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Clinical Study Protocol
A Phase 2a, Double-blind, Randomised, Placebo-controlled, Parallel Group, Multicentre Study on Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of Multiple Doses of VIT-2763 in Subjects with Non-transfusion Dependent Beta-thalassaemia

Clinical Protocol Number:	VIT-2763-THAL-201
Version Date:	12 April 2021
Version Number:	4.0
Investigational Drug:	VIT-2763
EudraCT Number:	2019-002221-29
Co-ordinating Investigator:	Prof. Vip Viprakasit, MD Faculty of Medicine Siriraj Hospital Mahidol University Bangkok, Thailand
Sponsor Contact:	Frank Richard, MD
Sponsor Address:	Vifor (International) Inc. Rechenstrasse 37 St. Gallen CH-9001 Switzerland
Medical Monitor:	[redacted]

[redacted]

SIGNATURE PAGE SPONSOR

Declaration of Sponsor

Title: A Phase 2a, Double-blind, Randomised, Placebo-controlled, Parallel Group, Multicentre Study on Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of Multiple Doses of VIT-2763 in Subjects with Non transfusion Dependent Beta-thalassaemia

Clinical Protocol Number: VIT-2763-THAL-201

Version/Amendment Number/Date: Version 4.0, Amendment 3, 12 April 2021

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 (ICH) of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice as amended.

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29-Apr-2021 | 08:41:55 CEST

Date (day month year)

29-Apr-2021 | 15:43:27 CEST

Date (day month year)

29-Apr-2021 | 08:32:39 CEST

Date (day month year)

29-Apr-2021 | 08:22:07 CEST

Date (day month year)

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INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

Title: A Phase 2a, Double-blind, Randomised, Placebo-controlled, Parallel Group, Multicentre Study on Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of Multiple Doses of VIT-2763 in Subjects with Non transfusion Dependent Beta-thalassaemia

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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 of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) 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.

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

Signature of Principal Investigator	Date (day month year)

Name, Title, Address, Telephone Number and Email of Principal Investigator

[redacted]

SIGNATURE PAGE

Declaration of Co-ordinating Investigator

Title: A Phase 2a, Double-blind, Randomised, Placebo-controlled, Parallel Group, Multicentre Study on Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of Multiple Doses of VIT-2763 in Subjects with Non-transfusion Dependent Beta-thalassaemia

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[redacted]

[redacted]

Date (day month year)

Professor of Haematology
Faculty of Medicine Siriraj Hospital
Mahidol University
Bangkok, Thailand

[redacted]

[redacted]

SYNOPSIS

Protocol Number VIT-2763-THAL-201

Title:	A Phase 2a, Double-blind, Randomised, Placebo-controlled, Parallel Group, Multicentre Study on Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of Multiple Doses of VIT-2763 in Subjects with Non-transfusion Dependent Beta-thalassaemia
Short Title:	Safety, Tolerability, Pharmacokinetics (PK), Pharmacodynamics (PD) and Preliminary Efficacy of VIT-2763 in β-thalassaemia (VITHAL)
Study Product(s):	VIT-2763
Study Population:	Adults and adolescents with non-transfusion dependent thalassaemia (NTDT)
Phase:	2a
Sponsor:	Vifor (International) Inc.
Protocol Number:	VIT-2763-THAL-201
Co-ordinating Investigator:	Professor Vip Viprakasit, MD-Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
Objectives:	Primary Objective: • To assess the safety and tolerability of VIT-2763 versus placebo in adult and adolescent NTDT subjects over a 12-week treatment period. Secondary Objectives: • To assess the preliminary efficacy of VIT-2763 versus placebo on iron markers in adult and adolescent NTDT subjects over a 12-week treatment period. • To evaluate the PK of VIT-2763 in adult and adolescent NTDT subjects over a 12-week treatment period (using a population PK approach). [redacted]
Design:	Phase 2a, multiple dose, multicentre, double-blind, placebo-controlled parallel group study in adult and adolescent male and female NTDT subjects. Adult and adolescent NTDT subjects will be enrolled in a randomised fashion. The study will commence with enrolment and treatment of adult NTDT subjects (Cohort I). Adult subjects will be randomised in an 8:8:4 ratio to receive either VIT-2763 once daily (QD) or twice daily (BID) or placebo, at a dose of 120 mg

	for subjects with a body weight ≥60 kg or at dose of 60 mg for subjects with a body weight <60 kg according to Table 2 below. A blinded interim analysis will be performed and the data reviewed by a Safety Review Team (SRT) once ≥10 subjects have completed the study Week 8 visit. For the purpose of the safety review in Cohort I, the randomisation algorithm should ensure that the first 10 subjects in Cohort I will match a 4:4:2 distribution to receive either 60/120 mg VIT-2763 QD or BID or matching placebo. Enrolment and treatment of adult NTDT subjects into Cohort I will continue during the study until up to 30 adult and/or adolescent subjects have completed the study Week 12 visit. Remaining adult NTDT subjects will be randomised to either 60 mg or 120 mg VIT-2763 or placebo according to the body weight assessed at screening. Following Cohort I review, the SRT will make recommendations on whether to enrol adolescent NTDT subjects into Cohort II. Adolescent subjects will be randomised in a 4:4:2 ratio to receive either VIT-2763 QD or BID or placebo, at a dose of 120 mg for subjects with a body weight ≥60 kg or at a dose of 60 mg for subjects with a body weight <60 kg according to Table 2 below. A blinded interim analysis will be performed and data reviewed by the SRT once ≥5 adolescent NTDT subjects have completed the study Week 8 visit. For the purpose of the safety review in Cohort II, randomisation algorithm should ensure that the first 5 subjects in Cohort II will match a 2:2:1 distribution to receive either 60/120 mg VIT-2763 QD or BID or matching placebo. Remaining adolescent NTDT subjects who have been screened and/or enrolled into Cohort II at the time of the interim analysis will continue in the study, whilst the enrolment of new subjects in the study will be suspended until after the SRT has reviewed the blinded safety and tolerability data of the first 5 adolescent subjects and has been given the recommendation to continue the enrolment of adolescent subjects (enrolment hold). Composition, and roles and responsibilities of the SRT will be detailed in an SRT charter. The SRT consists at a minimum of the Co-ordinating Investigator, 2 independent haematologists, Vifor Medical Monitor, and the Vifor Drug Safety Representative or their designee.
Duration:	The study comprises a non-treatment screening period of up to 4 weeks (28 days), a 12-week (84 days) treatment period and a safety follow-up period of 4 weeks (28±4 days) according to Figure 1.
Treatment:	**Active Treatment** Capsules of 1 dosage strength of VIT-2763 (60 mg) will be available. Capsules (VIT-2763) will be administered orally accordingly to achieve the specified dose and according to Table 2. **Placebo Treatment** Matching placebo capsules to VIT-2763 will be available, administered orally and according to Table 2. **Administration Schedule** Randomisation to all dosage groups will be done by using a validated centralised procedure (interactive web response system (IWRS)). Randomisation to active treatment groups will be done based on 2 body weight range groups (see Table 2).

