 8.8).

The following activities will be performed at Visit V2:

**Before Randomisation**

- Eligibility assessment will be conducted during screening and also prior to randomisation and receiving IMP. Any outstanding eligibility criteria (see Section 5.2 and Section 5.3) not available during screening need to be available before randomisation, including genotyping (local laboratory haemoglobinopathy evaluation/Hb electrophoresis; see Inclusion Criterion 3), in case not available previously. If a subject is found to meet eligibility criteria and is enrolled in the study, but then has a clinically significant change in status prior to administration of the first dose of IMP, for example is hospitalised for sickle cell crisis, the subject should be withdrawn from the study. Re-screening may be considered at the discretion of the Investigator and in consultation with the Sponsor.

- Perform physical examination. Body systems to be assessed include general appearance, head (eyes, ears, nose, and throat), cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymph nodes, and skin

- Assess vital signs, e.g., systolic blood pressure, diastolic blood pressure, and pulse, after subject has rested for at least 5 minutes, pre-dose (trough)

- Record body weight

- Perform a single 12-lead ECG at pre-dose (trough)

- Changes/additions made to concomitant medications will be re-assessed since signing the ICF and SAEs/AEs will be reported

- Draw blood sample for assessment of Hb to confirm eligibility (local laboratory)

- Prepare RBC blood smear (local laboratory) to assess for sickle cells (central laboratory)

- Urine pregnancy test (only in females of childbearing potential). Positive urine pregnancy test results need to be confirmed using a serum beta-hCG test (local laboratory assessment)

- Collect urinalysis samples for central laboratory assessment of:

  - pH, protein, glucose, ketone, RBCs, and WBCs (urinary dipstick test); quantitative measurement only if positive dipstick

  - Urinary microalbumin, creatinine, and microalbumin/creatinine ratio (spot urinary sample, morning void)

- Collect blood samples at pre-dose (trough) for central laboratory (as per Laboratory Manual) assessment of:
  - Haematology panel/RBC indices (to determine baseline value)
  - Serum chemistry panel
  - Haemolysis markers
  - Endothelial inflammation/dysfunction markers
  - Total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin (central laboratory assessment)
- Record number of VOC episodes within the last 8 weeks. Assess visceral infarctions as per standard of care

**Randomisation and Administration of the First Dose of IMP**

- Randomisation
- Dispense subject identification card
- The first dose of IMP must be administered at the site and the time of administration needs to be entered in the eCRF. The IMP total daily dose will be split depending on the subject's randomisation in 2 or 3 doses per day. If randomised to a cohort with BID treatment frequency, then dosing will occur in the morning and in the evening. If randomised to cohorts with TID treatment frequency, then dosing will occur in the morning, afternoon, and evening. For BID dosing the morning dose of the IMP will be administered with water, at least 1 hour before meals between 06:00 and 10:00 a.m. The evening dose will be administered 12 hours (±1 hour) after the morning dose 1 hour apart from meals. For TID dosing morning dose of the IMP will be administered with water, at least 1 hour before meals between 06:00 and 10:00 a.m. The afternoon dose will be administered 8 hours (±1 hour) after the morning dose 1 hour apart from meals. The evening dose will be administered 16 hours (±1 hour) after the morning dose 1 hour apart from any meals.
- Collect all 6 ASCQ-Me forms completed by subject
- Dispense IMP at site (via IWRS). Note: Only the morning dose on the visit day needs to be taken at site
- Perform a new single 12-lead ECG at 2 hours post-morning dose (±30 minutes).

- Collect samples (2 hours post-morning dose) for total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin and erythropoietin (central laboratory assessment)

- Dispense 2 copies of the following forms “Emotional Impact”, “Pain Impact”, “Sleep Impact”, and “Stiffness Impact”

- Inform subject to complete 1 copy of each form, 1 week after the visit, and a second copy the day before the next visit (Visit V3)

## 8.3 Visit 3 (Day 14±2 Days)

The following activities will be performed at Visit V3:

- Assess vital signs, e.g., systolic blood pressure, diastolic blood pressure, and pulse, after subject has rested for at least 5 minutes, pre-dose (trough)

- Perform a single 12-lead ECG at pre-dose

- Assess SAEs/AEs

- Assess changes/additions to concomitant medications and treatments

- Collect blood sample for safety assessment of Hb by local laboratory

- Prepare RBC blood smear (local laboratory) to assess for sickle cells (central laboratory)

- Urine pregnancy test (only in females of childbearing potential). Positive urine pregnancy test results need to be confirmed using a serum beta-hCG test (local laboratory assessment)

- Collect urinalysis samples for central laboratory assessment of pH, protein, glucose, ketone, RBCs, and WBCs (urinary dipstick test); quantitative measurement only if positive dipstick

- Collect samples at pre-dose (trough) for central laboratory assessment of:

  - Haematology panel/RBC indices

  - Serum chemistry panel

  - Haemolysis markers

  - Endothelial inflammation/dysfunction markers

  - Total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin (central laboratory assessment)

- Record VOC episodes (number of events and pain intensity (NRS: 0-10) compared to historical VOC episodes). Assess visceral infarctions as per standard of care

- Collect 2 copies of the forms “Emotional Impact”, “Pain Impact”, “Sleep Impact”, and “Stiffness Impact”

- Dispense IMP at site (via IWRS). Note: The morning dose on the visit day needs to be taken at site

- Collect samples (2 hours post-morning dose) for total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin (central laboratory assessment)

- Perform a single 12-lead ECG at 2 hours (±30 minutes) post-morning dose.

- Dispense 2 copies for all of the following forms “Emotional Impact”, “Pain Impact”, “Sleep Impact”, and “Stiffness Impact” and 1 copy of “Social Functioning Impact”

- Inform subject to complete 1 copy of the following forms “Emotional Impact”, “Pain Impact”, “Sleep Impact”, and “Stiffness Impact” 1 week after the visit, and a second copy the day before the next visit (Visit V4). The single form “Social Functioning Impact” needs to be completed the day before the next visit (Visit V4)

- Perform IMP accountability

## 8.4 Visit 4 (Day 28±4 Days)

The subject may attend the V4 visit in the afternoon/evening before to facilitate compliance and V4 visit procedures. Note: A planned overnight stay the day before Visit V4 does not fulfil the seriousness criteria of an SAE unless there is a medical requirement. The following activities will be performed at Visit V4:

- Perform physical examination. Body systems to be assessed include general appearance, head (eyes, ears, nose, and throat), cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymph nodes, and skin

- Assess vital signs, e.g., systolic blood pressure, diastolic blood pressure, and pulse, after subject has rested for at least 5 minutes, pre-dose (trough)

- Record body weight

- Perform a single 12-lead ECG at pre-dose

- Assess SAEs/AEs

- Assess changes/additions to concomitant medications

- Collect blood samples for safety assessment of Hb by local laboratory
- Prepare RBC blood smear (local laboratory) to assess for sickle cells (central laboratory)
- Urine pregnancy test (only in females of childbearing potential). Positive urine pregnancy test results need to be confirmed using a serum beta-hCG test (local laboratory assessment)
- Collect urinalysis samples for central laboratory assessment of:
  - pH, protein, glucose, ketone, RBCs, and WBCs (urinary dipstick test); quantitative measurement only if positive dipstick
  - Urinary microalbumin, creatinine, and microalbumin/creatinine ratio (spot urinary sample, morning void)
- Collect samples at pre-dose (trough) for central laboratory assessment of:
  - Haematology panel/RBC indices
  - Serum chemistry panel
  - Haemolysis markers
  - Endothelial inflammation/dysfunction markers
  - VIT-2763 PK parameters
  - Total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin (central laboratory assessment)
- Record VOC episodes (number of events and pain intensity (NRS: 0-10) compared to historical VOC episodes). Assess visceral infarctions as per standard of care
- Collect the ASCQ-Me forms completed by subject
- Dispense IMP at site (via IWRS). Note: The morning dose on the visit day needs to be taken at site
- Collect additional PK samples at 2 hours (±15 minutes), 4 hours (±30 minutes) and 6 hours (±30 minutes) post-morning dose (for central laboratory assessment)
- Collect samples (2 hours post-morning dose) for total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin (central laboratory assessment)
- Perform a single 12-lead ECG at 2 hours (±30 minutes) post-morning dose.

