STATISTICAL ANALYSIS PLAN (SAP)

Investigational Drug:	**VIT-2763**
Treatment:	**VIT-2763 in subjects with sickle cell disease**
Study Phase:	**Phase 2a**
Study 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)**
Protocol Number:	**VIT-2763-SCD-202**
Protocol Version:	**4.0**
Protocol Version date:	**09 March 2023**
Sponsor:	**Vifor (International) Inc. Rechenstrasse 37 St. Gallen CH-9014 Switzerland +41 58 851 80 00**
SAP Version:	**Final Version 2.0**
SAP Version Date:	**26 April 2024**
SAP Author:	PPD

APPROVAL SIGNATURES FOR SAP

Study 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)
Protocol Number:	VIT-2763-SCD-202
Protocol Version/Amendment No. and Date (if applicable)**:**	4.0/ 09 March 2023
New SAP Version and Date	Final Version 2.0 / 26 April 2024
Superseded SAP Version and Date (if applicable)**:**	1.0

As signed below, I approved the VIT-2763-SCD-202 Statistical Analysis Plan V2.0.

Prepared by: PPD

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

%	Percentage
AE	Adverse Event
ASCQ-Me	Adult Sickle Cell Quality of Life Measurement System
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BID	Twice daily
BMI	Body Mass Index
C_{max}	Maximum concentration
CI	Confidence interval
COVID-19	Coronavirus Disease of 2019
CRF	Case report form
CSP	Clinical Study Protocol
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
eTMF	Electronic Trial Master File
FPN	Ferroportin
Hb	Haemoglobin
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigation Medicinal Product (including VIT-2763 and Placebo)
INN	International Nonproprietary Name
ITT	Intent- to-Treat
IWRS	Interactive Web Response System
MCH	Mean cell Hb
MCHC	Mean cell Hb concentration
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
N	Number
PK	Pharmacokinetic
PPS	Per-Protocol Set
PT	Preferred Term
RBCs	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCD	Sickle Cell Disease
SI	Standard International
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment emergent adverse event
TIBC	Total Iron Binding Capacity
TID	Three times daily
TFL	Tables, figures and listings
VOC	Vaso-occlusive crises

SAP REVISION HISTORY

Version	Effective Date	Summary of Changes
Final V1.0	26Nov2021	First final version
Draft V1.2	24Jun2022	Updates to account for protocol amendment (V3) including but not limited to: • All sections referring to protocol design or impacted by cohort updates (1.1, 2.2, 2.3, 2.5, 5.1, 5.5), • Safety set section - actual treatment definition, • New aITT population added for managing data relative to the patient enrolled under protocol V2. Notion of important/non-important protocol deviation removed (minor/major definition kept).
Draft V1.3	02Dec2022	Integration of VUT details
Draft V1.4	10NOV2023	Deletion of VUT details added in V1.3. Two additional efficacy endpoints have been added: • Number of patients who had at least a 20% reduction in Indirect Bilirubin by cohort and at each post-baseline visit. • Number of patients who had at least a 5% reduction in CHCM/MCHC by cohort and at each post-baseline visit.
Final V2.0	26APR2024	Implementation of sensitivity analyses with the imputation of the missing data due to haemolysed samples at baseline or Visit 6

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under protocol VIT-2763-SCD-202. Pharmacokinetic (PK) analysis will be described in a separate analysis document.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol V4.0 dated 09 March 2023 and CRF dated 11 October 2022. Any further changes to the protocol or CRF may necessitate updates to the SAP. Statistical rationale and analysis methods specified in this document take precedence over those described in the protocol, should there be any differences.

1.1 Overall Study Design Rationale

Sickle cell disease (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. The pathophysiology of SCD arises from a single amino acid alteration in adult haemoglobin (Hb), the expression of which is primarily limited to red blood cells (RBCs).

VIT-2763 (INN Vamifeport) is developed by Vifor Pharma as a novel oral drug targeting ferroportin (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)

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 an animal model of SCD.

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.

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.

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.

This is a randomised, double-blind, placebo-controlled, parallel-group trial that explores three different dosing regimens of VIT-2763: 60 mg twice daily (BID), 120 mg BID and 120 mg 3 times daily (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, vascular inflammation, safety and tolerability, iron and erythropoiesis related blood parameters, pain and quality of life, and at the same time to discern possible adverse effects on iron restriction over the treatment time.

Placebo treatment will be used in a minority of adult SCD subjects 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.

The protocol V3.0 was developed based, among other VIT-2763 studies, on results from Study VIT-2763-THAL-201, where β-thalassemia patients were treated with either once daily 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 end of study. However, no changes in relevant haematological biomarkers such as Hb could be detected. The sponsor wants to explore at its best the pharmacodynamic (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. 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).

1.2 Changes from Protocol

Additional analysis sets for analysis purposes not defined in the protocol have been included in the SAP (see Section 4.4).

2 STUDY SUMMARY

2.1 Objectives

2.1.1 Primary Objective

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

2.1.2 Exploratory Objectives

The exploratory objectives of the study are as follows:

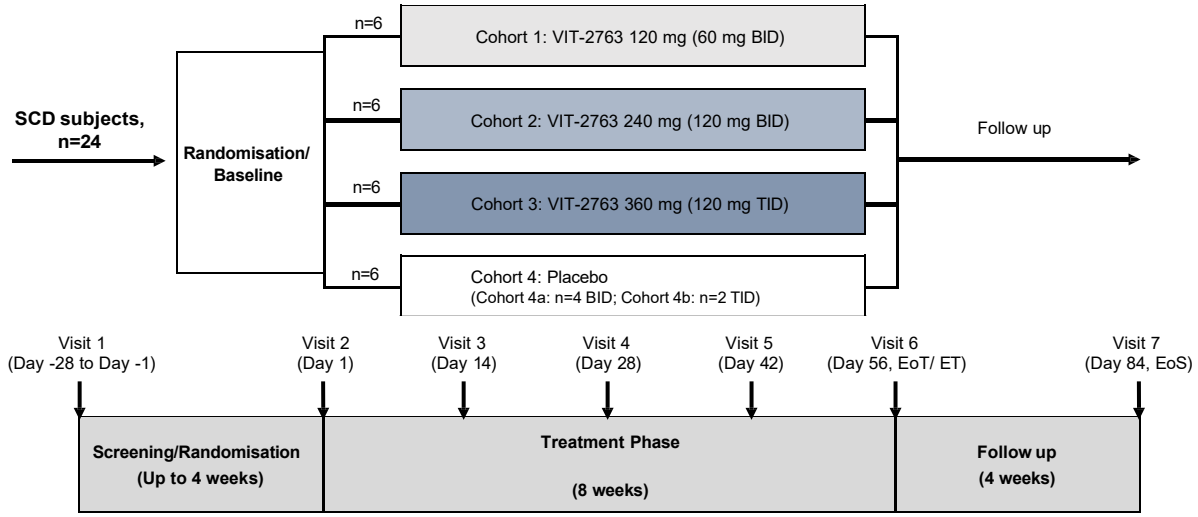
- To explore the safety and tolerability of VIT-2763.
- To explore the effect of VIT-2763 on haematological indices and vascular inflammation.
- To explore the effect of VIT-2763 on iron and erythropoiesis-related blood parameters.
- To explore the effect of VIT-2763 on patient-reported outcomes (pain 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.

2.2 Study Design

This is a Phase 2a, randomised, double-blind, placebo-controlled, parallel group trial in SCD subjects that explores three different dosing regimens of VIT-2763: 60 mg BID, 120 mg BID and 120 mg TID.