[redacted]

Dose Regimens Based on Body Weight at Screening

Subject Body Weight at Screening (kg)	Dose Schedule (mg VIT-2763 or Placebo)			
	Adults (Morning-Evening Dose)	**Adolescents (Morning-Evening Dose)**	**TDD**	**TDD/kg Body Weight (Min-Max)[1]**
40-59	60-placebo	60-placebo	60	1.0-1.5
	60-60	60-60	120	2.0–3.0
	Placebo-placebo	Placebo-placebo	N/A	N/A
60-100	120-placebo	120-placebo	120	1.2-2.0
	120-120	120-120	240	2.4-4.0
	Placebo-placebo	Placebo-placebo	N/A	N/A

1 Estimated total daily dose/kg body weight range based on individual plasma pharmacokinetic parameters versus dose level/body weight obtained from human Phase 1 study.
Notes: N/A=Not applicable; TDD=Total daily dose.

All treatments will be administered either at the study site in the context of study visits, or by the subjects at home from Day 1 to Day 84.

The study medication (VIT-2763 and/or matching placebo) will be administered for all subjects twice a day to maintain the blind, in the morning and in the evening.

Capsules (VIT-2763 and/or matching placebo) will be administered approximately 1 hour after meals at the same clock time (between 08:00 and 10:00 am for the morning dose, and between 20:00 and 22:00 pm for the evening dose, respectively). Food intake, except for water ad libitum, should be avoided for at least 1 hour prior to and 1 hour after the morning and evening dose administration.

Inclusion Criteria:

1. Documented diagnosis of NTDT, including a β-thalassaemia intermedia-phenotype.
2. NTDT is defined as subjects having received <5 units of red blood cells (RBCs) during the 24-week period prior to randomisation/first drug administration of VIT-2763 or placebo (Day 1; 1 unit is defined as 200 to 350 ml of transfused packed RBCs and last RBC transfusion must have been received ≥14 days prior to randomisation).

   Note: Subjects who are supposed to receive RBC transfusions after randomisation in the Investigator's opinion, and according to local practise, and having received at least 1 dose of VIT-2763, may be considered to stay on study treatment for safety reasons, and in case there are no tolerability concerns. Subjects will be censored for secondary efficacy.
3. Male and female adult* NTDT subjects, 18-65 years of age inclusive (Cohort I only) at time of screening.

[redacted]

	* Following section in italics is applicable for dedicated Thailand site(s) as per local site Ethics Committee (EC)/Institutional Review Board (IRB) guidance: *3. Male and female adult NTDT subjects, 20-65 years of age inclusive (Cohort I only) at time of screening.* 4. Male and female adolescent* NTDT subjects, 12-17 years of age inclusive (Cohort II only) at time of screening. * Following section in italics is applicable for dedicated Thailand site(s) as per local site EC/IRB guidance. *4 Male and female adolescent NTDT subjects, 12-19 years of age inclusive (Cohort II only) at time of screening.* 5. Subjects must have a mean baseline haemoglobin (Hb) ≤11 g/dl, based on at least 2 consecutive measurements ≥1 week apart within 6 weeks prior to randomisation/baseline. Note: If obtained Hb values show more than 10% relative difference and more than 1.0 g/dl absolute change between the highest and lowest value, the subject must be excluded. If there is 1 retrospective Hb value available for the subject at maximum of 2 weeks prior to screening (Day -28), the Hb value can be taken into consideration. A subject not meeting this criterion would be excluded but can be rescreened at maximum 2 times at a later time point. 6. Ability to understand the requirements of the study and abide by the study restrictions, and agreement to return for the required assessments. 7. Ability to swallow a capsule Size 0, to be assessed during the screening visit. 8. Subject and/or legally acceptable guardian has provided the appropriate written informed consent/assent. Subject and/or legally acceptable guardian must provide written informed consent/assent before any study specific procedures are performed including screening procedures, see Section 13.2. 9. Female subjects of childbearing potential, must have a negative pregnancy test at screening, 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). Female subjects must agree to use adequate contraception during the study and for 1 month after the last dose of study medication 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, intra-uterine 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 by the male partner; the condom should then be used together with a spermicide or adequate and approved alternatives.

	10. Male subjects must practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, and for at least 1 month (sufficiently exceeding 5 times the mean $t_{1/2}$ of VIT-2763 based on multiple dose human PK data) following investigational product discontinuation, even if he has undergone a successful vasectomy.
Exclusion Criteria:	Note: Assessment of Laboratory parameters and other baseline characteristics apply at screening Visit V1, if not indicated otherwise. 1. Documented diagnosis of transfusion dependent thalassaemia (TDT), including a beta-thalassaemia major phenotype (including β0/β0, β+/β+, β0/β+ genotype), and mixed compound heterozygous for sickling phenotype variants such as Hb S/β-thalassaemia, or transfusion dependent non-deletional Hb H disease (i.e., Hb constant spring) or Hb C disease. 2. Subjects on concomitant iron chelation therapy (ICT) or subjects on prior ICT which was discontinued less than 4 weeks prior randomisation. Note: If ICT was discontinued >4 weeks prior randomisation the subject is eligible. 3. Subjects with either serum ferritin <150 ng/ml or a documented LIC ≤1.5 mg/g liver dry weight assessed through MRI. Note: If documented LIC MRI scans retrieved within 24 months prior to randomisation are not available per local practice, serum ferritin will be used only to document iron overload status. 4. Subjects with TSAT <30%. 5. Subjects with documented LIC >15 mg/g liver dry weight assessed through MRI, or a documented myocardial T2-star (T2*) <20 ms, if available per local practise and retrieved within 24 months prior to randomisation. 6. Adult or adolescent subjects with body weight <40.0 kg or >100 kg at screening. 7. Chronic liver disease and/or alanine transaminase (ALT), aspartate transaminase (AST) or gamma-glutamyl transpeptidase (GGT) above 3-fold the upper limit of normal (ULN) range at screening. Note: A subject fulfilling this criterion will be excluded but can be rescreened at a later time point (in order to fulfil eligibility, ≥2 values within ≥1 week should be assessed and be within eligibility limits). 8. Estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 (according to chronic kidney disease classification Stage 4 or higher), and/or significant albuminuria >30 mg/mmol. eGFR should be estimated according to Chronic Kidney Disease Epidemiology Collaboration formula (CKI-EPI) in adults, and Schwartz formula in adolescents. 9. Newly diagnosed folate deficiency anaemia and/or Vitamin B_{12} megaloblastic anaemia. Subjects with known folate deficiency anaemia and/or Vitamin B_{12} megaloblastic anaemia who are on ≥12 weeks stable replacement therapy are eligible. Note: A subject fulfilling this criterion will be excluded but can be rescreened at a later time point.