- Dispense 2 copies of all of the following forms “Emotional Impact”, “Pain Impact”, “Sleep Impact”, and “Stiffness Impact”
- Inform subject to complete 1 copy of each form 1 week after the visit, and a second copy the day before the next visit (Visit V5)
- Perform IMP accountability

## 8.5 Visit 5 (Day 42±4 Days)

The following activities will be performed at Visit V5:

- Assess vital signs, e.g., systolic blood pressure, diastolic blood pressure, and pulse, after subject has rested for at least 5 minutes, pre-dose (trough)
- Perform a single 12-lead ECG at pre-dose
- Assess SAEs/AEs
- Assess changes/additions to concomitant medications and treatments
- Collect blood sample for safety assessment of Hb by local laboratory
- Prepare RBC blood smear (local laboratory) to assess for sickle cells (central laboratory)
- Urine pregnancy test (only in females of childbearing potential). Positive urine pregnancy test results need to be confirmed using a serum beta-hCG test (local laboratory assessment)
- Collect urinalysis samples for central laboratory assessment of pH, protein, glucose, ketone, RBCs, and WBCs (urinary dipstick test); quantitative measurement only if positive dipstick
- Collect samples at pre-dose (trough) for central laboratory assessment of:
  - Haematology panel/RBC indices
  - Serum chemistry panel
  - Haemolysis markers
  - Endothelial inflammation/dysfunction markers
  - Total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin (central laboratory assessment)

- Record VOC episodes (number of events and pain intensity (NRS: 0-10) compared to historical VOC episodes). Assess visceral infarctions as per standard of care

- Collect 2 copies of the forms “Emotional Impact”, “Pain Impact”, “Sleep Impact”, and “Stiffness Impact”

- Dispense IMP at site (via IWRS). Note: The morning dose on the visit day needs to be taken at site

- Perform a single 12-lead ECG at 2 hours (±30 minutes) post-morning dose

- Collect samples (2 hours post-morning dose) for total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin (central laboratory assessment)

- Inform the subject for the next visit (Visit V6/EoT) to bring the last morning dose of the day of Visit V6 to the site in order to be taken at site (no new IMP dispensation at Visit V6)

- Dispense 2 copies for all of the following forms “Emotional Impact”, “Pain Impact”, “Sleep Impact”, and “Stiffness Impact” and 1 copy of the forms “Social Functioning Impact” and “Pain Episode Frequency and Severity”

- Inform subject to complete 1 copy of the following forms “Emotional Impact”, “Pain Impact”, “Sleep Impact”, and “Stiffness Impact” 1 week after the visit, and a second copy the day before the next visit (Visit V6). The single forms “Social Functioning Impact” and “Pain Episode Frequency and Severity“ need to be completed the day before the next visit (Visit V6)

- Perform IMP accountability

## 8.6 EoT (or ET) Procedures/Visit 6 (Day 56±4 Days)

On completion of treatment (or if subject is discontinued/withdrawn early), assessments for Visit 6/Day 56±4 days (per Table 1) should be performed:

- Perform physical examination. Body systems to be assessed include general appearance, head (eyes, ears, nose, and throat), cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymph nodes, and skin

- Assess vital signs, e.g., systolic blood pressure, diastolic blood pressure, and pulse, after subject has rested for at least 5 minutes

- Record body weight

- Perform a single 12-lead ECG at pre-dose

- Assess SAEs/AEs
- Assess changes/additions to concomitant medications and treatments
- Prepare RBC blood smear (local laboratory) to assess for sickle cells (central laboratory)
- Urine pregnancy test (only in females of childbearing potential). Positive urine pregnancy test results need to be confirmed using a serum beta-hCG test (local laboratory assessment)
- Collect urinalysis samples for central laboratory assessment of:
  - pH, protein, glucose, ketone, RBCs, and WBCs (urinary dipstick test); quantitative measurement only if positive dipstick
  - Urinary microalbumin, creatinine, and microalbumin/creatinine ratio (spot urinary sample, morning void)
- Collect samples at pre-dose (trough) for central laboratory assessment of:
  - Haematology panel/RBC indices
  - Serum chemistry panel
  - Haemolysis markers
  - Endothelial inflammation/dysfunction markers
  - Total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin (central laboratory assessment)
- IMP administered, the morning dose on the visit day needs to be taken at site
- Perform a single 12-lead ECG at 2 hours (±30 minutes) post-morning dose
- Collect samples (2 hours post-morning dose) for total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin (central laboratory assessment)
- Record VOC episodes (number of events and pain intensity (NRS: 0-10) compared to historical VOC episodes). Assess visceral infarctions as per standard of care
- Collect the ASCQ-Me forms completed by subject
- Perform IMP accountability

## 8.7 EoS (Follow-up) Procedures/Visit 7 (Day 84)

On completion of the study (Visit 7/Day 84±4 days), all assessments per Table 1 should be performed.

All subjects whether completing the treatment or who have withdrawn prematurely, will be followed up for 4 weeks (28±4 days after EoT) after their last administration of IMP to collect, at a minimum, any potential new AEs and concomitant medications (or other endpoints as defined in Table 1). If the Investigator has not seen the subject at in-hospital visit at the end of the reporting period, the Investigator must attempt 3 telephone calls to the subject, and if there is no response, the source documents and the eCRF should document the reason for study discontinuation as "lost to follow-up".