A total of 24 subjects with confirmed diagnosis of SCD will be randomised. IMPs will be administered for 8 weeks each according to Figure 1, Table 1 and Table 2.

Figure 1 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 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

Notes: 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).

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 each 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.

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 each 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 08:00 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.

Table 2 Administration Schedule

Administration Schedule		
Total Daily Dose of VIT-2763	**Number of Capsules/Day**	
	VIT-2763	**Placebo**
120 mg	4 × 30 mg or 2 × 60 mg	2 × placebo[1]
240 mg	4 × 60 mg	N/A
360 mg	6 × 60 mg	N/A
0 mg	N/A	4[2] or 6[3] × placebo

[1] Only together with the 60 mg strength.
[2] Cohort 4a.
[3] Cohort 4b.
Note: N/A=Not applicable.

As specified in the IRT configurable requirements of the study, kits of 30 mg capsules will be dispensed to cohort 1 subjects (group with a total daily dose of 120 mg). The administration schedule chosen for cohort 1 is then 4 capsules of 30 mg per day (the option with 2 capsules of 60 mg and 2 capsules of placebo per day was not retained).

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 subject participating in the trial and the end of subject s' data collection.

2.3 Schedule of Events

Table 3 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	L	L
hsCRP	C						
RBC smear preparation		L	L	L	L	L	L
Urine pregnancy test[5]		L	L	L	L	L	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 pregnancy test[6]	C						
Serum virology (HbsAg, HBV, HCV, HIV)	C						
Urinalysis[7]	C	C	C	C	C	C	C
Haematology panel/RBC indices[8]	C	C	C	C	C	C	C
Serum chemistry panel[9]	C	C	C	C	C	C	C
Haemolysis markers[10]		C	C	C	C	C	C
Endothelial inflammation/dysfunction markers[11]		C	C	C	C	C	C
Iron-related parameters/markers of erythropoiesis [12]	C	C	C	C	C	C	C
RBC smear assessment for sickle cells		C	C	C	C	C	C
VIT-2763 pharmacokinetic[13]				C			
VOC episodes/visceral infarctions[14]		X	X	X	X	X	X
Dispense IMP at site (IWRS)		X	X	X	X		
Collect, dispense, and inform subjects on ASCQ-Me questionnaires[15]	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 of Clinical Study Protocol (CSP)) 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 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).
8 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.
9 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.
10 Haemolysis markers sampled at pre-dose (trough) include LDH, free haptoglobin, and direct/total bilirubin (indirectly calculated).
11 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.
12 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, TSAT, and TIBC will be sampled for exclusion criteria only.
13 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.
14 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.
15 For more details see the respective visit in Section 8 of CSP.

Notes: abs=Absolute; ASQ-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; sP=Soluble cell adhesion molecule; TIBC=Total iron-binding capacity; TNF=tumour necrosis factor; TSAT=Transferrin saturation; V=Visit; VOC=Vaso-occlusive crises; WBC=White blood cell.

2.4 Sample Size Determination

This is an exploratory Phase 2a study of VIT-2763 in SCD subjects, therefore no formal sample size calculations have been conducted.

2.5 Randomisation and Blinding

Upon completion of the baseline visit procedures/assessments, 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.

For randomisation IWRS will be used, a validated centralised procedure 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).

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. A subject can only be randomised once. Randomised subjects who withdraw consent for further follow-up cannot be re-screened. Re-screening may be considered at the discretion of the Investigator and in consultation with the sponsor at a later point for subjects who fail to meet the protocol eligibility criteria. In such a case, the re-screened subject will be allocated a new screening number.

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 with a number randomization number until at least 5 subjects, with no major protocol deviation impacting the primary objective of the trial, per treatment/placebo (Cohorts 4a and 4b combined) arm have passed Visit V6. 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.

The randomisation schedules, as described in Biostatistics Addendum Subject Randomisation List (BA-S) V2.0 dated 16 March 2022, will be generated and maintained by ALMAC Clinical Technologies. The schedule and the seed will be sequestered until the study database is locked and the study is unblinded. Data will also be unblinded for closed sessions of DSMB meetings.

2.5.1 Interim Analysis

No interim analysis is planned.

2.5.2 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Committee (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 members will be unblinded.

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 has established a Charter document explaining the working procedures and responsibilities of the DSMB. The Charter has been agreed to by the DSMB.

2.6 Study Endpoints

2.6.1 Primary Endpoint

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

2.6.2 Secondary Endpoint(s)

- 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 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.

2.6.3 Exploratory Endpoint(s)

- 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).

- 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: 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 (maximum concentration (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 trough 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.

3 HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Due to the exploratory nature of this trial, no formal power calculations will be performed and therefore no statistical hypothesis testing has been defined.

3.2 Statistical Decision Rules

There is no formal statistical decision rule for this study, and all analyses are considered descriptive.

4 ANALYSIS SETS

In accordance with ICH E3 [1] and E9 [2] guidelines, the analysis sets are defined as follows:

4.1 Safety Set

The safety set consists of all randomised subjects under protocol version 3.0 or higher who have taken at least one dose of IMP. The subjects in the safety set will be analysed based on the treatment they received, regardless of randomisation.

The actual treatment is determined as the highest dose dispensed during the study for subjects who have taken at least one dose of IMP. More precisely:

- If the highest VIT-2763 kit dosage dispensed during the study is 30 mg, then the actual treatment will be “Cohort 1: VIT-2763 60 mg BID”.
- If at least one VIT-2763 kit of 60 mg dosage is dispensed during the study AND the maximum number of VIT-2763 kits dispensed during a visit is ≤3, then the actual treatment will be “Cohort 2: VIT-2763 120 mg BID”.
- If at least one VIT-2763 kit of 60 mg dosage is dispensed during the study AND the maximum number of VIT-2763 kits dispensed during a visit is 4, then the actual treatment will be “Cohort 3: VIT-2763 120 mg TID”.
- If only placebo kits are dispensed during the study, then the actual treatment will be “Cohort 4: Placebo”.

4.2 Intent-To-Treat Population

The Intent-To-Treat (ITT) population consists of all subjects who are randomly assigned to a treatment group under protocol version 3.0 or higher. The subjects will be analysed based on the treatment they were randomised to.

4.3 Per-Protocol Set

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 impacting the primary objective of the trial (as defined in the protocol deviation plan and finalised during the blind data review meeting). Subjects with a study drug compliance (see Section 5.6) lower than 80% of prescribed doses or upper than 110% of prescribed doses will be considered as major deviations.

Subjects who did not complete the study as per protocol as indicated in study termination CRF form or who discontinued the treatment prematurely as recorded in treatment termination form will be considered as not having completed the study and will then be excluded from PPS in addition to subjects with major protocol deviations. The subjects will be analysed based on the treatment they were randomised to.

4.3.1 Protocol deviations

All subjects with major protocol deviations impacting the primary objective as defined in the latest protocol deviations plan will be excluded from PPS. They will be reviewed during the blind data review meeting.

4.4 Other Analysis Sets

For the purposes of subjects’ disposition tables and listings an additional analysis population is defined:

- **Randomized population:** all subjects who are randomly assigned to any treatment group under protocol version 3.0 or higher.
- **Enrolled population:** all subjects who have signed informed consent on any protocol version.
- **Advanced Intent-To-Treat Set:** The advanced ITT (aITT) population consists of all subjects who are randomly assigned to any treatment group under any protocol version. The subjects will be presented based on the treatment they were randomised to.