	10. Any history or clinically important finding of cardiac disorders, such as clinically relevant cardiac arrhythmia, cardiomyopathy, coronary disease, valve disorder, or heart failure according to New York Heart Association classification 3-4. 11. Subjects with history of partial or total splenectomy within 6 months prior to screening. 12. 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). 13. Known history, and/or positive result on screening for hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV), hepatitis C virus (HCV) or HIV infection, or AIDS. Note: Subjects with known HBsAg positivity and/or anti-HCV antibody positivity will be allowed to participate only if the disease has been treated efficiently/is not active. 14. Any infection requiring hospitalisation or intravenous antimicrobial therapy within 6 months prior to randomisation, or any infection requiring antimicrobial therapy in the 2 weeks prior to randomisation. 15. Use of any prohibited medication(s) as per protocol section "Prohibited Therapy and Concomitant Treatment", including but not limited to: • Prior or concomitant use of any medication that is known to prolong the QT/QTc interval or the PR/QRS interval, within 3 weeks prior to screening or during the treatment phase and until end of study (EOS). • Previous treatment with activin receptor ligand traps (e.g., luspatercept, sotatercept) or JAK2 inhibitors (e.g., ruxolitinib) in the 24 weeks prior to randomisation. • Initiation of previous hydroxyurea treatment <6 months prior to randomisation, and previous erythropoietin stimulating agent (ESA) treatment in the 12 weeks prior to randomisation, or any prior gene therapy. Note: Concomitant hydroxyurea treatment with stable doses ≥6 months is allowed. • Previous iron therapy as of 4 weeks prior to screening and until EOS. • Any investigational drug, as of 30 days prior to screening and until EOS. 16. Known sensitivity to any of the components of the study medication to be administered. 17. Participation in any other investigational medicinal device or drug study within 30 days prior to screening. 18. Pregnant (e.g., positive pregnancy test) or currently breastfeeding females. 19. History of drug or alcohol abuse within 2 years prior to screening, positive screen for drug abuse or alcohol at screening.

	20. History or concomitant solid tumours and/or haematological malignancies unless resolved in the ≥5 past years. Basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, incidental histologic finding of prostate cancer (T1a or T1b according to the Classification of Malignant Tumours clinical staging system). 21. 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. Note: A subject tested positive using nucleic acid amplification testing, antigen or antibody detection for SARS-CoV-2 test within 2 weeks preceding screening or during screening will be excluded but can be rescreened once at a later time point as per Investigator's judgement and if confirmation of a negative SARS-CoV-2 test is being available based on standard of care. 22. 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. 23. Any employee or their close relatives of Vifor Pharma Group, or of the Contract Research Organisation (CRO) involved or of a study site involved in the study.
Primary and Secondary Endpoints:	<u>Primary Safety Endpoints</u>: • Reported or observed adverse events (AEs): by system organ class (SOC) and preferred term (PT) (Medical Dictionary for Regulatory Activities (MedDRA) coded term), by severity and relation to study product in each treatment group. • Reported or observed serious adverse events (SAEs): by SOC and PT MedDRA coded term, by severity and relation to study product in each treatment group. • Changes in vital signs (blood pressure and pulse rate), clinical laboratory safety tests (haematology, serum biochemistry, coagulation, and urinalysis), 12-lead electrocardiogram (ECG), and physical examination findings. <u>Secondary Endpoints</u>: • Assessment of iron parameters (total serum iron, serum ferritin, serum transferrin, calculated transferrin saturation (TSAT), from baseline over a 12-week period (absolute and change from baseline)). • PK parameters: Sparse sampling for determination of VIT-2763 plasma concentration following multiple dosing will be obtained from pre-dose trough to 3 hours or 4 hours post-dose at selected study visits. A population PK approach in adult and adolescent subjects will be applied to estimate PK parameters (C_{max}, clearance, distribution volume, area under the curve (AUC)).

[redacted]

[redacted]

- Only in subjects who consent in writing to provide blood samples for biomarkers and genotyping, whole blood samples will be taken and stored for later determination of biomarkers and genotyping. The biomarker and pharmacogenetic endpoints will be defined at a later time point, taking into account further scientific and clinical data.

[redacted]

Procedures:	See Table 1 for full details of protocol required procedures and applicable visits (and timings of each visit). **Screening Visit V1 (Day -28 to Day -1)** Screening Visit V1 – performed in-hospital: • Subjects who have a documented diagnosis of β-thalassaemia intermedia or (mixed) variants according to inclusion criteria will be screened to determine potential eligibility to participate in the VIT-2763-THAL-201 trial. • The Investigator will obtain written informed consent/assent from potentially eligible subjects and/or legally acceptable guardian before any trial related procedure is performed. In case of extraordinary events (e.g., COVID-19 pandemic) it is acceptable to have the informed consent via e-mail, SMS or a verbal consent (a witness is required) if allowed per local country guidance. Written consent has to be provided as soon as possible and must be properly recorded in the source documentation.

[redacted]

	• As of the date of informed consent for each subject, the sites will document in the electronic Case Report Form (eCRF) all AEs and changes/additions made to concomitant medications. SAEs will be reported as they occur but no later than 24 hours after the Investigator's awareness of the event. • Subject demographics and baseline characteristics will be assessed according to Table 1, including medical/medication history, physical examination, vital signs, weight and height. • A single 12-lead ECG will be conducted, and the ECG print-out will be filed. • A blood test will be drawn, which will be analysed centrally, to determine if the subject is eligible according to the main inclusion and exclusion criteria. The main assays to be performed in order to assess eligibility are: Hb, serum ferritin. In addition, other clinical biochemistry, haematology, clotting parameters will be taken from the same blood draw. Date and time of blood draw will be documented in the eCRF. In addition the results from urinalysis parameters and urine drug and alcohol screen will be assessed locally and reported in the eCRF. • During the same blood draw, a serum pregnancy test will be taken for females of childbearing potential. • A serology test will be conducted to determine HBsAg, HBV, HCV, HIV. **Screening Visit V2 (Day -15±3 Days, Optional)** Screening Visit V2 – performed in-hospital (optional): • If a subject did fulfil the main inclusion criteria and did not meet exclusion criteria observed from the Visit V1, they may be asked to attend a second screening Visit V2 in order to determine the Hb level. If for logistical reasons the subject may not be able to attend the Visit V2, the V1 screening Hb value in conjunction with a historical Hb value obtained at maximum 2 weeks prior to screening (Day -28), or an additional Hb value taken prior to randomisation can be assessed. • In addition, other eligibility criteria including changes in AEs and changes/additions made to concomitant medications will be re-assessed and it will be determined whether the subject is still eligible. • In case there is no retrospective Hb value, it is allowed to schedule an optional screening visit V2 and baseline V3 the same day providing that local Hb result can be obtained on the day of combined V2/V3 visit and that there should be at least 1 week between screening Visit V1 and the combined V2/V3 visit. If V2 andV3 are done the same day, site should only complete V3 in electronic data capture (EDC). **Screening Visit V3 (Baseline, Day 1)** Screening visit V3 – Performed In-hospital • If a subject did fulfil the main inclusion criteria and did not met the exclusion criteria observed from the Visits V1 and V2, they will be asked to attend baseline Visit V3. The Investigator will perform/complete the baseline procedures/assessments as shown in Table 1.

- To accommodate local hospital practice, the subject may attend the V3 visit either at the day of the first dose of study treatment, or the day before the planned randomisation day. Note that a planned overnight stay prior study treatment administration does not fulfil the criteria of an SAE unless there is a medical reason for doing this.
- Eligibility criteria including changes in AEs and changes/additions made to concomitant medications will be re-assessed and it will be determined whether the subject is still eligible.
- Determination of Hb levels will be processed locally. Subjects must have a mean baseline Hb ≤11 g/dl, based on at least 2 consecutive measurements ≥1 week apart within 6 weeks prior to randomisation/baseline.

  Note: If obtained Hb values show more than 10% relative difference and more than 1.0 g/dl absolute change between the highest and lowest value, the subject must be excluded
- In addition, for female subjects of childbearing potential, the urine pregnancy test must be negative.
- Further safety laboratory blood draws, as well as PD biomarkers and a urine sample will be taken according to Table 1.
- A baseline PK sample for determination of VIT-2763 concentrations will be taken.
- 12-lead ECG.
- Only in subjects who consent in writing to provide blood samples for biomarkers and genotyping, whole blood samples will be taken and stored for later determination of biomarkers and genotyping.