The following activities will be performed at Visit V7:

- Perform physical examination. Body systems to be assessed include general appearance, head (eyes, ears, nose, and throat), cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymph nodes, and skin
- Assess vital signs, e.g., systolic blood pressure, diastolic blood pressure, and pulse, after subject has rested for at least 5 minutes
- Perform a single 12-lead ECG
- Assess SAEs/AEs
- Assess changes/additions to concomitant medications
- Prepare RBC blood smear (local laboratory) to assess for sickle cells (central laboratory)
- Urine pregnancy test (only in females of childbearing potential). Positive urine pregnancy test results need to be confirmed using a serum beta-hCG test (local laboratory assessment)
- Collect urinalysis samples (urinary dipstick test) for central laboratory assessment of pH, protein, glucose, ketone, RBCs, and WBCs
- Collect samples for central laboratory assessment of:
  - Haematology panel/RBC indices
  - Serum chemistry panel
  - Haemolysis markers
  - Endothelial inflammation/dysfunction markers

  - Total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, and erythropoietin

- Record VOC episodes (number of events and pain intensity (NRS: 0-10) compared to historical VOC episodes). Assess visceral infarctions as per standard of care

## 8.8 Allowed Adaptations for Assessments During Site Visits

To provide some flexibility for specific assessments during the site visits, which can be performed post-dose instead of pre-dose as required per the current protocol, the following assessments must be performed before VIT-2763 morning dose administration at the site:

- Collection of AEs and changes/additions made to concomitant medications
- Vital signs assessment
- Pre-dose single 12-lead ECG
- Pre-dose PK blood sample
- Blood sample to assess Hb to confirm eligibility at Visit V2 to assess whether the study therapy can be continued (Visits V2–V5) (local laboratory)
- Blood sample for pre-dose iron-related parameters

After Visit V2, the following assessments can also be performed post VIT-2763 morning dose administration at the site:

- Physical examination
- Body weight recording
- RBC blood smear (local laboratory) to assess for sickling cells (central laboratory)
- Urinalysis sample for central laboratory
- Blood sample for haematology panel/RBC indices (sample for central laboratory)
- Blood sample for serum chemistry panel (sample for central laboratory)
- Blood sample for haemolysis markers
- Blood sample for inflammatory endothelial markers
- VOC episodes recording and visceral infarction as per standard of care assessment
- ASCQ-Me Questionnaire collection

Other assessments not mentioned within this list are to be followed as per protocol.

## 8.9 Allowed Adaptations in Case of Extraordinary Events, e.g., COVID-19

Extraordinary events may call for specific measures to maintain subject safety and guarantee conduct of clinical investigations according to established general and specific guidelines and regulations to meet agreed regulatory, quality, and scientific expectations.

For this, the following adaptations are considered for specific situations:

- Site visits are not possible within the defined time window, possibly leading to delayed:
  - Physical examination: consultation by local physician, follow-up assessment and guidance on drug adaptations via phone, remote visits at subject's home (e.g., home nursing)
  - Laboratory assessments: consultation by local physician, visit at local laboratory for blood analysis, or via home nursing
  - Adaptation of IMP: dispense sufficient amount of IMP at previous visit, delivery to subject's home by qualified designee as assigned by the Principal Investigator, or consider handover of IMP to relatives if allowed and in compliance with the applicable International Council for Harmonisation (ICH) Good Clinical Practice and other applicable laws and regulations, phone call by treating physician to guide dose adaptation of drugs
  - On-site monitoring: accept delayed on-site monitoring, conduct remote monitoring
  - On-site auditing: accept delayed on-site auditing, conduct remote auditing
  - AE/SAE/special situation reporting: frequent phone call visits
- Site visits are not possible within the defined time window, possibly leading to no:
  - Physical examination: consultation by local physician, follow-up clinical assessment via phone remote visits at subject's home (e.g., home nursing)
  - Laboratory assessments: consultation by local physician, local laboratory for blood analysis, or via home nursing
  - Adaptation of IMP: dispense sufficient amount of IMP at previous visit, delivery to subject's home by qualified designee as assigned by the Principal Investigator, or consider handover of IMP to relatives if allowed and in compliance with the applicable ICH Good Clinical Practice and other applicable laws and regulations, phone call by treating physician to guide dose adaptation of drugs

- On-site monitoring: accept delayed on-site monitoring, conduct remote monitoring
- On-site auditing: accept delayed on-site auditing, conduct remote auditing
- AE/SAE/special situation reporting: frequent phone call visits

# 9. STUDY ASSESSMENTS

## 9.1 Demographics and Medical History

Subject's demographics (gender, age, race, and ethnicity) and baseline characteristics including body weight, and medical history will be taken during the baseline visit. Information to be collected will include the aetiology and clinical presentation of SCD (including HbS/S or HbS/βT0) and SCD-related events (including pain crisis and VOC episodes, 8 weeks before baseline), and the date when SCD was first diagnosed, and other clinically relevant past and present medical conditions which were diagnosed/occurred up to at least 6 months prior to signing the informed consent and/or for which the subject is currently treated. Any medically important conditions sustained by the subject which extend beyond 6 months prior to informed consent, should also be reported in the medical history eCRF. Also, the date of the last RBC transfusion obtained will be recorded in the eCRF.

## 9.2 Symptoms and Signs of Anaemia

The Investigator must assess signs and symptoms associated to anaemia in SCD:

- Fatigue, weakness
- Shortness of breath
- Pale or yellowish skin
- And others as per standard of care, including laboratory assessments

Any new clinically relevant symptom or sign of worsening of SCD associated anaemia, or any other comorbidity, as assessed by the Investigator, must be reported as an AE (see Section 10).

The SCD associated genotype, clinical presentation and RBC transfusion needs received during the past 24 weeks prior to randomisation which are part of the inclusion criteria, must be documented in the source data (see Section 5.2).

## 9.3 Physical Examination and Vital Signs

The body systems to be assessed include:

- General appearance
- Head (eyes, ears, nose, and throat)
- Cardiovascular
- Respiratory

- Abdomen
- Musculoskeletal
- Neurological
- Lymph nodes
- Skin

In the study, physical examination is performed at screening/Visit V1 (i.e., Day -28 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.

Vital signs measurements include diastolic blood pressure, systolic blood pressure, and pulse rate. Vital signs are assessed at every visit. Vital signs should be performed before IMP administration (trough), after a resting period of at least 5 minutes. Any new clinically relevant change as assessed by the Investigator, in blood pressure readings, pulse rhythm or rate must be reported as an AE (see Section 10).

## 9.4 12-lead ECG Assessment

The subject should be resting quietly for a minimum of 5 minutes prior to obtaining the single 12-lead ECG (locally).

Each lead shall be recorded for at least 3 beats at a speed of 25 mm/s. The following parameters will be recorded: ventricular rate, PR interval, QRS duration, QT interval and QTcF. These parameters plus the judgement by the physician will be entered in the eCRF. Print-outs of ECGs will have to be signed, dated, and filed at the site.

At baseline, the Investigator must document clinically relevant ECG findings on the appropriate baseline eCRF pages and in the subject's hospital records. Any new clinically relevant ECG finding, or aggravation/worsening of an already existing finding as assessed by the Investigator, must be reported as an AE (see Section 10).

## 9.5 Documentation of Prior and Concomitant Treatments

All medications and treatments prescribed at the moment of informed consent must be documented on the appropriate eCRF pages. In addition, treatments prescribed up to at least 3 months prior to obtaining the informed consent must be documented on the appropriate eCRF pages, irrespective if the treatment is still ongoing at the time of screening. All changes to or addition of concomitant treatments as of informed consent must be recorded (including changes in dose, change in formulation, starting or stopping medications) in the eCRF. If the indication for changing a subject's concomitant treatment constitutes a new medical condition or a worsening of an existing clinical condition which is considered by

the Investigator as being clinically relevant, the indication must be documented as an AE (see Section 10).

## 9.6 ASCQ-Me

The ASCQ-Me system is a set of questions assessing varying aspects of quality of life associated with SCD. The total ASCQ-Me measure set consists of both computer-adaptive and static (i.e., fixed; short forms) scales [31]. However, in this study the short paper forms will be used, and these forms need to be completed out by the subject.