The following analysis set may also be defined:

- **Modified Intent-To-Treat Set (optional):** The modified ITT (mITT) will consist of all subjects of ITT with no major Coronavirus Disease of 2019 (COVID-19) related protocol deviation (as defined in the protocol deviation plan and finalised during the blind data review meeting). This population may be used depending of the number of subjects with major COVID-19 related-protocol deviations and the potential impact on the analyses. Decision to use or not this analysis set for sensitivity analyses will be taken during the blind data review meeting and it will be documented in the blind data review minutes before unblinding.

The **analysis population for PK** will be described in a separate document.

5 DESCRIPTION OF THE STATISTICAL ANALYSIS

This section describes the statistical analyses, presentation of the results, and the study endpoints/measures that will be collected and/or derived during the study at the time points specified in the Schedule of Events (see Section 2.3).

5.1 General Considerations

The software used for all summary statistics and statistical analyses will be SAS® Version 9.4 or later (SAS Institute, Inc.).

MedDRA [Version 24.0] and the current version of the World Health Organization Drug (WHO Drug) dictionary [Mar2021 B3] will be used for coding.

Derived datasets will be generated by the Labcorp/Covance Biostatistics and Programming Department from the Clinical Interchange Standard Consortium (CDISC) Study Data Tabulation Model (SDTM [version 3.3]) datasets in accordance with CDISC ADaM version 2.1 and the ADaM Implementation Guide v1.1.

All blinded study team members will remain blinded to the randomisation arms until complete cleaning of the data and blind data review meeting. For the final analysis after final database lock the blinded statistical team will be unblinded according to the project specific unblinding plan and following sponsor approval. This does not concern the independent unblinded statistician responsible for the DSMB report preparation.

The final versions of the SAP (along with TFL shells documents) will be filed at trial completion in the electronic trial master file (eTMF) study documentation and eTMF plan will be followed for biostatistics documents filing.

The data collected for the one randomised subject under protocol version 2.0 will be listed only.

5.1.1 Standard Descriptive Statistics

Continuous Variables

Unless specified otherwise, the following standard descriptive statistics by treatment group will be obtained for continuous variables: number, mean, standard deviation, median, minimum and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. Mean, median, and quartiles will be displayed to one more decimal place than collected value and standard deviation will be displayed to two more decimal place than the collected value.

Categorical Variables

Unless specified otherwise, the following standard descriptive statistics by treatment group will be presented for categorical values: total number of available values and missing values, number of values in each category and the corresponding percentage of the total number of values available will be calculated. The percentages will be displayed using one decimal.

Percentages will be calculated using the total subjects per randomised treatment group, except for outputs in the PPS and the safety set, where percentages are based on the total subjects per actual treatment group.

5.1.2 Definition of Baseline

The baseline value for a variable will be defined as the last available (non-missing) value before the first administration of study drug. Study day 1 is defined as the day of the first study drug administration. For analysis relative day, if considered date is before the first study drug administration date, then analysis relative day will be computed as date minus first study drug administration date, otherwise, it will be computed as date minus first study drug administration date + 1.

5.1.3 Planned Assessment Windows

Table 4 describes the analysis visit windows (i.e. the relative study day ranges) to be applied to the assessments or sample collections dates to determine the analysis visit.

Table 4 Planned and Analysis visits Windows

Analysis Visit Label	**Target Day**	**Planned Visit Window** (Protocol Specified)	**Analysis Visit Window**
Baseline	1	--	Before first IMP intake
Visit 3 (Day 14)	14	± 2 days	From Day 2 to Day 21
Visit 4 (Day 28)	28	± 4 days	From Day 22 to Day 35
Visit 5 (Day 42)	42	± 4 days	From Day 36 to Day 49
Visit 6 (Day 56)	56	± 4 days	From Day 50 to Day 70
Visit 7 (Day 84)	84	± 4days	From Day 71 and higher

Assessments (planned and unscheduled) will be re-mapped into the analysis windows. For a parameter, the following rules will be applied:

- if several assessments fall into the same analysis window, the closest to the target day will be considered for the analysis.
- When there are 2 assessments closest to the target day, the latest one will be considered for the analysis.
- if several assessments are available at the selected day, the average of the values will be taken.

In all statistical tables by visit, the analysis visits will be considered. In listings presenting data by visit, both nominal and analysis visits will be provided.

5.1.4 Treatment Start/Stop Dates

Treatment start date is collected at baseline visit in the study treatment administration form of the CRF. If there is no treatment date available in this CRF page, date of randomisation will be imputed as the start of treatment date, if it is known that the subject received study drug (information recorded in the study treatment administration page or in patient supply accountability log page of the CRF or any information from monitoring).

Treatment stop date is collected in the treatment termination form of the CRF. If the date of last intake of study medication is missing in this form, the latest start date from study treatment administration page (CRF does not record the end date) would be used to impute end of treatment date.

5.1.5 Tables and Listings Presentation

For all analyses, summary statistics will be tabulated for the 5 following treatment groups as presented in Table 5 and corresponding to the 3 VIT-2763 cohorts, the pooling of the 2 placebo cohorts and the pooling of all VIT-2763 subjects.

Table 5 Treatment groups labels

Treatment Groups Labels	**Treatment Groups Short Labels**	**Table order[1]**
Cohort 1: VIT-2763 60 mg BID	VIT-2763 60 mg BID	1
Cohort 2: VIT-2763 120 mg BID	VIT-2763 120 mg BID	2
Cohort 3: VIT-2763 120 mg TID	VIT-2763 120 mg TID	3
Cohorts 1-2-3: All VIT-2763	All VIT-2763	4
Cohort 4a/4b: Placebo	Placebo	5

[1] From left to right in statistical tables

Shorts labels will be used in tables while entire labels will be used in listings and figures for both randomized and actual treatment arms.

The listings will display all the data contained in the CRF, including the screen failure patients collected information if appropriate. The listings will be ordered by dose (from lowest to highest) and for all subjects receiving placebo (Cohorts 4a and 4b combined) and subject number.

5.1.6 Analysis Populations

The safety set will be used for all safety analyses.

The safety set excluding subjects who did not received any dose of VIT-2763 will be used for PK concentration summary statistics analyses. PK concentration listings will be done on the ITT.

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 if it differs.

All exploratory analyses will be performed on the ITT and will be repeated on the PPS if it differs and on the mITT (except for ASCQ-Me, VOC and visceral infarctions endpoints) if applicable.

The mITT may be used depending on the number of subjects with major COVID-19 protocol deviations and the impact on analyses. The decision to use or not this population will be made prior to unblinding. In case the decision is to use mITT, all primary, secondary and exploratory endpoints tables will be repeated on mITT.

Demographics and baseline characteristics will be summarised on the safety set, ITT, and the PPS (and mITT if applicable). Medical history and concurrent medical conditions, prior and concomitant medications and procedure and study drug exposure and compliance will be described on the ITT and the PPS.

Only sets with different attributes will be presented. The enrolled or aITT populations will be used as applicable for listings except specific safety listings to be generated on safety set (see Section 5.8.1),

5.1.7 Pooling of Sites/Country

Not applicable for this study

5.1.8 Analysis of Subgroups

Not applicable for this study

5.1.9 Methods for Handling and Imputation of Missing Data

Missing and/or incomplete dates/times for AEs will be imputed in a manner resulting in the earliest onset or the longest duration during the treatment period, taking additionally into account that the start date/time should not be after the stop date/time. Stop dates/times will not be imputed if the AE is ongoing. This will be done as follows:

For a missing/incomplete start date/time the minimum of the following will be imputed:

- The maximum of the earliest possible start date/time and the date/time of first study medication administration.
- The latest possible start date/time.
- The latest possible stop date/time.