[redacted]

Randomisation and Administration of the First Dose of Study Treatment

- Upon completion of the baseline visit procedures/assessments, eligible subjects will be randomised using a validated centralised procedure (IWRS) to receive VIT-2763 or placebo according to the randomisation scheme (Cohort I and II).
- The first dose of study treatment must be administered on the same day as randomisation.

[redacted]

- The medication (VIT-2763 or placebo) will be administered in the morning in conjunction with water approximately 1 hour apart from meals between 08:00 to 10:00 a.m. Subjects are asked to stay in the hospital until up to 4 hours post administration at selected visits. To maintain the BID dosing schedule, i.e., after having received a dose in the morning at the hospital, the subjects will be advised in taking the study medication in the evening approximately 1 hour apart from meals and with water at approximately the same clock time each day between 8:00 p.m. and 10:00 p.m. in the evening. Subjects will receive study medication for home intake until the next visit.

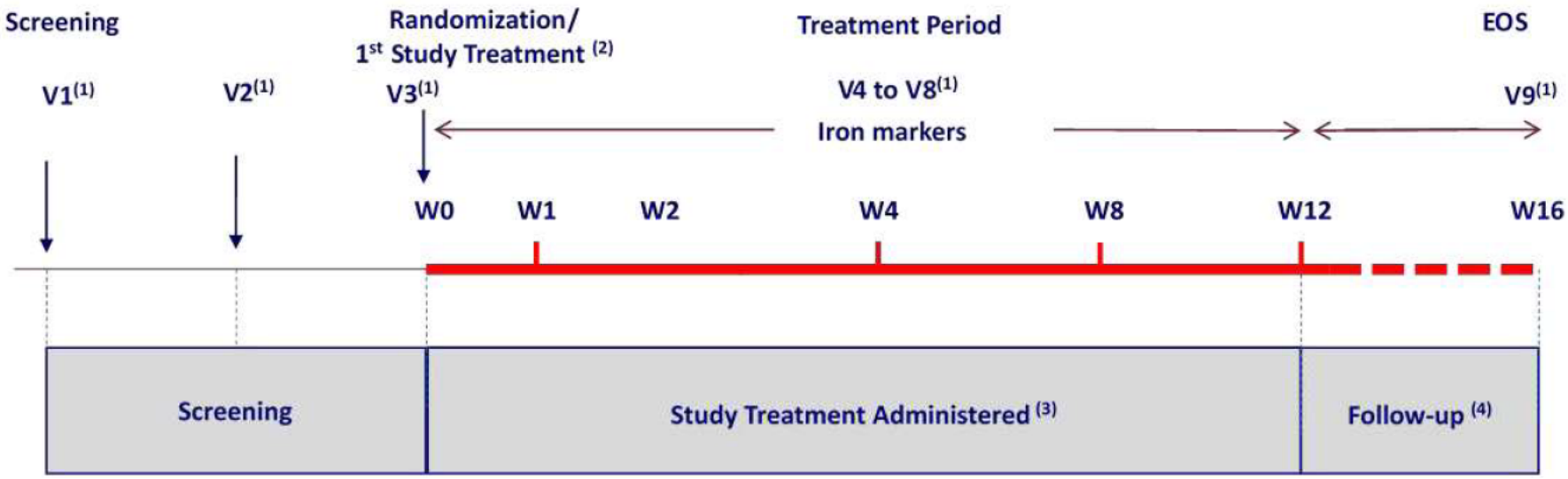
Visits V4 to V8 (or Early Discontinuation)

- Subjects will return to the out-patient clinic at 1 (±1 day), 2 (±2 days), 4 (±3 days), 8 (±3 days) and 12 weeks (±3 days) after randomisation.
- If a subject cannot return to the site for a study visit due to COVID-19 pandemic, the Investigator will conduct a remote visit (e.g., telemedicine, phone call), a visit at the subject's home, or in facilities near to the subjects' home to evaluate subject safety and eligibility to continue the study therapy, if applicable and as per local country guidance.
- During the out-patient clinic visits, the Investigator will perform the procedures/assessments as shown in Table 1 for the respective visit.
- [redacted]
- At Weeks 1 (Visit 4), 2 (Visit 5), 4 (Visit 6), 8 (Visit 7) and 12 (Visit 8) an additional blood test will be performed and analysed locally for the assessment of Hb levels and will be documented in the eCRF. In addition, a urine pregnancy test will be drawn.
- For female subjects of childbearing potential, dosing will only be done for whom the urine pregnancy test is negative.
- After procedures/assessments are performed, the morning dose (VIT-2763 or placebo) will be administered in conjunction with water approximately 1 hour after meals between 08:00 to 10:00 a.m.
- At the remote/home visits the Investigator should at minimum perform the following: evaluation of the subject's general condition, collection of information on any new and ongoing adverse events, collection of information on the investigational medicinal product (IMP) intake and concomitant medications use. Scheduled urine samples may be collected at a home visit, or in laboratories near to the subject's home and should be processed locally. Scheduled blood samples may also be collected at home visit or laboratories near subject's home and sent to the central laboratory if possible, otherwise processed locally. Safety analyses such as haematology panel (RBC, Hb, haematocrit, mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration, white blood cell count with differential, platelets count), coagulation (prothrombin time, activated partial thromboplastin time, thrombin time) and liver function tests (ALT, AST, GGT total bilirubin, alkaline phosphatase) should be done at the minimum.

	Follow-up Visit V9 (EOS) • All subjects, whether completing the treatment or who have withdrawn prematurely, will be followed up 4 weeks (28±4 days) after their last administration of study treatment to collect any new AEs and concomitant medications. This visit may be conducted by telephone call or as an in-clinic visit. **Study Committees and Trial Oversight** • A Steering Committee (SC) and an SRT, will be established for this trial. The SC will ensure the scientific integrity of the trial in addition to overseeing the operational conduct. The SRT will be constituted to oversee the safety of study participants by assessing blinded preliminary efficacy and AE data and to make recommendations to enrol adolescent NTDT subjects into Cohort II. Predefined interim analyses steps will be employed in order to assess safety and preliminary efficacy data in a blinded fashion in regards to active or placebo for NTDT adult and adolescent subjects.
Sample Size:	This is a Phase 2a study of VIT-2763 in adult and adolescent NTDT subjects, therefore no formal sample size calculation was conducted. A total of approximately 36 subjects are planned to be randomised in order to have up to 30 male and female adult and/or adolescent NTDT subjects completing the trial. Based on an anticipated drop-out rate of approximately 20%, it is estimated that approximately 6 subjects will be additionally enrolled. Eligible subjects will be randomised to either VIT-2763 or matching placebo using a validated centralised procedure (IWRS) that automates the random assignment of treatment groups to randomisation numbers.
Study Sites:	NTDT subjects will be screened and randomised from approximately 20 study sites globally.
Statistical Methods:	There will be up to 2 blinded interim analyses during the trial as described in Section 12.10. The primary endpoint will be calculated based on the full analysis set (FAS). All secondary and other exploratory endpoints will be analysed on the FAS and per-protocol set (PPS) and presented descriptively. Concerning the safety data, the total number of events and number (%) of subjects with events will be presented by MedDRA SOC and PT by treatment group. 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). In addition, preliminary exploratory graphical analyses will be done to assess the potential relationship between VIT-2763 exposure (PK) and PD endpoints.