The paper forms cover 6 topics:

1. Pain episodes, frequency, and severity (assessing the last 12 months)
2. Social functioning impact (assessing the last 30 days)
3. Emotional impact (assessing the last 7 days)
4. Pain impact (assessing the last 7 days)
5. Sleep impact (assessing the last 7 days)
6. Stiffness impact (assessing the last 7 days)

## 9.7 Laboratory Parameters

In case of pandemic (e.g., COVID-19) related restriction and impossibility of sample shipment, or inability of subject to visit the site, inform the Medical Monitor of the study, and laboratory assessments may be performed in a local laboratory at site or near to subject's home. In order to ensure subject's safety and study data continuity, these parameters should include at minimum: haematology panel, chemistry panel, and urine pregnancy test.

### 9.7.1 Local Laboratory Parameters

The following laboratory parameters will be assessed locally:

- Hb levels from Visit V2 to Visit V5.
- RBC smear sickling preparation from baseline (Visit V2) to EoS (Visit V7).
- Optional blood sample for SCD genotyping.
- Urine pregnancy test: beta-hCG for females of childbearing potential from baseline/V2 to EoS/V7.

### 9.7.2 Central Laboratory Parameters

Details concerning the central blood samples collection, blood withdrawal, processing and storage will be provided in a laboratory instruction manual. The following laboratory parameters will be assessed by central laboratory according to Table 1.

See Table 4 for the list of central laboratory assays.

**Table 4 List of Central Laboratory Assays**

| Panel | Parameters |
|---|---|
| Pregnancy Test: | beta-hCG |
| Serum Virology: | HBsAg, HBV, HCV, HIV |
| Haematology/RBC Indices | Haemoglobin<br>Reticulocytes (abs/%)<br>RBC count<br>Hct<br>MCH<br>MCV<br>MCHC<br>RDW<br>% hypochromic RBC<br>CHCM<br>WBC<br>Neutrophils (abs, %)<br>Lymphocytes (abs, %)<br>Monocytes (abs, %)<br>Eosinophils (abs, %)<br>Basophils (abs, %)<br>Platelets |
| Serum Chemistry: | Calcium<br>Sodium<br>Magnesium<br>Potassium<br>Phosphorus<br>Chloride<br>Bicarbonate<br>Blood urea nitrogen<br>Uric acid<br>Creatinine kinase<br>Creatinine<br>Folic acid<br>Albumin<br>Total protein<br>Globulin (calculated)<br>Alanine transaminase<br>Aspartate transaminase<br>Alkaline phosphatase<br>Glucose<br>Triglycerides<br>Cholesterol |
| Haemolysis Markers: | LDH<br>Free haptoglobin<br>Direct/total bilirubin (indirectly calculated) |

**Table 4 List of Central Laboratory Assays (Cont'd)**

| Panel | Parameters |
|---|---|
| Endothelial Inflammation/Dysfunction: | hsCRP<br>IL-1<br>IL-6<br>TNF-alpha<br>sP-selectin<br>sVCAM-1<br>Xanthine oxidase<br>Endothelin-1 |
| Iron-related Parameters/ Markers of Erythropoiesis: | Total serum iron<br>Serum ferritin<br>Transferrin<br>TSAT<br>TIBC<br>Hepcidin<br>Erythropoietin |
| Sickling: | Smear assessment |
| VIT-2763 Pharmacokinetic: | $C_{max}$, clearance, distribution volume, AUC |
| Urinalysis: | pH<br>Protein<br>Glucose<br>Ketone<br>RBCs<br>WBCs<br>Spot urine sample for urinary microalbumin, creatinine, and microalbumin/creatinine ratio |

Notes: abs=Absolute; AUC=Area under the curve; CHCM=Corpuscular Hb concentration mean; Hb=Haemoglobin; HBsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; hCG=Human chorionic gonadotropin; Hct=Haematocrit; HCV=Hepatitis C virus; hsCRP=High sensitivity C-reactive protein; IL=Interleukin; LDH=Lactate dehydrogenase; MCH=Mean corpuscular Hb; MCHC=Mean corpuscular Hb concentration; MCV=Mean corpuscular volume; RBC=Red blood cell; RDW=Red blood cell distribution width; sP=Soluble platelet; sVCAM=Soluble vascular cell adhesion molecule; TNF=tumour necrosis factor; TIBC=Total iron-binding capacity; TSAT=Transferrin saturation; WBC=White blood cell.

# 10. EVALUATION, RECORDING AND REPORTING OF AEs

## 10.1 Definition of AE

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the IMP.

## 10.2 AE Reporting Period

The AE reporting period begins at the time the ICF is signed by the subject. The AE reporting period ends at the last study contact Visit 7/28±4 days after EoT.

## 10.3 Eliciting AE

If the subject reports an AE, it is the Investigator's responsibility to acquire sufficient information in order to assess causality and providing rationales for assessment. This may require additional laboratory testing, physical examinations, telephone contacts, etc.

In order to avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as "How are you feeling?" It is also important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. This information should be collected prior to completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the Investigator will be assessed as AEs.

## 10.4 Assessing AE

### 10.4.1 Intensity/Severity

The intensity of certain events e.g., laboratory parameters, may be determined according to the Common Terminology Criteria for AEs, where the Common Terminology Criteria grades relate to severity as follows:

1. Mild
2. Moderate
3. Severe
4. Life-threatening
5. Death

Every change in intensity of a particular AE experienced by the subject during the event is recorded.

It is important to note the distinctions between severe AEs and SAEs. Severity is a classification of intensity of a specific event (as in mild, moderate, or severe myocardial infarction); however, the event itself may be of relatively minor medical significance (such as severe headache). An SAE is an adverse reaction which either results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect. It is an AE that meets any of the regulatory specified criteria required for designation as seriousness (described in Section 10.7.1), i.e., a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs.

### 10.4.2 Causality and Reporting

An Investigator who is qualified in medicine must make the determination of relationship to the IMP and any auxiliary medications for each AE and SAE. The Investigator should decide whether, in his or her medical judgement, there is a reasonable possibility that the event may have been caused by the investigational product, providing the rationales for his assessment.

If there is no valid reason for suggesting a relationship, then the AE/SAE should be classified as unrelated or unlikely related and an alternative suspected aetiology should be provided if available (i.e., concomitant medications, intercurrent illness/events). Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a cause-and-effect relationship between the investigational product and the occurrence of the AE/SAE, then the AE/SAE should be considered certainly, probably/likely, or possibly related with a rationale behind this assessment provided.

The following additional guidance may be helpful:

| Term | Relationship | Definition |
|---|---|---|
| Certain | Yes | • Event or laboratory test abnormality, with plausible time relationship to drug intake<br>• Cannot be explained by disease or other drugs<br>• Response to withdrawal plausible (pharmacologically, pathologically)<br>• Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon)<br>• Rechallenge satisfactory, if necessary |
| Probable/ Likely | Yes | • Event or laboratory test abnormality, with reasonable time relationship to drug intake<br>• Unlikely to be attributed to disease or other drugs<br>• Response to withdrawal clinically reasonable<br>• Rechallenge not required |

| Term | Relationship | Definition |
|---|---|---|
| Possible | Yes | • Event or laboratory test abnormality, with reasonable time relationship to drug intake<br>• Could also be explained by disease or other drugs<br>• Information on drug withdrawal may be lacking or unclear |
| Unlikely | No | • Event or laboratory test abnormality with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanation |
| Unrelated | No | • Event or laboratory test abnormality which is clearly related to circumstances not connected with the drug intake |

If the causal relationship between an AE/SAE and the IMP is determined to be "certainly, probably/likely, or possibly related", the event will be considered to be related to the IMP for the purposes of expedited regulatory reporting.