For a missing/incomplete stop date/time the maximum of the following will be imputed:

- The minimum of the latest possible stop date/time and the date/time of last study medication administration.

- The earliest possible stop date/time.
- The earliest possible start date/time.

The earliest/latest possible date is defined as:

- The date itself if it is complete.
- The date of the first/last day of the month, if month and year are available but day is missing.
- The date of the first/last day of the year, if year is available but day and month are missing. A very early/late date, e.g., 01JAN2000 (01JAN2100), if the date is completely missing.

For medications and procedures, imputation of missing or partial dates will be done to identify concomitant medications and procedures as follows:

- If the start date of the medication/procedure is unknown (i.e., complete missing date), the worst-case scenario will be assumed. The medication/procedure will be considered as both a prior medication/procedure and a concomitant medication/procedure.
- If the month and the day of the start date of the medication/procedure are missing, the month and the day will be imputed to January, 1st of the year specified.
- If the day of the start date of the medication/procedure is missing, the day will be imputed to the first day of the month specified.
- If the end date is unknown (i.e., missing), the date will be kept as missing however the medication/procedure will be considered concomitant.
- If the month and the day of the end date of the medication/procedure are missing, the month and the day will be imputed to December, 31st of the year specified.
- If the day of the end date of the medication/procedure is missing, the day will be imputed to the last day of the month specified.

For treatment group dose intake day missing (or Unknown), the day will be imputed to the end day of the previous visit.

The original incomplete, missing or partial dates and corresponding imputed dates will be presented in the listings.

During the conduct of the study, a non-neglectable number of missing data for the primary endpoint (indirect bilirubin) have been observed at baseline and Visit 6. Sensitivity analyses will be performed for the primary endpoint with different imputations for the missing data. Only missing data due to haemolysed samples will be imputed as they can be considered as missing at random while missing data because of withdrawal of the study cannot. Imputations will be as following:

- Missing baseline data will be imputed with the median of the non-missing baseline indirect bilirubin of the pooled subjects of all cohorts.
- For missing data at visit 6, 3 types of imputation will be performed: the minimal value, the mean and the maximal value within the Cohort of the subject.

5.2 Subject Disposition

The subject disposition data will be summarised as follows:

Number of subjects screened will be summarised overall. Number and percentage of subjects re-screened, will be also summarised overall along with number and percentage of subjects that failed screening with the reason of screen failure. This will be tabulated on the enrolled population.

Number and percentage of subjects randomised, treated, receiving a different treatment than they were randomised to and subjects that were randomised but not treated, will be summarised on the ITT by treatment group as described in Table 5.

Subjects included and excluded from safety set, ITT, PPS and mITT (in case applicable) with the reason of exclusion from any analysis set will be summarised and listed on the ITT. Subjects discontinued from treatment with reasons and who did not complete the study with reasons for discontinuations will be summarised on the ITT and listed on the aITT. Additionally, the time on study in days will be described in this table. It will be computed as the number of days from the randomisation date to the last known date of the subject in the study.

The following data will be presented in the listings:

- Date of informed consent.
- Date of randomisation.
- Date of completion/discontinuation from study
- Date of first and last intake of study medication.

Classification of protocol deviations into major and minor sponsor's definitions will be applied as per Project Specific Protocol Deviation Category List. The protocol deviations will be identified for all subjects by either site monitoring, medical review process or programming. The classification will be confirmed prior to database lock i.e. they will be classified prior to unblinding of treatment.

The number of unique subjects with at least one major protocol deviation as well as the number of subjects in each major protocol deviation category will be presented by default descriptive summary statistics on the ITT.

All protocol deviations will be listed on the aITT, including the nature of the protocol deviation, major or minor and their relation with Covid-19.

5.3 Demographics and Baseline Subject Characteristics

The following subject demographic data collected on the Demographics CRF page will be summarised:

- Sex
- Age (years)
- Age in categories for adults: <18/18-29/30-49/50-65/ >65 years
- Race: American Indian or Alaska Native/Asian/Black or African American/Native Hawaiian or Other Pacific Islander/White/Not Reported/Unknown, Other, Multiple

- Ethnicity: Hispanic or Latino/Not Hispanic or Latino/Not Reported/Unknown

The following baseline characteristics collected at screening or at baseline will be tabulated:

- Height (cm), body weight (kg), body mass index (BMI) (kg/m²) [derived as body weight / (height)^2], BMI in categories for adults: <18.5/ 18.5 to <25/ 25 to <30/ ≥30 kg/m²

Heights collected in inches will be converted in cm for analysis (multiplied by 2.54). Body weights collected in lb will be converted in kg for analysis (multiplied by 0.4536).

- Aetiology of SCD collected on the Aetiology and Clinical Presentation CRF page and including underlying genotype (HbS/S or HbS/βT0), time between sickle cell disease diagnosis and informed consent (months) (derived as date of written informed consent obtained - date of sickle cell disease diagnosis / (365.25/12), number of VOC episodes within 12 months prior to screening, time between last hospitalization due to SCD and informed consent (months) (date of written informed consent obtained-derived as last hospitalization due to SCD/(365.25/12)).
- Visceral infarctions within the last 8 weeks before baseline (yes/no), number of visceral infarctions within the last 8 weeks before baseline, VOC episodes within the last 8 weeks before baseline (Yes/No), number of VOC episodes within the last 8 weeks before baseline and maximum duration of VOC episodes and maximum pain intensity in categories (0 = No pain, 1-3 = Mild pain, 4-6 = Moderate pain, 7-10 = Severe pain).

The Demographics and baseline characteristics will be summarised for the ITT, safety set, PPS and mITT (if applicable). In case some analyses sets are identical, summary statistics will not be repeated. Listings will be provided on the Enrolled Population for demographics characteristics and on aITT for baseline characteristics.

Serum virology parameters (HbsAG, HBV, HCV, HIV) and serum pregnancy test will be listed at baseline on aITT population.

5.4 Medical History and Concurrent Medical Conditions

Medical history will consist of significant conditions or diseases that stopped at or before screening. Ongoing medical conditions recorded in medical history will be considered as concurrent medical conditions. Medical history and concurrent medical conditions will be coded using MedDRA [Version 24.0]. All medical history and associated concurrent medication condition will be listed on aITT, and the number and percentage of subjects with any medical history will be summarised by SOC and PT on the ITT and PPS.

The SOC and PTs are to be sorted by decreasing order frequency of SOC and PTs in the overall subjects receiving VIT-2763. In case of equal frequency of SOC or PT, alphabetical order will be used. Subjects are included only once in each SOC and PT, even if they experienced multiple events in that SOC or PT.

5.5 Prior and Concomitant Medications and Procedures

Medications:

All medications will be coded using the current version of the World Health Organization Drug (WHO Drug) dictionary [Mar2021 B3].

Prior medications will be defined as all medications taken before the first dose of study drug with a stop date prior to the first dose of study drug.

Concomitant medications will be defined as all medications with a start date before, on or after the first dose of study drug and with a stop date on or after the first dose of study drug or with a missing stop date.

Prior and concomitant medication will be summarised by number and percentage of subjects by treatment group as defined in Table 5- on ITT and PPS. The summary tables will be sorted by decreasing frequency of overall subjects receiving VIT-2763 and decreasing frequency of drug or procedure name in a given drug class (therapeutic subgroup [2nd level of the anatomical therapeutic chemical (ATC) classification], chemical subgroup [4th level of the ATC classification] and Preferred Name). In case of equal frequency regarding drug or procedure class, alphabetical order will be used. A same medication or procedure during the study for one subject will be counted once.