[redacted]

Figure 1 Flow Chart – Adults (Cohort I) and Adolescents (Cohort II)



1 Performed in-hospital. Optional Visit 2 in order to determine the Hb level. If for logistical reasons the subject may not be able to attend Visit V2, the screening Hb value in conjunction with a historical Hb value obtained at maximum 2 weeks prior to screening, or an additional Hb value taken prior to randomisation can be assessed. V9 may be conducted by telephone call or as an in-clinic visit.
2 Randomisation: Adult subjects will be randomised in an 8:8:4 ratio to receive either VIT-2763 QD or BID or placebo. Adolescent subjects will be randomised in a 4:4:2 ratio to receive either VIT-2763 QD or BID or placebo. Allocation to dosing will be performed according to Table 1.
3 A first blinded interim analysis will be performed and the data reviewed by a SRT once ≥10 adult subjects have completed the study Week 8 visit. For the purpose of the safety review in Cohort I, the randomisation algorithm should ensure that the first 10 subjects in Cohort I will match a 4:4:2 distribution to receive either 60/120 mg VIT-2763 QD or BID or matching placebo. A second blinded interim analysis will be performed and data reviewed by the SRT once ≥5 adolescent NTDT subjects have completed the study Week 8 visit. For the purpose of the safety review in Cohort II, randomisation algorithm should ensure that the first 5 subjects in Cohort II will match a 2:2:1 distribution to receive either 60/120 mg VIT-2763 QD or BID or matching placebo.
4 All subjects, whether completing the treatment or who have withdrawn prematurely, are asked to attend a follow-up visit 4 weeks (28±4 days) after their last administration of study treatment to collect any new AEs and concomitant medications. This visit may be conducted by telephone call or as an in-clinic visit.

Notes: AE=Adverse event; BID=Twice daily; EOS=End of study; Hb=Haemoglobin; NTDT=Non-transfusion dependent thalassaemia; QD=Once daily; SRT=Safety Review Team.

[redacted]

Table 1 Schedule of Events

Visit	Screen V1	Screen V2	Baseline V3	V4 Week 1	V5 Week 2	V6 Week 4	V7 Week 8	V8 Week 12/ EOT	FUP V9 Week16/ EOS
Study Day	**-28 to -1**	**-15 (Optional)[16]**	**1**	**7**	**14**	**28**	**56**	**84**	**112**
Visit Windows	**N/A**	**±3**	**N/A**	**±1**	**±2**	**±3**	**±3**	**±3**	**±4**
Informed consent	X[17]								
(Review of) eligibility criteria	X	X	X[1]						
Demographics	X								
Medical/medication history	X	X	X						
Physical examination[2]	X		X					X	
Body weight and height	X							X (weight)	
Vital signs (blood pressure, pulse rate)	X		X	X	X	X	X	X	
Single 12-lead ECG	X		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	
Safety and Haematology Laboratory									
Haematology[4], biochemistry[4]	X		X	X	X	X	X	X	
Coagulation	X		X			X		X	
Serum ferritin, TSAT[4]	X								
Urinalysis (pH, protein, glucose, ketone, blood, spot urine for protein/ creatinine and albumin/creatinine ratio)	X		X	X	X	X	X	X	
Urine drug screen, alcohol	X								
Pregnancy test[5]	X[5]		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	
Serology (HBsAg, HBV, HCV, HIV)	X								
PD iron and [redacted]			[redacted]						

[redacted]

Visit	Screen V1	Screen V2	Baseline V3	V4 Week 1	V5 Week 2	V6 Week 4	V7 Week 8	V8 Week 12/ EOT	FUP V9 Week16/ EOS
Study Day	**-28 to -1**	**-15 (Optional)[16]**	**1**	**7**	**14**	**28**	**56**	**84**	**112**
Visit Windows	**N/A**	**±3**	**N/A**	**±1**	**±2**	**±3**	**±3**	**±3**	**±4**
Haemoglobin local[9]		X	X	X	X	X	X	X	
VIT-2763 PK[10]			X			X	X	X	
[redacted]									
Adverse events	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Study drug dispensation			X	X	X	X	X		
Study drug administration[12]			X	X	X	X	X	X	
Study drug accountability				X	X	X	X	X	
[redacted]									

1 Any outstanding criteria not available on Day -15 (screening Visit 2) 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 At 2-3 hours post-administration post-morning dose.
4 [redacted] Biochemistry sample including electrolyte status (sodium, potassium, magnesium, calcium, chloride), total bilirubin, urea, uric acid, creatinine, total protein, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, glutamate dehydrogenase, lactate dehydrogenase, haptoglobin, amylase, bicarbonate, unconjugated bilirubin, creatine phosphokinase, folic acid, Vitamin B_{12}, albumin, glucose, total cholesterol, and triglycerides. Clotting: prothrombin time, activated partial thromboplastin time, thrombin time. Serum ferritin, serum iron, unsaturated iron binding capacity, calculated transferrin saturation (screening visit only); all parameters will be assessed centrally.
5 For female subjects only; beta-human chorionic gonadotropin in serum at screening and V8 (Samples will be derived from serum biochemistry tube); in urine at baseline and all other visits.
6 PD measurements include serum iron, serum ferritin, serum transferrin, unsaturated iron binding capacity, calculated transferrin saturation, [redacted] will be assessed centrally. Samples will be collected on Visits 3 to 8 approximately 2 hours post-dose
7 [redacted]
8 [redacted]
9 Haematology sample to assess Hb will be taken locally at study site and results must be available at day of dosing (sample at optional Visit V2).
10 PK samples will be collected on Visit 3 and Visit 7 at pre-dose trough and at approximately 1 hour and 4 hours post-dose, and on Visits 6 and 8 at pre-dose trough and approximately at 1 hour and 3 hours post-dose.
11 [redacted]

[redacted]

12 Administered in the morning approximately between 08:00 a.m. and 10:00 a.m., first morning dose administered in the hospital on Day 1, and at all Visits V4-V8; self-administration (morning and evening) at home for the whole study period at non-study visits, from Day 2 to Day 84. Food intake, except for water, to be avoided for at least 1 hour prior to and post dosing. Study drug accountability will be performed at V4-V8

13 [redacted]

14 Liver iron concentration (mg/g dry weight) in adult NTDT subjects to be assessed, in subjects who have given their informed consent. [redacted]

15 [redacted]

16 In case there is no retrospective Hb value, it is allowed to schedule optional screening visit V2 and baseline V3 the same day providing that local Hb result can be obtained on the day of combined V2/V3 visit and that there should be at least 1 week between screening Visit V1 and the combined V2/V3 visit. If V2 and V3 are done the same day, site should only complete V3 in EDC.

17 In case of extraordinary events (e.g., COVID-19 pandemic) it is acceptable to have the informed consent via e-mail, SMS or a verbal consent (a witness is required), if allowed per local country guidance. Written consent has to be provided as soon as possible and must be properly recorded in the source documentation.