### 10.4.3 Outcome Categorisation

Outcome may be classified as: recovered/resolved (i.e., without sequelae); recovered/resolved with sequelae; recovering/resolving; not recovered/not resolved; fatal; or unknown (if follow-up is not possible).

If the outcome of an SAE is reported as recovered/resolved with sequelae, the Investigator should specify the type of sequelae on the SAE form. If the outcome of an SAE is reported as unknown, the Investigator should specify (on the SAE form) the rationale why unknown was selected.

"Fatal" should be recorded as an outcome when the AE results in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for the AE that, in the opinion of the Investigator, is the most plausible cause of death. All other ongoing AE/SAEs will be recorded as not recovered/not resolved at the time of death.

In case of a fatal outcome, the Investigator should provide a working diagnosis (event which caused outcome, e.g., death due to fatal myocardial infarction) instead of reporting only death, and an autopsy report should be provided whenever available where possible. If the cause of death later becomes available (e.g., after autopsy), this working diagnosis should be replaced by the established cause of death.

Although "fatal" is usually an outcome of an event, events such as sudden death or unexplained death should be reported as SAEs.

## 10.5 Recording and Reporting

### 10.5.1 Persistent or Recurrent AE

AEs that extend continuously, without resolution, between trial assessments should only be recorded once in the eCRF.

The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens.

AEs that resolve and subsequently recur should have each recurrence recorded separately in the eCRF.

All AEs persisting at the time of study completion will be followed by the Investigator through contact with the subject until resolution or stabilisation, or the subject is lost to follow-up and cannot be contacted. The outcome must be documented in the subject's source documents.

### 10.5.2 Diagnosis Versus Signs and Symptoms

Where possible, the Investigator should report a diagnosis rather than individual signs and symptoms or abnormal laboratory values. However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

The Investigator should use standard medical terminology/concepts; avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in each event field in the eCRF.

### 10.5.3 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the medical history eCRF. A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

### 10.5.4 Clinical Laboratory Evaluations

Not every out-of-range laboratory result qualifies as an AE. A laboratory investigation result must be reported as an AE if it is clinically significant and meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalaemia) or a change in concomitant therapy

- Presents shift of a parameter from a normal value to a pathological value, or results in a deterioration of Common Terminology Criteria grade, or a further worsening of an already pathological value

- Is clinically significant in the Investigator's judgement

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgement should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the EoT with the IMP, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are pathological laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE. If the Investigator considers such an AE as serious (e.g., medically significant event fulfilling criteria per Section 10.7.1), it must be reported as an SAE.

If a laboratory abnormality meeting the above criteria is a sign of a disease or syndrome only the diagnosis should be recorded in the eCRF.

If a laboratory abnormality meeting the above criteria is not a sign of a disease or syndrome, the abnormality itself should be recorded in the eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium").

If the laboratory abnormality can be characterised by a precise clinical term per standard definitions, the clinical term should be recorded as the AE; for example, hypercalcaemia or hypoglycaemia. Observations of the same laboratory abnormality from visit to visit should not be repeatedly recorded in the eCRF unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

All pathological laboratory findings/values diagnosed throughout the treatment period should be reviewed by the Investigator to provide a final clinical assessment in view of the dynamic of laboratory changes/abnormalities.

### 10.5.5 Worsening of the Disease Under Study

Signs or symptoms of the disease under study (SCD) that have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as AEs or SAEs, and clearly marked as worsening of the signs or symptoms in the eCRF.

### 10.5.6 Abnormal Vital Signs and Other Abnormalities

Not every abnormal vital sign, ECG, or other safety assessment qualifies as an AE. A result must be reported as an AE if it meets the AE definition (Section 10.1) any of the following criteria:

- Accompanied by clinical symptoms or leads to a diagnosis (in such case the symptom or diagnosis will be recorded as an AE)
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention, a change in concomitant therapy, or subject referral for further testing outside the protocol
- Clinically significant abnormality in the Investigator's judgement

It is the Investigator's responsibility to review all vital signs, ECG, and other safety findings. Medical and scientific judgement should be exercised in deciding whether an isolated abnormality should be classified as an AE.

If a clinically significant abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded in the eCRF.

Observations of the same clinically significant abnormality from visit to visit should not be repeatedly recorded in the eCRF unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

## 10.6 ADR and Reference Safety Information

### 10.6.1 Adverse Drug Reaction

An adverse reaction is a response to a medical product (any dose administered) that is noxious and unintended related to any dose administrated. A causal relationship between an IMP and an AE is at least a reasonable possibility. This means that there are facts (evidence) or arguments to suggest a causal relationship.

All AEs judged as having a reasonable causal relationship to an IMP will be designated as ADRs.

### 10.6.2 Reference Safety Information

The Reference Safety Information presents the basis for expectedness assessment of an adverse reaction for expedite reporting and annual safety reporting, as well as surveillance of subject's safety in a clinical trial by regulatory (and ethic) bodies.

With limited clinical data about previously observed adverse reactions from human studies being available, no serious ADRs are considered expected by the Sponsor for the purpose of expedited safety reporting of SUSARs and annual/aggregate safety reporting.

## 10.7 Serious Adverse Event

### 10.7.1 Definition of SAE

An SAE is defined as any untoward medical occurrence which either results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect:

- Results in death
- Is life-threatening (the term life-threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation, unless elective surgery (a planned, non-emergency medical procedure)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (i.e., medically significant)

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events should also be considered as serious.

Any worsening of a pre-existing medical condition or any new medical condition that meets the above SAE criteria should be considered as an SAE.

The Investigator is encouraged to discuss with the Sponsor (or its delegate, e.g., CRO), any AEs for which the issue of seriousness is unclear or questionable.

#### 10.7.1.1 Situations That Are Not Considered SAEs

The following situations are not considered as SAEs:

- Visits to the emergency room or hospital department that do not result in a hospital admission lasting more than 24 hours
- Elective or pre-planned surgery for a pre-existing condition that has not worsened
- Routine health assessments requiring admission not associated with any deterioration in condition
- Social admission (lack of housing, family circumstances, etc.)
- A planned overnight stay for logistical reasons only prior to study treatment administration does not fulfil the criteria of an SAE unless there is also a medical reason for the admission

### 10.7.2 SAE Reporting

The SAE reporting period begins at the time the ICF is signed by the subject. The SAE reporting period ends 4 weeks following the last study visit or until at least 4 weeks after last IMP administration, whichever is longer. The final follow-up visit may be conducted as a telephone call rather than a formal visit, but the Investigator must report any SAEs that occur during this period. In circumstances where the Investigator is unable to make contact with the subject (or his/her relatives), the Investigator must provide a written statement (recorded in the subject's source documents) to the Sponsor (or its delegate, e.g., CRO), confirming that the subject is lost to follow-up. Follow-up information must be handled in the same way and reported within the same time frame as the initial SAE report.