A listing with all prior and concomitant medications will be provided including the flag for prior or concomitant on Enrolled population.

Procedures:

Prior procedures will be defined as all procedures performed before the first dose of study drug with a stop date prior to the first dose of study drug.

Concomitant procedures will be defined as all procedures with a stop date on or after the first dose of study drug or with a missing stop date.

All procedures will be coded using the MedDRA 24.0.

A listing with all prior and concomitant procedures will be provided including the flag for prior or concomitant on Enrolled population. Procedures will not be tabulated.

5.6 Study Drug Exposure and Compliance

The following durations of study drugs (including VIT-2763 and Placebo) will be computed in days:

Duration of study drug (in days) = Treatment stop date – Treatment start date + 1

Treatment start and stop dates will be derived as defined in Section 5.1.4.

The total amount of VIT-2763 taken in mg will be calculated for each subject from the difference between the amount of VIT-2763 dispensed in mg and the amount of VIT-2763 returned in mg. It will be compared to the amount expected to be taken for subjects randomised in a VIT-2763 cohort to calculate the percentage compliance to VIT-2763. Derivation details are provided below.

Total amount of VIT-2763 (mg) = 30*(Number of VIT-2763 30 mg capsules dispensed - Number of VIT-2763 30 mg capsules returned) + 60*(Number of VIT-2763 60 mg capsules dispensed - Number of VIT-2763 60 mg capsules returned).

The total amount of VIT-2763 taken will be computed for all randomised subjects and will be equal to 0 if no dispensation error occurred in Placebo cohort. In case of miss allocation for a patient receiving VIT-2763 instead of Placebo, the amount will be counted for VIT-2763.

Expected amount of VIT-2763 (mg) for cohort 1 = 120*(Duration of study drug in days -1) + 60.

Expected amount of VIT-2763 (mg) for cohort 2 = 240*(Duration of study drug in days -1) + 120.

Expected amount of VIT-2763 (mg) for cohort 3 = 360*(Duration of study drug in days -1) + 120.

VIT-2763 compliance (%) = (Total amount of VIT-2763 (mg) / Expected amount of VIT-2763 (mg)) for cohort 1-2-3 *100.

The total number of capsules of study drug (VIT-2763 or Placebo) taken will be calculated for each subject from the difference between the total number of capsules dispensed and the total number of capsules returned. It will be compared to the expected number of capsules to be taken by subject to calculate the percentage compliance to study drug.

Total amount of study drug (number of capsules) = Number of capsules dispensed - Number of capsules returned

Expected amount of study drug (number of capsules) for cohorts 1, 2, 4a = 4 * (Duration of study drug in days -1) +2

Expected amount of study drug (number of capsules) for cohort 3, 4b = 6 * (Duration of study drug in days -1) +2

Study drug compliance (%) = (Total number of capsules taken / Expected number of capsules taken) *100

Duration of study drug, total and expected amount of VIT-2763 and total and expected amount of study drug in terms of number of capsules taken will be summarised using standard descriptive statistics for continuous variables on the ITT population and the PPS if they differ.

The calculated percentages of compliance will be categorized as:

- < 80% compliance
- ≥ 80% to ≤ 110% compliance
- > 110% compliance

Compliances for VIT-2763 and for study drug will be summarized for the ITT population and the PPS if they differ as follows:

- Percent compliance presented by default summary statistics for continuous variables.
- Number and percentage of subjects within each of the compliance categories.

The number and percentage of subjects who had at least one incidence of a change/interruption to their dosing will be summarised along with reasons of dose change/interruption for the ITT population and the PPS if they differ.

A listing of exposure data will also be presented together with compliance on ITT.

5.7 Efficacy Analyses

5.7.1 Primary Efficacy Analysis

The changes in indirect bilirubin from baseline to Visit 6 (after 8 weeks of treatment) will be summarised using standard descriptive statistics for continuous variables with 95% confidence interval (CI) of the mean on the ITT population by randomised treatment groups as described in Table 5.

Analysis visit windows will be considered for the primary efficacy analysis (see Section 5.1.2). The analysis will be repeated on the PPS by actual treatment group and on mITT if applicable.

Three sensitivity analyses will be run on the ITT population as the primary analysis, with the imputation of the missing data due to haemolised samples at baseline or Visit 6 (see section 5.1.9). Analyses will be:

- Imputation of missing baseline with the median of the non-missing baseline of the pooled subjects. Imputation of Visit 6 missing data using the minimal value within the same cohort.

- Imputation of missing baseline with the median of the non-missing baseline of the pooled subjects. Imputation of Visit 6 missing data using mean value within the same cohort.

- Imputation of missing baseline with the median of the non-missing baseline of the pooled subjects. Imputation of Visit 6 missing data using maximum value within the same cohort.

5.7.2 Secondary Efficacy Analysis

Summaries of change from baseline values will be reported at Visit 6 (after 8 weeks of treatment) for direct and total bilirubin, LDH, potassium, Hb and free haptoglobin using standard descriptive statistics for continuous variables with 95% CI of the mean by randomised treatment groups as described in Table 5 on the ITT population.

The analysis will be repeated on the PPS as well by actual treatment group and on mITT if applicable.

5.7.3 Exploratory Efficacy Analysis

Summaries of values and changes from baseline for each haemolysis marker (indirect, direct and total bilirubin, LDH, potassium, Hb and free haptoglobin) will be reported for each visit using standard descriptive statistics for continuous variables on the ITT population by randomised treatment groups as described in Table 5. Analyses will be repeated on the PPS by actual treatment group and on mITT if applicable.

Summaries of absolute and percent changes from baseline for indirect bilirubin, CHCM and MCHC will also be reported for each visit using the same approach.

Number and percentage of subjects who had at least 20% reduction in Indirect Bilirubin from baseline will be summarized at each post-baseline visit.

Number and percentage of subjects who had at least 5% reduction in CHCM and MCHC from baseline will be summarized at each post-baseline visit.

Analyses will be repeated on the PPS by actual treatment group and on mITT if applicable.

For each haemolysis marker, 3 figures will be provided:

- Line plots by subject: individual marker values (y-axis) in function of target visit day (x-axis) joined by subject and plotted in separate windows for the randomised cohorts (1, 2, 3, 4).
- Line plots by subject in log scale: same plot as previous with individual marker values displayed in a $\log_{10}$ scale (y-axis)
- Means with 95% CIs of changes from baseline marker values for the 4 randomised cohorts (y-axis) in function of target visit day (x-axis). Means will be joined by group.

All graphics will be done on the ITT.

5.8 Safety Analyses

Safety evaluations will be performed using the safety set and analysed according to the analysis methods described in 5.1.1 unless specified otherwise. Missing values will not be imputed unless stated otherwise.

5.8.1 Adverse Events

AE data are collected from the time that ICF has been signed.

A treatment-emergent adverse event (TEAE) is defined as an AE that occurred or increased in severity on the same date or after the first dose of study medication.

A serious TEAE is defined as a serious adverse event (SAE) occurring or increasing in severity on the same date or after the first dose of study medication. An AE will be classified as related to study medication if the causality was recorded as certain, probable/likely and possible. An AE will be classified as unrelated to study medication if it was recorded as unlikely and unrelated. Additionally, AEs that have missing causality (after data querying) will be assumed to be related to study medication.

An AE leading to study discontinuation will be defined as an AE where the reason for study withdrawal was recorded as being due to this AE on the Study Termination CRF page or the response to Other Action taken on the Adverse Events CRF page, was recorded as early study termination.