Notes: ECG=Electrocardiogram; EDC=Electronic data capture; EOS=End of study; EOT=End of treatment; [redacted] FUP=Follow-up; [redacted] factor; Hb=Haemoglobin; HBsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; HCV=Hepatitis C virus; [redacted] N/A=Not applicable; [redacted] NTDT=Non-transfusion dependent thalassaemia; PD=Pharmacodynamic; PK=Pharmacokinetic; [redacted]

[redacted]

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LIST OF ABBREVIATIONS

[redacted]

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
BID	Twice daily
C_{avg}	Average concentration at steady state
[redacted]	
COVID-19	Coronavirus disease of 2019
C_{max}	Maximum concentration
CRO	Contract Research Organisation
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of study
EPO	Erythropoietin
[redacted]	
ESA	Erythropoietin stimulating agent
[redacted]	
FAS	Full analysis set
FPN	Ferroportin
[redacted]	
GGT	Gamma-glutamyl transpeptidase
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen

[redacted]

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High density polyethylene
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICT	Iron chelation therapy
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IWRS	Interactive web response system
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NTBI	Non-transferrin bound iron
NTDT	Non-transfusion dependent thalassaemia
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per-protocol set
PRO	Patient Reported Outcome
PT	Preferred term
q12h	Every 12 hours
QD	Once daily
QoL	Quality of life
RBC	Red blood cells
[redacted]	
RSI	Reference Safety Information

SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAP	Statistical Analysis Plan
SC	Steering Committee
[redacted]	
SOC	System organ class
SRT	Safety Review Team
SS	Safety set
sTFR	Soluble transferrin receptor
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach maximum concentration
TSAT	Transferrin saturation
ULN	Upper limit of normal

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 low molecular weight molecule, which has been identified by Vifor Pharma as ferroportin (FPN) inhibitor and hepcidin-mimetic.

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, it 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 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]. Secondary causes for iron overload are thalassaemia, other inherited or acquired anaemias, myelodysplastic syndrome, chronic liver diseases, transfusions, and haemodialysis [5].

Inherited Hb disorders, including thalassaemia and sickle-cell disease, are the most common monogenic diseases worldwide. Several clinical forms of α-thalassaemia and β-thalassaemia, including the co-inheritance of β-thalassaemia with Hb E resulting in Hb E/β-thalassaemia, have been described. The disease hallmarks include imbalance in the α/β-globin chain ratio leading to ineffective erythropoiesis, chronic haemolytic anaemia, compensatory haemopoietic expansion, hypercoagulability, and increased intestinal iron absorption. Subjects with β-thalassaemia have been typically categorised as minor, major, or intermedia on the basis of their α-globin or β-globin gene lesions, α-globin or β-globin chain imbalance, severity of anaemia, and clinical picture at presentation [6]. The underlying disease process in subjects with thalassaemia remains similar for those subjects categorised as having NTDT or transfusion dependent thalassaemia, and the role of transfusion therapy in ameliorating much of these pathogenic mechanisms [6]. NTDT subjects usually do not require lifelong regular transfusions for survival, although they may require occasional or even frequent transfusions in certain clinical settings and for defined

periods of time. NTDT encompasses 3 clinically distinct forms: β-thalassaemia intermedia, Hb E/β-thalassaemia (mild and moderate forms), and α-thalassaemia intermedia (Hb H disease) [7].

In NTDT, erythropoiesis is ineffective due to the imbalance in the production of α- and β-globin chains. Unstable globin chain tetramers precipitate and undergo oxidation into methaemoglobin and haemichromes with eventual separation of haem from globin. The free iron released from haem disintegration in thalassaemia erythroid cells eventually catalyses the formation of reactive oxygen species, which lead to oxidation of membrane proteins, structural membrane defects, and exposure of red cell senescence antigens like phosphatidylserine causing premature cell death within the bone marrow (ineffective erythropoiesis) or peripheral circulation (haemolysis) [8].

The availability of blood transfusion and iron chelation strategies for subjects with severe forms of β-thalassaemia now allow long-term disease control and improved QoL. Moreover, advances in haematopoietic stem cell transplantation techniques have provided a potentially curative option for some subjects. Despite important improvements in the management of β-thalassaemia, there are still many challenges to overcome before global disease control is achievable. Additionally, the convenience of administration and cost of most available therapies for this chronic disease remain challenging [9].

In the context of pharmacological treatment of ineffective erythropoiesis, there is increasing interest in applying iron restriction, paradoxically to improve the effectiveness of erythropoiesis in thalassaemia syndromes. Animal models have shown that by restricting iron delivery to the thalassaemic erythron, Hb in thalassaemic mice could be improved, which in turn decreased iron delivery to normoblasts, thereby decreasing haeme synthesis, decreasing haemichrome formation, and hence decreasing reactive oxygen species-mediated oxidative stress and apoptosis [10].

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 iron loading anaemias and thalassaemia. Since no FPN inhibitors or hepcidin-mimetic drugs are yet available for the treatment of such conditions, 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

[redacted]

VIT-2763 is an inhibitor of the iron exporter FPN, and thus acts as a hepcidin-mimetic. 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. [redacted]

The ineffective erythropoiesis in thalassaemia causes iron over-absorption, due to feedback compensatory responses to the ineffective erythropoiesis [8] and to subsequent hypoxia [11], which both suppress hepcidin. Since the abnormally high iron levels that result from the reduction of hepcidin further impair erythropoiesis, anaemia and iron overload are worsened in a vicious circle [2]. Because VIT-2763 is not affected by these mechanisms, it may effectively substitute for hepcidin and prevent iron overload.

The nonclinical studies found that VIT-2763 inhibits FPN in all relevant cell types, including macrophages supplying iron to developing erythroid precursors in bone marrow and spleen. By limiting the availability of iron for erythropoiesis, VIT-2763 decreases the membrane alpha-globin aggregates (haemichromes) in developing erythrocytes, thereby improving their survival, increasing Hb, and interrupting the vicious pathophysiological circle in thalassaemia.

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.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.2.3 Summary of Completed Clinical Studies

A Phase 1 study in healthy subjects 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.

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 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 means of the 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 7-day treatment with oral doses of 60 mg QD, 120 mg QD, 60 mg q12h and 120 mg q12h were well tolerated by healthy male and female subjects. 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.

PK analyses revealed that the initial oral absorption of VIT-2763 was relatively fast, most subjects had detectable levels already at 15-30 minutes post-dose and T_{max} for VIT-2763 ranged from 0.50 hours to 3 hours post-dose. A second peak or shoulder in the concentration time profile was observed around 3-4 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 q12h 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 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 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 EPO and serum sTFR levels on both Day 1 and Day 7.

2. RATIONALE

2.1 Rationale to Investigate the Effects of VIT-2763 on Iron Restricted Erythropoiesis

The first-in-human study in male and female healthy volunteers study demonstrated based on the mechanism of action of the hepcidin-mimetic VIT-2763, a temporary decrease in serum iron levels following administration of VIT-2763. The effect was accompanied by temporarily increased serum hepcidin levels following the highest single dose levels of 60 mg, 120 mg and 240 mg VIT-2763, and following all multiple dose levels of VIT-2763. Single and multiple oral VIT-2763 doses showed overall a favourable safety profile and were well tolerated by healthy male and female subjects.

Nonclinical studies with VIT-2763 showed improved anaemia, extended the life-span of RBCs, and prevention of iron loading. Additionally, amelioration of ineffective erythropoiesis, myelopoiesis and splenomegaly in th3/+ mice, a murine thalassaemia disease model, could be shown. Administration of mini-hepcidins, short peptides that mimic the activity of endogenous hepcidin, improved ineffective erythropoiesis, anaemia, and iron overload in thalassaemic mice [8,12]. Several clinical trials are currently planned in NTDT patients investigating the effect of hepcidin or mini-hepcidins on TSAT, NTBI and hence erythropoiesis control. Secondary effects on iron uptake by myocardium are also under investigation [9].