A death occurring during the study or which comes to the attention of the Investigator within 4 weeks after the last study visit or until at least 4 weeks after the last IMP administration, whichever is longer, whether considered treatment-related or not, must be reported to the Sponsor (or its delegate, e.g., CRO). Death is an outcome and not an event; therefore, the cause of death is required whenever known. If an autopsy was performed, an autopsy report should be provided. If an autopsy was not conducted, a death certificate should be provided, if obtainable.

Any SAE considered to have a causal relationship (i.e., related) to the IMP and discovered by the Investigator at any time after the study should be reported. A rationale for the assessment of a causal relationship must be provided by the Investigator. Any safety information that is obtained after clinical database lock will be documented in the safety database and implications for handling the data in the clinical database assessed on an individual case basis.

The occurrence of an SAE must be immediately reported to the Sponsor (or its delegate, e.g., CRO) within 24 hours of awareness by facsimile, email, or telephone/via electronic

data capture or as defined in the study monitoring plan. This includes all SAEs (independent of relationship to study treatment).

The onset date of the SAE is defined as the date the signs and symptoms/diagnosis became serious (i.e., met at least one of the criteria for seriousness; see Section 10.1). If the condition started as a non-serious event and then became serious, 1 AE and 1 SAE will be recorded. The resolution date of the SAE is defined as when the symptoms resolve, or the event is considered chronic (e.g., sequelae) or stable, and/or if the seriousness criteria are no longer applicable.

### 10.7.3 Suspected Unexpected Serious Adverse Reaction

The definition of a SUSAR is any ADR (see Section 10.6.1) that is both serious (see Section 10.7.1) and unexpected (per the Reference Safety Information; see Section 10.6.2) that, based on the opinion of the Investigator or Sponsor, is felt to have a reasonable possibility or suspected causal relationship to an IMP.

#### 10.7.3.1 SAE Expedited Reporting

The Sponsor will notify all Investigators of all SAEs requiring expedited reporting to Regulatory Authorities.

The Investigator is responsible for notifying the Institutional EC in accordance with local regulations of all SAEs that occur. The Investigator must review and file the safety report with the Investigator's Brochure.

### 10.7.4 Unblinding Treatment Allocation

The Sponsor will only report SUSARs for which the treatment allocation of the subject is unblinded to the pertinent Competent Authority. Investigators should only receive blinded information unless unblinded information is judged necessary for safety reasons.

When an event may be a SUSAR, the blind should be broken only for that specific subject (Section 6.1.1).

Unblinded information should only be accessible to those who need to be involved in the safety reporting to pertinent Regulatory Authorities, ECs, and the Medical Monitor (i.e., the individual performing ongoing safety evaluations during the study). Unblinding must always be performed according to the procedures that are specified in applicable CRO Standard Operating Procedures.

## 10.8 Special Situations

### 10.8.1 Definition of Special Situations

The following are defined as special situations:

- Use of an IMP during pregnancy or breastfeeding

- Use of an IMP in a paediatric or elderly population (if this is not the population under investigation)

- Medication error: Any unintentional error in the prescribing, dispensing or administration of an IMP during the study

- Medication misuse: an intentional and inappropriate use of an IMP not in accordance with the protocol dose, route of administration, and/or the indication(s)

- Medication overdose: the administration of a quantity of IMP given per administration or cumulatively per day which is above the protocol maximum recommended permitted dose

- Drug interaction involving IMP

Special situations including medication errors impacting subject's compliance shall be assessed taking into consideration the full period of drug intake and based on criteria defined in the study-specific protocol deviation list.

Suspected AEs associated with medication errors of the IMP or use outside that foreseen in the protocol (e.g., overdose,) are also considered as ADRs. Any special situation occurring with/without ADR/AE shall be recorded in the study-specific documentation.

### 10.8.2 Special Situation Recording and Reporting

All special situations have to be documented in the subject's eCRF and source documents. The Investigator should also complete and submit the Sponsor paper Special Situation form immediately (i.e., within 24 hours of awareness) to the Sponsor, following the same procedure as for SAEs (Section 10.7.2).

If any special situation leads to an SAE (see Section 10.8.1), then the event has to be immediately reported to the Sponsor (or its delegate, e.g., CRO) within 24 hours of awareness by facsimile, email, or telephone/via electronic data capture, and as defined in the safety management plan.

### 10.8.3 Pregnancy Exposure and Birth Events

#### 10.8.3.1 Definition of Pregnancy Exposure and Birth Events

When a female subject becomes pregnant during the study and study treatment has been administered to the subject, the outcome of the pregnancy needs to be monitored and the safety of the mother and unborn child need to be safeguarded (as per protocol, pregnancy is an exclusion criteria). Therefore, the outcome of all such pregnancies (including normal births) must be followed up and documented, even if the subject was withdrawn from the study or the study has been completed.

Women of childbearing potential, defined as a premenopausal female capable of becoming pregnant, must have a negative serum pregnancy test prior to randomisation. IMP should not be initiated by the Investigator until a report of a negative pregnancy test has been obtained.

Highly effective contraception must be used in female subjects before beginning IMP, during study dosing, and until at least 1 week following discontinuation of IMP or if co-medication is used that requires contraception, e.g., hydroxyurea, as per Prescription Information, or according to local requirements, whichever is longer, even when there has been a history of infertility, unless due to hysterectomy. The Investigator should be always consulted in all cases of contraceptive discontinuation during the study.

Highly effective contraception must be used (refer to synopsis) unless abstinence is the chosen method (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) or subject has been surgically sterilised at least 6 months prior to the study. Please also refer to the exclusion/inclusion criteria (Section 5).

A female subject must immediately inform the Investigator if she becomes pregnant during the study and be instructed to stop taking IMP. The Medical Monitor must be contacted immediately to break the blind. The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The Investigator/Sponsor is responsible for monitoring the subject and pregnancy outcome. Every effort should be made to gather information regarding the pregnancy outcome until 90 days postpartum (or otherwise as appropriate). It will be the responsibility of the Sponsor, together with the appropriate support of the Investigator, to obtain this information.

#### 10.8.3.2 Pregnancy Exposure and Birth Events Recording and Reporting

Any report of pregnancy recorded for any female subject or for a female partner of a male subject should be reported to the Sponsor/CRO within the same timelines as an SAE, i.e., within 24 hours of awareness. The outcome of all such pregnancies (including normal births) must be followed up and documented, even if the subject was discontinued from the study. Complications of pregnancy such as abortion (spontaneous or induced), premature birth (before 37 weeks gestational age), or congenital abnormality are considered SAEs and should be reported using the study-specific Sponsor SAE form.

All pregnancies occurring in a female subject or the female partner of a male subject within 30 days after discontinuation of the IMP should be reported within the same timelines as an SAE to the Sponsor/CRO.

### 10.8.4 AEs of Special Interest

#### 10.8.4.1 Definition of AEs of Special Interest

An AE of special interest is a medical occurrence specific to the product or programme, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate. Such an event, depending on the nature and the outcome, may be serious (see Section 10.7.1) or non-serious.

There are currently no AEs of special interest identified for this study.

# 11. DSMB PROCEDURES

An independent DSMB will oversee the safety and conduct of the trial on an ongoing basis. The DSMB will be comprised of medical and statistical representatives.

The DSMB will regularly, but also on an ad-hoc manner as needed, assess the safety information of the enrolled subjects, and can provide recommendations to the Sponsor regarding stopping the study or discontinuing a treatment arm or otherwise modifying the study design or conduct.