An AE leading to treatment discontinuation is defined as an AE where the reason for treatment discontinuation was recorded as being due to this AE on the Treatment Termination CRF page or the action taken with study drug of the event was recorded as drug withdrawn on the Adverse Events CRF page.

AEs will be reported on a per-subject basis and per-event. On a per-subject basis, subjects with more than one AE overall or within a particular SOC/PT will be counted only once for that SOC/PT or overall. On a per-event basis (event counts), all severities of a same AE will be counted as only 1 AE. As, in CRF, every change in severity of a particular AE is recorded as a new AE log line and with a new AE number (the previous AE is reported with a resolved outcome and end date specified as the date the previous grade ended) a AE group number will be derived at time of analysis (regrouping all severities of a same AE) using the following rule:

- Any AE record with a start date on the day or 1 day after the stop date of another AE record of the same PT will be considered as a continuation of the previous AE and will have the same AE group number as the previous log line. AE group numbers with more than one record overall or within a particular SOC/PT will be counted as only 1 AE for that SOC/PT or overall in tables presenting AEs counts.

The imputation methods for completely or partially missing dates of AEs described in Section 5.1.9 will only be used to derive treatment emergence flag and to determine the day of the event relative to the first administration of study medication.

Only TEAEs will be tabulated. AEs that occurred during the study but before first IMP intake will be only listed on the Enrolled population.

The overall summary of TEAEs table will include the counts and percentage of subjects with at least 1 TEAE and the number of events with each of the following, tabulated on actual treatment:

- Any TEAEs
- Any TEAEs of severity ≥ 3
- Any TEAEs related to study medication
- Any TEAEs of severity ≥ 3 related to study medication
- Any TEAEs leading to discontinuation of study medication
- Any TEAEs leading to study discontinuation
- Any serious TEAEs
- Any serious TEAEs related to study medication
- Any TEAEs leading to death (outcome “fatal”)
- Any TEAEs leading to death related to study medication

The number and percentage of subjects reporting each TEAE and the count of number of events will be summarized by SOC and PT for the following types of TEAEs:

- All TEAEs
- TEAEs related to study medication
- TEAEs of severity ≥ 3 related to study medication
- Serious TEAEs
- TEAEs by maximum severity
- TEAEs by relationship to study medication

The SOC and PTs are to be sorted by decreasing order frequency of SOC and PTs in the overall subjects receiving VIT-2763.

For summaries by maximum severity, subjects with multiple TEAEs within a particular SOC/PT will be counted under the category of their most severe TEAE within that SOC/PT. TEAEs with missing severity will be counted in a missing category.
Listings of all AEs, all SAEs, all AEs leading to death, all AEs leading to treatment discontinuation, all AEs leading to study discontinuation and all AEs related to Study Drug with flag for AE within the treatment emergent period will be provided including relative day and duration of AE. Listings of all SAEs, all AEs leading to death and all AEs leading to treatment discontinuation will be specifically provided on safety set. Listings of all AEs will be provide on Enrolled population. Listings on all AEs leading to study discontinuation and all AEs related to Study Drug will be provided on the aITT.

Secondary Safety Endpoint

Secondary safety endpoint is the 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.

All TEAEs with a start date in the 88 days (corresponding to the target day 84 of the end of treatment visit plus the 4 days of visit window allowed in protocol) will be selected for this analysis. If missing start date, imputation method described in Section 5.1.9 will apply.

The number and percentage of subjects and the count of number of events reported in the 60 days after first dose of study treatment will be summarized by SOC and PT for the following types of TEAEs:

- All TEAEs
- TEAEs related to study medication
- Serious TEAEs
- TEAEs by maximum severity

The SOC and PTs are to be sorted by decreasing order frequency of SOC and PTs in the overall subjects receiving VIT-2763).

5.8.2 Clinical Laboratory Evaluations

The list of all protocol specified clinical laboratory safety tests (serum biochemistry, safety haematology and urinalysis) is given in Appendix A Table 6. Laboratory safety tests will be performed at each study visit in accordance with the Schedule of Events in Section 2.3. For tabulations, analysis windows (see Section 5.1.2) are considered for each visit.

Clinical laboratory tests are planned to be performed by central laboratory. However, in case of pandemic (e.g., COVID-19) related restriction and impossibility of sample shipment, or inability of subject to visit the site or inform the Medical Monitor of the study, the laboratory assessments may be performed in a local laboratory at site or near to subject's home. If any, the total number of values tabulated provided from a local laboratory will be indicated in the footnote of tables.

All laboratory data will be reported in standard international (SI) units. All quantitative values for haematology and serum biochemistry parameters at each assessed visit will be compared with the relevant reference range in SI and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

For all haematology and serum biochemistry parameters displayed in Appendix A Table 6, descriptive statistics will be performed on a continuous scale for the values by visit (from baseline) and for changes from baseline by post-baseline visit for actual treatment groups on the safety set. This analysis will be repeated on the ITT, PPS and mITT if applicable (see Section 4.4 for the mITT definition). Urinalysis results will only be listed on the aITT. Abnormal haematology and serum biochemistry results (defined as results below or above reference range) will also be listed separately on the safety set.

The number and percentage of subjects within each categorized shift relative to the reference range (low, normal and high) at baseline compared to each post-baseline visit for haematology and serum chemistry will be tabulated by actual treatment groups on the safety set. Subject with missing values will be classified in a missing category.

All laboratory results (serum biochemistry, safety haematology and urinalysis) will be listed, including all unscheduled visits for the aITT.

In addition, listings will be provided for urine Pregnancy Test and for hemoglobin local laboratories measurements.

5.8.3 Electrocardiogram (ECG) Evaluations

PR interval (ms), QRS duration (ms), QT interval (ms), RR interval (ms), QTcF (ms) interval and ventricular rate (bpm) will be evaluated at each visit at pre-dose and 2 hours (±30 minutes) post-morning dose.

QT corrected using Fridericia formula is defined as:

$$QTcF(ms) = QT(ms)/\sqrt[3]{RR\ (ms)}$$

Pre-dose and 2 hours post morning dose values will be described by visit from baseline as well as changes from baseline (pre first dose measures) to each post baseline measures at pre-dose and at 2 hours post morning dose for all parameters by actual treatment groups on the safety set. For tabulations, analysis windows (see Section 5.1.3) will be considered for each visit but no window will be considered for the time-points (pre or 2 hours post-dose).

For each ECG parameter, the following figure will be provided: individual values (y-axis) in function of target visit day and time-point (nominal x-axis scale: “D1”, “D1+2h etc…) joined by subject and plotted in separate windows for the randomised cohorts (1, 2, 3, 4) and for overall subjects randomised in VIT-2763 (5-window panel plot). All graphics will be done on the Safety set.

All ECG parameters results will be listed with changes from baseline as well as overall ECG interpretation on the aITT.

5.8.4 Vital Signs and Body Weight Evaluations

The values and changes from baseline results of Systolic Blood Pressure (SBP) (mmHg), Diastolic Blood Pressure (DBP) (mmHg), pulse rate (bpm) and body weight (kg) will be summarised by visit by actual treatment groups on the safety set. For tabulations, analysis windows (see Section 5.1.3) will be considered for each visit.

Vital sign results with changes from baseline will be presented for individual subjects in data listings on the aITT.

5.8.5 Physical Examinations

All clinically significant abnormalities in physical examination will be collected in the general medical history or the adverse event eCRF pages as appropriate. Therefore, no specific analysis of physical examination will be performed.