2.2 Study Design Rationale

This is a randomised, double-blind, placebo-controlled parallel group trial. The 12 weeks observation period following randomisation is considered appropriate to investigate the primary objective of safety and tolerability of multiple doses of VIT-2763 versus placebo in subjects with NTDT.

Subjects will be required to have received less than 5 RBC units within the preceding 24 weeks prior to randomisation, which is the current commonly agreed transfusion limit amongst thalassaemia consortia and scientific experts defining transfusion independence. Hence subjects are not expected to require RBC transfusions during a 3 months treatment schedule whilst participating in the trial, in order to maintain the subjects' usual practise of medical and/or procedural treatment.

Treatment of subjects with NTDT with a documented history of iron overload, and for short treatment period of 3 months, is justified, following the totality of evidence from the completed first-in-human study in healthy male and female subjects as well as available nonclinical pharmacology and toxicology data.

The mechanism of action for VIT-2763 is known and is likely similar for animals and humans assuming hepcidin–mimetic activity [10,12]. The pharmacodynamic effect can be easily monitored in humans by determination of iron levels and haematological parameters. Data from the completed first-in-human study revealed that oral administration of VIT-

[redacted]

2763 to healthy male and female subjects 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 humans was well tolerated with virtually no difference between active dose groups and placebo both in terms of frequency and intensity of AEs following all 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. VIT-2763 exposures following QD or BID dosing with up to 120 mg BID in subjects with NTDT are not expected to differ from exposures obtained in humans in the first-in-human study (see also Section 2.3).

In the upcoming trial it is planned to include NTDT adolescents (age ≥12 years up to 17 years, or deviating according to local country definitions, up to N=10, (Cohort II)). Enrolment of adolescent NTDT subjects will start only after relevant blinded safety and tolerability data, as well as blinded PK data in ≥10 adult NTDT subjects completed Week 8 of treatment has been received, including an initial benefit/risk review by an SRT. This will provide additional safety relevant information before treatment of adolescents will commence. VIT-2763 is expected to act in the same way in adults and children. No major differences in the PK profile of adolescents and adult humans are expected, based on the relative maturity of the metabolic system in adolescents.

[redacted]. Systemic exposure and clearance of drugs are generally similar in adolescent and adult patients after taking into account the effect of body size on PK [13] [redacted] Early start of treatment with VIT-2763 in patients with beta-thalassaemia may restrict iron to the thalassaemic erythron, may decrease iron overload associated complications and may result in normalisation of Hb levels. Therefore, children and adolescents may benefit most from treatment with VIT 2763.

Hence taking into account the relatively short period of initial drug treatment in NTDT adolescents of 3 months, including the staggered approach as the adolescent cohort will follow the evaluation of adults, the weight of evidence supports the treatment in human adolescents without additional nonclinical investigations.

[redacted]

Placebo treatment will be used in a minority of adult and adolescent NTDT patients in order to discriminate potential side-effects of active treatment from non-active treatment, [redacted] Placebo-treatment in this study does not bear an additional risk for patients, given the fact that there is no proven preventive nor effective standard treatment in NTDT patients. Hence the use of a placebo arm is considered ethically justified.

The main treatment option for most beta-thalassaemia patients is supportive care, where blood transfusions and ICT is mandated primarily for transfusion dependent thalassaemia patients. As such, NTDT patients may need transfusion therapy occasionally or for limited periods of time, especially during periods of growth and development, surgery, or pregnancy [9]. In the upcoming trial, patients will be treated for a short period of time, considering that the required period of RBC transfusions-free interval prior to and during the study is being justified and medically acceptable. Also, iron chelation naïve subjects or subjects who discontinued their regular treatment with oral iron chelators at least 4 weeks prior randomisation will be included into the study.

In case there is a need of initiation of transfusion and/or adding ICT, based on the judgement of the treating physician, patients may need to be withdrawn. In order to assess changes in the laboratory parameters, and changes of the well-being of patients randomised into the study, an SRT will be installed to protect the safety of study participants.

2.3 Selection of Doses

Two dosage strengths (5 and 60 mg) of VIT-2763 have been initially developed so far. The drug product is a hard capsule, Size 0, filled with 5 or 60 mg drug substance, intended as an immediate release oral dosage form. For this study the 60 mg capsules will be used only.

In the first-in-human study, the geometric mean C_{max} increased with dose and ranged between 52.0 ng/ml and 3,386 ng/ml over the single dose range of 5 mg to 240 mg VIT-2763.

The predefined stopping criterion of a C_{max} exceeding 3,805 ng/ml was not reached following 7 days of dosing in any of the multiple dose cohorts. At steady state on Day 7, the geometric mean C_{avg} was about 280 ng/ml after a daily dose of 120 mg VIT-2763, irrespective of the administration as 120 mg QD or 60 mg BID. On Day 7, C_{max} was 916 ng/ml for 60 mg BID and 1,480 ng/ml for 120 mg BID, indicating an increase of approximately 62% with doubling of the VIT-2763 dose. The results for safety laboratory parameters, vital signs, 12-lead ECG, telemetry and physical examination in male and female healthy volunteers showed no trends or clinically relevant changes over time. Further PK/PD exploratory analyses of the human Phase 1 data assessed the correlation between the pooled individual exposure parameters C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and $AUC_{0\text{-12}}$,

and the received dose divided by the subject's body weight. The data showed that the exposure (C_{max} and AUC) increased almost proportionally to dose and minimal accumulation was seen over 7 days repeated dosing. The majority of subjects exhibited a dose/kg body weight relation of approximate 1.7-2, corresponding to a VIT-2763 C_{max} between approximately 2,000 to 2,500 ng/ml. Individual subjects in the 240 mg single dose group reached a dose/kg body weight equation of 4 or above, associated with a C_{max} of up to 4,870 ng/ml.

The documented PD on serum and hepcidin proved the mode of action of VIT-2763 acting as a hepcidin-mimetic. Whilst increasing the dose from 60 to 120 mg appeared to increase the PD effect (serum iron AUC_{0-12}) both after single dose and repeated dose, a further increase to 240 mg/day (which related to exposures up to 4,870 ng/ml in 1 subject in the first-in-human study) did not seem to further increase the PD effect on serum iron significantly, suggesting a flat dose-response curve between 2,000 and 4,000 ng/ml. There was also no major difference between 60 mg QD or 60 mg BID VIT-2763 dosing on serum iron AUC_{0-12h} at Day 1 or Day 7, nor a major difference between 120 mg QD or 120 mg BID on serum iron AUC_{0-12h} at Day 1 or Day 7.

Adult subjects will be randomised in an 8:8:4 ratio to receive either VIT-2763 QD or BID or placebo, at a dose of 120 mg for subjects with a body weight ≥60 kg or at a dose of 60 mg for subjects with a body weight <60 kg. Accordingly, adolescent subjects will be randomised in a 4:4:2 ratio to receive either VIT-2763 QD or BID or placebo, at a dose of 120 mg for subjects with a body weight ≥60 kg or at dose of 60 mg for subjects with a body weight <60 kg, as shown in Table 2.