The Sponsor will establish a Charter document explaining the working procedures and responsibilities of the DSMB. The Charter should be agreed to by the DSMB.

# 12. STATISTICAL ANALYSIS

## 12.1 Statistical Methods

All statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute Inc. SAS/STAT, Cary, NC). The detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP that will be finalised prior to database lock and the unblinding of the study.

For continuous parameters, summary statistics will include the number of subjects, mean, standard deviation, quartiles, minimum and maximum, and the 95% confidence interval of the mean (if appropriate). For categorical parameters, summary statistics will include counts, percentages, and the 95% confidence interval of the percentages (if appropriate) in each category.

Summary statistics will be provided on overall subjects receiving VIT-2763, by dose and for all subjects receiving placebo. Subjects from Cohort 4a and Cohort 4b will be combined into 1 placebo group.

## 12.2 Sample Size and Power Calculations

No specific sample size calculations have been performed for this study.

It is planned to randomise 24 subjects in a 3:3:3:2:1 ratio into 3 VIT-2763 dose groups and 2 placebo groups.

## 12.3 Randomisation

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and subject names to enable records to be found at a later date.

Randomisation of the subject will be performed before start of treatment with IMP using a validated centralised IWRS. Stratified randomisation (balanced allocation across treatment groups) will be used according to genotype (HbS/S - HbS/βT0).

Subjects eligible for randomisation will receive a randomisation number. Randomised subjects who terminate their study participation for any reason regardless of whether the IMP was taken or not, will retain their randomisation number. The next subject will be given the next randomisation number.

Subjects included to replace subjects who withdraw or drop out or with major protocol deviations impacting the primary objective of the trial, will be assigned to the same cohort as the subjects they are replacing.

## 12.4 Analysis Sets

### 12.4.1 ITT Population

The ITT population consists of all subjects who are randomly assigned to a treatment group. The subjects will be analysed based on the treatment they were randomised to.

### 12.4.2 Per-protocol Set

The PPS consists of all subjects who, in addition to the ITT criteria, completed the study and had no major protocol deviations impacting the primary objective of the trial (as defined in the SAP and finalised during the blind data review meeting). The subjects will be analysed according to the treatment they received.

### 12.4.3 Safety Set

The safety set consists of all randomised subjects who have taken at least 1 dose of IMP. The subjects in this group will be analysed based on the treatment they received.

## 12.5 Background and Demographic Characteristics

Demographic characteristics (gender, age, race, ethnicity) and baseline characteristics, including body weight, body mass index, blood haemolysis parameters (LDH, indirect/total bilirubin), iron parameters (total serum iron, serum ferritin, serum transferrin, calculated TSAT, hepcidin, erythropoietin, and TIBC) will be summarised on overall subjects receiving VIT-2763, by dose group and on subjects receiving placebo.

Summary statistics will be provided for the 3 analysis sets. In case some analyses sets are identical, summary statistics will not be repeated.

## 12.6 Study Medication

The total amount of IMP taken will be calculated for each subject from the difference between the amount of drug given and the amount of drug returned. It will be compared to the amount expected to be taken by subject to calculate the percentage compliance to treatment. Treatment compliance will be summarised on overall subjects, overall subjects receiving VIT-2763, by dose group and on placebo subjects.

It will be provided for the ITT population and the PPS if they differ.

## 12.7 Concomitant Therapy

Prior and concomitant medications will be categorised according to a standard dictionary (World Health Organization Drug Classification). Prior medications are defined as the medications that were stopped prior to first IMP intake and concomitant medications as the medications ongoing or started after the first IMP intake.

For both prior and concomitant medications, counts and percentages of subject use for each medication will be computed and summarised by Anatomical Therapeutic Chemical Levels

2 and 4 and by preferred name on overall subjects receiving VIT-2763, by dose group and on subjects receiving placebo.

Analyses will be performed on the ITT and the PPS. In case both analysis sets are identical, analysis will not be repeated.

## 12.8 Primary and Secondary Efficacy Evaluations

The changes in haemolysis markers from baseline to Visit V6 (after 8 weeks of treatment) will be summarised on overall subjects receiving VIT-2763, by dose group and on all subjects receiving placebo.

The ITT population will be used for the analysis of the primary and secondary endpoints related to haemolysis markers. These analyses will also be repeated on the PPS.

## 12.9 Safety Evaluations

All safety analyses will be performed on the safety set.

**Adverse Events**

Only TEAEs defined as events with an onset date later or on the same date as first IMP intake will be tabulated. AEs that occurred during the study but before first IMP intake will be only listed.

Summary tables with the counts and percentage of subjects and the number of events will be provided on overall subjects receiving VIT-2763, by dose group and on all subjects receiving placebo for any TEAEs, any severe TEAEs, any serious TEAEs, any TEAEs leading to study withdrawal and any TEAEs leading to death.

All AEs will be coded according to a standard dictionary (MedDRA).

Tables of the counts and percentages of subjects with at least 1 TEAE by SOC and PT will be provided for all TEAEs and TEAEs by severity and by relationship over 8 weeks of treatment (secondary endpoint) and up to 4 weeks after EoT. Similar tables will be provided for serious TEAEs, TEAEs leading to premature discontinuation of the study and TEAEs leading to death.

**Clinical Laboratory Tests**

Values by visit from baseline and changes from baseline by post-baseline visit for the haematologic, biochemistry, and urinalysis parameters will be summarised on overall subjects receiving VIT-2763, by dose group and on all subjects receiving placebo.

Shift tables crossing counts of baseline values lower, within and higher than laboratory normal range with the counts of each post-baseline visit will be provided for the haematologic, biochemistry, and urinalysis parameters on the same treatment groups.

### Vital Signs and Body Weight

Values by visit from baseline and changes from baseline by post-baseline visit for blood pressure, pulse rate, and body weight will be summarised on overall subjects receiving VIT-2763, by dose group and on all subjects receiving placebo.

### ECGs

Values by visit from baseline and changes from baseline by post-baseline visit for PR interval, QRS duration, QT interval, and QTcF interval will be summarised on overall subjects receiving VIT-2763, by dose group and on all subjects receiving placebo.

Abnormal ECG findings will be listed.

## 12.10 Exploratory Efficacy Evaluations

All exploratory analyses will be performed on the ITT and the PPS.

### Laboratory Parameters

Exploratory analyses will be performed for blood haemolysis parameters, iron parameters and markers of erythropoiesis, blood inflammatory markers, haematological indices, and abnormal RBCs measured by peripheral blood smear.

Values by visit from baseline and changes from baseline by post-baseline visit will be summarised for all laboratory parameters on overall subjects receiving VIT-2763, by dose group and on all subjects receiving placebo. Shift tables crossing counts of baseline categorical values with each post-baseline visit value may also be provided when appropriate.

### Quality of Life

The modified ASCQ-Me questionnaire will be summarised at baseline. The baseline scores from the pain episode questionnaire will be summarised as well as individual item response levels.

For the impact questionnaires collected longitudinally, T-Score values by visit from baseline and changes from baseline by post-baseline visit will be summarised on overall subjects receiving VIT-2763, by dose and on all subjects receiving placebo.

### VOC Episodes and Visceral Infarctions

Shift tables summarising the number of episodes 8 weeks prior to baseline versus 8 weeks after baseline will be provided. Number of events and pain intensity (NRS: 0-10) at each visit compared to historical VOC episodes will be described.