5.9 Other Analyses

5.9.1 Iron-related parameters and blood inflammatory markers

Iron-related parameters include total serum iron, serum ferritin, transferrin, TSAT, hepcidin and erythropoietin.

Blood inflammatory markers include 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.

All data will be reported in SI. For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

For all iron-related parameters and blood inflammatory markers, standard descriptive statistics for continuous variables will be tabulated for the values by visit (including baseline) and for changes from baseline by post-baseline visit for randomised treatment groups as described in Table 5 on the ITT. Analysis windows (see Section 5.1.3) will be considered for each visit.

Analyses will be repeated on the PPS by actual treatment group if it differs and on mITT if applicable.

For each iron-related parameter and blood inflammatory marker, the following figure will be provided: individual values (y-axis) in function of target visit day (x-axis) joined by subject and plotted in separate windows for the randomised cohorts (1, 2, 3, 4) and for overall subjects randomised in VIT-2763 (5-window panel plot). All graphics will be done on the ITT.

Finally, all parameter results with changes from baseline will be listed, including all unscheduled visits, for the aITT.

5.9.2 Abnormal RBC sickling

RBC smear assessment for sickle cells from central laboratory will include sickle cell counts in percentage.

Standard descriptive statistics for continuous variables will be tabulated for the values by visit (including baseline) and for changes from baseline by post-baseline visit for treatment groups, as described in Table 5 on the ITT. Analysis windows (see Section 5.1.3) will be considered for each visit.

Analyses will be repeated on the PPS by actual treatment group if it differs and on mITT if applicable.

All parameters' results will be listed, including all unscheduled visits, for the aITT.

5.9.3 Quality of Life

The Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me) is a patient-centered data collection tool that is made available for clinical study of adults who have SCD for understanding: (1) the impact of SCD, and (2) interventions to improve the treatment of adults with SCD on their functioning and wellbeing.

The health domains assessed by ASCQ-Me include:

1. Emotional impact (5 questions assessing the past 7 days with 5 possible answers)
2. Pain impact (5 questions assessing the past 7 days with 5 possible answers)
3. Sleep impact (5 questions assessing the past 7 days with 5 possible answers)
4. Stiffness impact (5 questions assessing the past 7 days with 5 possible answers)
5. Social functioning impact (5 questions assessing the past 30 days with 5 possible answers)

6. Pain episodes, frequency, and severity (5 questions assessing the past 12 months with 5 to 12 possible answers).

The 4 impact domains emotional, pain, sleep and stiffness were assessed at baseline, Visit 3, Visit 4, Visit 5 and Visit 6.

The social functioning impact domain was assessed at baseline, Visit 4 and Visit 6.

The Pain episodes, frequency, and severity domains were assessed at baseline and Visit 6.

Impact short-forms T-score computation:

Each of the 5 impact domains will be scored by summing the values for each response (1 worst health to 5 best health) and using the conversion tables presented in Appendix B to obtain the T-scores (for ease of interpretation, each T-score is on the same scale, which was done by standardizing the scores to have a mean of 50 and a standard deviation of 10). A higher score always represents a healthier status. For example, if a subject chooses the worst health response on all five items, that subject's total raw score will be 5. If this were the Emotional Impact short form, that subject's T-score will be 26.8 on emotional impact.

A score could be approximated if a subject skips one out of the five questions in a short form. However, a short form cannot be scored if three or fewer items were answered. If four responses were provided on a short form, the sum of the response scores will be computed from the items that were answered, then multiply this sum by the total number of items in the short form (5), and finally, divide by the number of items that were answered (4). If the result is a fraction, the pro-rated score will be rounded up to the nearest whole number and then translated into a final T-score using Table 7 in Appendix B (from ASCQ-Me User's Manual http://www.healthmeasures.net/images/ASQMe/ASCQ-Me_Scoring_Manual.pdf).

Individual items scoring for pain episodes, frequency, and severity short-form:

The ASCQ-Me Pain Episode question set includes five questions regarding the frequency, timing, and severity of sickle cell pain events. Each answer to the 5 questions will be scored according to Table 8 in Appendix B. All five items have an option with some variant of "I never had a pain attack." This response category is always initially coded as a 99 to examine the frequency distribution of responses for each item.

Frequency measure computation for pain episodes short-form:

The two first questions refer to frequency of pain episodes—one to a simple count of the number of attacks (more attacks indicate worse experience), and one to how long ago the most recent pain attack occurred. For these items, more pain attacks or having a more recent attack, respectively, is considered a worse experience. The frequency composite score is the sum of the values for these two first items which results in a raw composite score with a potential range of 0 to 11. The raw response score of 99 must be replaced with a zero, before calculating any composite scores. The composite score will then be standardized. This will be done by creating z-scores, which are also called standard scores, because this method makes scores derived from different raw score units comparable. The formula for the z-score is the individual score in question minus the mean of the score distribution divided by the standard deviation of the score distribution. The means and standard deviations used to create z-scores for the Pain Episode Frequency are in Table 9 appendix B. T-score transformation will finally be performed by multiplying the score by 10 so that the range of scores is greater than absolute 1 and by adding 50 so that the range of scores is positive.

Severity measure computation for pain episodes short-form:

Three questions refer to the severity of pain during a pain episode: one question asks the respondent to rate the severity of the pain for the most recent attack, the second asks the respondent to indicate the degree to which the most recent attack interfered with his or her ability to be active, and the third refers to the duration of the pain attack. The Severity composite represents the sum of the values for these three items, which results in a raw composite score with a potential range of 0 to 22. The composite score will be transformed in a T-score using the same methodology as described for frequency measure.

Analyses:

The baseline and Visit 6 scores for each individual item of the pain episodes, frequency, and severity questionnaire will be summarised with standard descriptive statistics for qualitative variables.

For the 5 impact questionnaires and for pain episode frequency and severity measures, T-Score values by visit and changes from baseline at each post-baseline visit will be summarised. Analysis windows (see Section 5.1.3) will be considered for each visit.

The ITT population will be used, and summaries will be repeated on the PPS as well.

5.9.4 VOC Episode and Visceral Infarctions

The number of VOC episodes occurring over 8 weeks of treatment will be computed as the number of VOC episodes collected with a start date in the 60 days after baseline (corresponding to the target day 56 of the end of treatment visit plus the 4 days of visit window allowed in protocol).

The number of visceral infarctions occurring over 8 weeks of treatment will be computed as the sum of the number of visceral infarction collected at Visit 3, Visit 4, Visit 5 and Visit 6 (number of infarction since last visit collected at each visit in CRF).

Episodes counts will be categorized as:

- 0
- 1
- 2
- >2

Shift tables summarising the number of VOC episodes and the number of visceral infarctions in categories in the 8 weeks after baseline versus 8 weeks prior baseline will be provided.

The number of VOC episodes occurring over 4 weeks after end of treatment will be computed as the number of VOC episodes collected with a start date in the 28 days after treatment stop date.

The number of visceral infarctions occurring over 4 weeks after end of treatment will be the number of visceral infarction collected at Visit 7.

The number of VOC episodes occurring over 4 weeks after end of treatment, the number of visceral infarctions recorded at each visit and occurring over 4 weeks after end of treatment will be listed on the aITT. Each VOC episode with its pain intensity (NRS: 0-10) will be described by visit in a listing.

The ITT population will be used, and summaries will be repeated on the PPS as well.

5.9.5 Pharmacokinetics Analyses

Sparse sampling for determination of VIT 2763 plasma concentration following multiple dosing will be obtained from pre-dose trough to 2, 4 and 6 hours post-morning dose at study Visit 4 (V4).

The population pharmacokinetic analysis will be described in a separate analysis plan.

Pharmacokinetic plasma concentration of VIT-2763 will be summarised for the ITT and listed by subject for the aITT for each sampling time point by visit for cohorts 1, 2 and 3 (Placebo group not displayed), using descriptive statistics (including geometric mean and CV%, arithmetic mean, standard deviation, arithmetic CV%, median, maximum, minimum, and N). No formal statistical tests are planned.

The observed plasma concentration-time profiles will be plotted by subject using spaghetti plots for cohorts 1, 2 and 3.

The following rules will be applied if there are values that are below the limit of quantification (BLQ) or if there are missing values in a plasma concentration data sets to be summarised.

- For the calculation of summary statistics, BLQ values will be set to the limit of quantification.
- If non-missing values are obtained from at least 3 subjects in a treatment group, the summary statistics will be calculated.
- If non-missing values are obtained from less than 3 subjects in a treatment group, only minimum and maximum will be displayed, other arithmetic and geometric summary statistics will be denoted as NC (not computed).

If an embedded BLQ value is considered anomalous within the concentration time profile, it may be decided to update this analysis excluding this value from the summary statistics.

REFERENCES

1. ICH E3: Structure and Content of Clinical Study Reports, 30 Nov 1995.
2. ICH E9: Statistical Principles for Clinical Trials, 05 Feb 1998.
3. Treadwell MJ, Hassell K, Levine R, Keller S. Adult sickle cell quality-of-life measurement information system (ASCQ-Me): conceptual model based on review of the literature and formative research. Clin J Pain. 2014 Oct30(10):902-14

APPENDICES

APPENDIX A: CLINICAL LABORATORY SAFETY PARAMETERS

Table 6 Clinical laboratory safety parameters (from central laboratory)

Haematology Test	Serum Chemistry Test	Urinalysis

• Haemoglobin
• Reticulocytes (abs and %)
• Red Blood Cell Count
• Hct
• MCH
• MCV
• MCHC
• RDW
• % hypochromic RBC
• CHCM
• White Blood Cell Count
• Differential WBC (abs and %)
  ○ Neutrophils
  ○ Lymphocytes
  ○ Monocytes
  ○ Eosinophils
  ○ Basophils
• Platelet count
	• 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
	• Cholesterol
		• pH
		• Protein
		• Glucose
		• Ketone
		• Red Blood Cell
		• White Blood Cell
		• Microalbumin
		• Creatinine
		• Microalbumin/Creatinine ratio

All these parameters will be analysed in SI unit.

APPENDIX B : ASCQ-ME QUESTIONNAIRES SCORINGS

Table 7 Translation of Raw Scores to T-scores for ASCQ-Me Impact Short-Forms Measures

Emotional Impact		Social Functioning Impact		Pain		Stiffness		Sleep	
Raw Score	T-score	Raw Score	T-score	Raw Score	T-score	Raw Score	T-score	Raw Score	T-score
5	26.8	5	26.0	5	24.8	5	24.9	5	27.9
6	30.8	6	29.8	6	28.8	6	29.0	6	32.3
7	33.3	7	32.5	7	31.0	7	31.5	7	35.1
8	35.3	8	34.7	8	33.0	8	33.5	8	37.3
9	37.0	9	36.8	9	34.9	9	35.3	9	39.5
10	38.5	10	38.7	10	36.7	10	36.9	10	41.4
11	39.9	11	40.4	11	38.3	11	38.4	11	43.2
12	41.2	12	42.1	12	39.9	12	39.9	12	45.0
13	42.5	13	43.9	13	41.5	13	41.3	13	46.7
14	43.7	14	45.6	14	43.0	14	42.7	14	48.2
15	44.9	15	47.2	15	44.4	15	44.0	15	49.7
16	46.2	16	48.8	16	45.7	16	45.4	16	51.1
17	47.4	17	50.5	17	47.1	17	46.7	17	52.5
18	48.7	18	52.2	18	48.5	18	48.1	18	53.9
19	50.1	19	54.0	19	49.9	19	49.5	19	55.3
20	51.5	20	55.8	20	51.2	20	51.0	20	56.7
21	53.3	21	57.7	21	52.5	21	52.7	21	58.2
22	55.2	22	59.8	22	54.0	22	54.7	22	59.9
23	57.3	23	62.1	23	55.8	23	57.0	23	61.9
24	60.5	24	64.9	24	58.0	24	59.9	24	64.4
25	65.6	25	69.8	25	63.8	25	65.4	25	69.1

Table 8 Individual item scoring for Pain Episode Measures

Questions	Responses	Score	Recoded Score
Pain Episode Q1. In the past 12 months, how many sickle cell pain attacks (crises) did you have?	I did not have a pain attack (crisis) in the past 12 months	99	0
	1	1	
	2	2	
	3	3	
	4 or more	4	
Pain Episode Q2. When was your last pain attack (crisis)?	I've never had a pain attack/crisis	99	0
	More than 5 years ago	1	
	1–5 years ago	2	
	7–11 months ago	3	
	1–6 months ago	4	
	1–3 weeks ago	5	
	Less than a week ago	6	
	I have one right now	7	
Pain Episode Q3. Using any number from 0 to 10, where 0 is no pain and 10 is the worst imaginable pain, how severe was your pain during your last pain attack (crisis)?	No pain	0	
	1	1	
	2	2	
	3	3	
	4	4	
	5	5	
	6	6	
	7	7	
	8	8	
	9	9	
	Worse pain imaginable	10	
Pain Episode Q4. How much did your last pain attack (crisis) interfere with your life?	I've never had a pain attack (crisis)	99	0
	Not at all, I did everything I usually do	1	
	I had to cut down on some things I usually do	2	
	I could not do most things I usually do	3	
	I could not take care of myself and needed some help from family or friends	4	
	I could not take care of myself and needed constant care from family, friends, doctors, or nurses	5	
Pain Episode Q5. About how long did your most recent pain attack (crisis) last?	I've never had a pain attack (crisis)	99	0
	Less than 1 hour	1	
	1–12 hours	2	
	13–23 hours	3	

	1–3 days	4	
	4–6 days	5	
	1–2 weeks	6	
	More than 2 weeks	7	

Table 9 Pain Episode Frequency and Severity Mean & Standard Deviation

Measure	Mean	Standard Deviation
Frequency	7.525	2.573
Severity	15.018	4.275

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Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Complete with DocuSign: VIT-2763-SCD-202_SAP Final Version V2_26APR2024.pdf
Source Envelope:
Document Pages: 43 Signatures: 4
Certificate Pages: 5 Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

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PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 4/26/2024 4:42:13 AM Viewed: 4/26/2024 4:50:55 AM Signed: 4/26/2024 4:55:30 AM
Electronic Record and Signature Disclosure: Accepted: 4/26/2024 4:50:55 AM ID: PPD		
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PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 4/26/2024 4:42:14 AM Viewed: 4/26/2024 5:50:05 AM Signed: 4/26/2024 5:51:35 AM
Electronic Record and Signature Disclosure: Accepted: 4/26/2024 5:50:05 AM ID: PPD		
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Electronic Record and Signature Disclosure: Accepted: 4/26/2024 9:35:35 AM ID: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	4/26/2024 4:42:15 AM
Certified Delivered	Security Checked	4/26/2024 9:35:35 AM
Signing Complete	Security Checked	4/26/2024 9:36:37 AM
Completed	Security Checked	4/26/2024 9:36:37 AM

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