## 12.11 Other Evaluations

### 12.11.1 Pharmacokinetics

The PK concentrations will be listed by subject for each sampling time point for Visit V4 for all subjects who received VIT-2763. It will be summarised with the addition of the geometric mean and its standard deviation and the coefficient of variation to the summary statistics performed on overall VIT-2763 subjects, by dose group.

A population PK approach combined with suitable mathematical/statistical analysis, using nonlinear mixed-effects modelling will be applied to estimate PK parameters. Details will be specified in a dedicated SAP.

# 13. STUDY ETHICAL CONSIDERATIONS

## 13.1 Ethical Conduct of the Study

The study will be conducted according to the principles of the World Medical Association's Declaration of Helsinki [32], and the ICH guidelines for Good Clinical Practice [33] as amended. The Sponsor will ensure that the study complies with all local, federal, or country regulatory requirements.

The Investigator must ensure the anonymity of all subjects participating in the study. Each subject will be assigned a unique subject number, and this should be used on all forms associated with the subject's documents or samples that will be supplied to the Sponsor or any party completing testing on behalf of the Sponsor (e.g., blood for central laboratory assessments).

All anonymous data remains the property of the Sponsor.

## 13.2 Informed Consent

The ICF used for the study must comply with the Declaration of Helsinki, federal regulations, and ICH guidelines; and must have been approved by the appropriate IRB/Independent Ethics Committee (IEC) prior to use. The Investigator or an authorised associate must explain orally and in writing the nature of the study and the treatment in such a manner that the subject is aware of potential benefits and risks. Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects must be provided sufficient time to consider participation, including discussion with family members prior to signing the ICF. Documentation of the discussion and the date of informed consent must be recorded in the source documentation. Subjects must give informed consent in writing. If applicable, consent from female partners (who become pregnant during the study) of male subjects will also be acquired.

## 13.3 Institutional Review Board or IEC

The protocol, any protocol amendments and consent form for the proposed clinical study and any other documents required by the local IRB/IEC must be submitted by the Investigator for review and approval to the IRB/IEC. The Investigator must also ensure that the IRB/IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of the approval letter must be forwarded to the Sponsor before the study is implemented.

# 14. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator must ensure that all trial-related site source data, trial-related documents, and reports will be available, and that the provision of direct access for monitoring and auditing by the Sponsor or its designees will be permitted. In addition, the Investigator must ensure that all trial-related site source data, study related documents and reports will be made available for Sponsor audit and inspection by the appropriate Regulatory Authority and review by the IRB/IEC.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the site's source data and records by the Medical Monitor (source document verification), and the maintenance of a drug dispensing log by the Investigator. The data collected will be entered (electronic data capture) into the study database in a timely manner. A comprehensive validation check programme will verify the data and queries will be generated for resolution by the Investigator and his/her study team. Throughout the study, the Sponsor or its designates may review data as deemed necessary.

The following steps will be taken to ensure that the trial is conducted by the investigational site in compliance with the study protocol, Good Clinical Practice, and other applicable regulatory requirements:

- Investigator meeting and/or
- Investigator site initiation
- Routine site monitoring
- Documented protocol and Good Clinical Practice training
- eCRF and query review against source documents (source data verification)
- Collection of local laboratory normal ranges
- All equipment used during the study is to be adequately maintained/calibrated

## 14.1 Quality Management: Critical Processes and Data

The following processes and data have been identified during the risk management activities for this trial as critical to ensure human subject protection and the reliability of trial results.

The Sponsor and its designees will ensure a close oversight of the site's activities related to the trial. Throughout the study, the clinical study team will work to ensure that the trial is operationally feasible and focuses on study activities essential to human subject protection and the reliability of trial results, including (but not limited to):

- Study protocol design and implementation

- Tools and procedures supporting data collection and processing
- Tools and procedures safeguarding the rights and protection of human subjects
- Activities essential to trial decision-making and compliance

# 15. REPORTING AND RECORDING OF DATA

All required study data must be entered in the eCRF created for the study. Training on the system will be provided to all sites, including instructions on how to address missing data, corrections, query procedures, and electronic signatures. Only individuals who are identified on the authorised signature page may enter/correct data in the eCRF. For those subjects who withdraw before completion of the study, all available efficacy and safety data must be entered in the eCRF. Incomplete or inconsistent data on the eCRF will result in data queries addressed to the Investigator for resolution.

## 15.1 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which case reports for each subject are based. They are to be separate and distinct from eCRFs. These records should include detailed notes on:

- The medical history up to 6 months prior to participation in the study
- The basic identifying information, such as demographics that link the subject's source documents with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided and any other data on the condition of the subject
- The subject's exposure to study treatment
- All AEs and pregnancies
- All special situations as defined in Section 10.8.1
- The subject's exposure to any concomitant therapy (including date and quantity dispensed)
- All relevant observations and data on the condition of the subject throughout the study
- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation

All data for the trial must be available in the source documentation.

## 15.2 Records Retention

The Investigator must arrange for the retention of all study documentation (such as paper CRFs, eCRF files or printed forms, research files, and master files) for the duration specified in their respective site contract or as specified by the applicable Regulatory Authority, whichever is longer. The Sponsor will inform the Investigator in writing when

files can be destroyed. Archived data may be held on microfiche or electronic record, provided that a back-up copy exists and that a hard copy can be generated if required.

The Investigator must inform the Sponsor immediately if any documents are lost, to be transferred to a different facility, or to be transferred to a different owner.

## 15.3 Site Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

# 16. PROCEDURE FOR MODIFICATION OF PROTOCOL OR PREMATURE TERMINATION OF THE STUDY

## 16.1 Protocol Deviations

The Investigator will not deviate from the protocol without prior written approval from the Sponsor, except in medical emergencies. In the event of a medical emergency, the Investigator must notify the Sponsor Medical Expert as soon as possible. Any other change to the protocol must be implemented as an amendment to the protocol (see Section 16.2). The criteria describing protocol deviation(s) and how they will be handled will be documented in the SAP.

## 16.2 Protocol Amendments

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of the Sponsor. Each applicable Regulatory Authority/IRB/IEC will review and approve amendments prior to their implementation. Regulatory Authority/IRB/IEC approval need not be obtained prior to removal of an immediate hazard to subjects.

## 16.3 Study Termination

The Sponsor reserves the right to terminate the study in its entirety or at a site at any time. Reasons for termination may include (but are not limited to) unsatisfactory subject enrolment with respect to quality and/or quantity, site is unable to comply with the requirements of the protocol or Good Clinical Practice, or data recording is inaccurate and/or incomplete.

In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subject's interests. Both parties will arrange the procedures on an individual basis after review and consultation and in accordance with the study contract.

To protect clinical trial subjects from immediate hazards to their health and safety, urgent safety measures, e.g., procedures (including temporary halt of a study) that are not defined by the protocol, may be initiated immediately by the Investigator or Sponsor and without the need to gain prior authorisation by Regulatory Agencies and Competent Authorities/Ethic Committees. Detailed guidance and training regarding procedures for immediate reporting of urgent safety measures will be provided to the Investigators and sites prior to study initiation.

# 17. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The Sponsor is committed to the timely communication of data from clinical research trials, following the Pharmaceutical Research and Manufacturers of America principles [34]. The Clinical Trial Agreement describes the Sponsor's publication terms.

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