Table 2 Dose Regimens Based on Body Weight at Screening

Subject Body Weight at Screening (kg)	Dose Schedule (mg VIT-2763 or Placebo)			
	Adults (Morning – Evening Dose)	Adolescents (Morning-Evening Dose)	Total Daily Dose	TDD/kg Body Weight[1]
40-59	60-placebo	60-placebo	60	1.0-1.5
	60-60	60-60	120	2.0-3.0
	Placebo-placebo	Placebo-placebo	N/A	N/A
60-100	120-placebo	120-placebo	120	1.2-2
	120-120	120-120	240	2.4-4.0
	Placebo-placebo	Placebo-placebo	N/A	N/A

1 Estimated total daily dose/kg body weight range based on individual plasma PK parameters versus dose level/body weight obtained from human Phase 1 study.

Notes: N/A=Not applicable; PK=Pharmacokinetic.

[redacted]

In summary, based on the known pharmacology, nonclinical studies including repeated dose toxicity data, and the available clinical data in adult healthy male and female volunteers to date with VIT-2763, no unacceptable risk is expected for the intended doses of 60 mg or 120 mg QD or BID, administered in adult (Cohort I) and adolescent (Cohort II) NTDT subjects over a 3-month treatment duration.

[redacted]

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

- To assess the safety and tolerability of VIT-2763 versus placebo in adult and adolescent NTDT subjects over a 12-week treatment period.

3.2 Secondary Objectives

- To assess the preliminary efficacy of VIT-2763 versus placebo on iron markers in adult and adolescent NTDT subjects over a 12-week treatment period.

- To evaluate the PK of VIT-2763 in adult and adolescent NTDT subjects over a 12-week treatment period (using a population PK approach).

[redacted]

3.4 Primary Endpoint(s)

3.4.1 Primary Safety Endpoints

- Reported or observed AEs: by SOC and PT (MedDRA coded term), by severity and relation to study product in each treatment group.

- Reported or observed SAEs: by SOC and PT (MedDRA coded term), by severity and relation to study product in each treatment group.

- Changes in vital signs (blood pressure and pulse rate), clinical laboratory safety tests (haematology, serum biochemistry, coagulation, and urinalysis), 12-lead ECG, and physical examination findings.

3.5 Secondary Endpoints(s)

- Assessment of iron parameters (total serum iron, serum ferritin, serum transferrin, unsaturated iron binding capacity, calculated TSAT, from baseline over a 12-week period (absolute and change from baseline)).

[redacted]

- PK parameters: Individual estimates of C_{max}, clearance, distribution volume, AUC will be obtained using a population PK approach in adult and adolescent subjects combined with suitable mathematical/statistical analysis, using nonlinear mixed-effects modelling. Sparse sampling for determination of VIT-2763 plasma concentration following multiple dosing will be obtained from pre-dose trough to 3 or 4 hours post-dose at selected study visits.

[redacted]

- Only in subjects who consent in writing to provide blood samples for biomarkers and genotyping, whole blood samples will be taken and stored for later determination of biomarkers and genotyping. The biomarker and pharmacogenetic endpoints will be defined at a later time point, taking into account further scientific and clinical data.

[redacted]

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a Phase 2a, placebo-controlled, multiple dose, parallel group multicentre study in adult and adolescent male and female subjects with NTDT.

The study will commence with enrolment and treatment of adult NTDT subjects (Cohort I). Adult subjects will be randomised in an 8:8:4 ratio to receive either VIT-2763 QD or BID or placebo at a dose of 120 mg for subjects with a body weight ≥60 kg or at a dose of 60 mg for subjects with a body weight <60 kg.

A blinded interim analysis will be performed and the data reviewed by an SRT once ≥10 subjects have completed the study Week 8 visit. For the purpose of the safety review in Cohort I, the randomisation algorithm should ensure that the first 10 subjects in Cohort I will match a 4:4:2 distribution to receive either 60/120 mg VIT-2763 QD or BID or matching placebo. Enrolment and treatment of adult NTDT subjects into Cohort I will continue during the study until up to 30 adult and/or adolescent subjects have completed the study Week 12 visit. Remaining adult NTDT subjects will be randomised to either 60 mg or 120 mg VIT-2763 or placebo according to the body weight assessed at screening.

The SRT will make recommendations whether to enrol adolescent NTDT subjects into Cohort II.

Adolescent subjects will be randomised in a 4:4:2 ratio to receive either VIT-2763 QD or BID or placebo, at a dose of 120 mg for subjects with a body weight ≥60 kg or at dose of 60 mg for subjects with a body weight <60 kg.

A blinded interim analysis will be performed and data reviewed by the SRT once ≥5 adolescent NTDT subjects have completed the study Week 8 visit. For the purpose of the safety review in Cohort II, the randomisation algorithm should ensure that the first 5 subjects in Cohort II will match a 2:2:1 distribution to receive either 60 mg or 120 mg VIT-2763 QD or BID or matching placebo. Remaining adolescent NTDT subjects who have been screened and/or enrolled into Cohort II at the time of the interim analysis will continue in the study, whilst the enrolment of new adolescent subjects in the study will be suspended until after the SRT has reviewed the blinded safety and tolerability data of the first 5 adolescent subjects and has been given the recommendation to continue the enrolment of adolescent subjects (enrolment hold).

The SRT may also make recommendations to reduce the dose level at any given interim steps, or to unblind any subject due to safety concerns, or to stop the trial. The SRT consists at a minimum of the Co-ordinating Investigator, 2 independent haematologists, the Vifor Medical Monitor, and the Vifor Drug Safety Representative or their designee.

Study stopping rules are defined in Section 5.4.3. If any of these rules are met, no further subject must be dosed and the study will be stopped. In this event, all scheduled tests and

[redacted]

evaluations should, whenever possible, still be carried out for the subjects already enrolled. Treatment stopping rules for individual subjects are defined in Section 5.4.2.

See Table 1 for full details of protocol required procedures and applicable visits (and timings).

4.2 Duration of Subject Participation and Study

The expected duration of subject participation is a maximum of 16 weeks as of randomisation. The EOS is defined as the last subject last visit.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects

In total, approximately 36 subjects are planned to be randomised in order to have up to 30 male and female adult and/or adolescent NTDT subjects completing the trial. For the initial safety review in Cohort I, in order to keep a required 4:4:2 ratio, if 1 adult NTDT subject prematurely discontinues the study for reasons other than safety before completing the study Week 8 visit, he or she will be replaced. Accordingly, for the initial safety review of adolescent NTDT subjects in Cohort II, in order to keep a 2:2:1 ratio, if 1 adolescent NTDT subject prematurely discontinues the study for reasons other than safety before completing the study Week 8 visit, he or she will be replaced. Subjects included to replace subjects in the initial safety reviews of Cohort I and Cohort II will receive the same treatment as the subjects they are replacing.

For the remaining subjects in Cohort I and Cohort II, no additional subject(s) will be enrolled. Based on an anticipated drop-out rate of approximately 20%, it is estimated that approximately 6 subjects will be additionally randomised.

For detailed justification of the sample size please refer to Section 12.2.

5.2 Inclusion Criteria

The following inclusion criteria must be met for each subject:

1. Documented diagnosis of NTDT, including a β-thalassaemia intermedia-phenotype.

2. NTDT is defined as subjects having received <5 units of red blood cells (RBCs) during the 24-week period prior to randomisation/first drug administration of VIT-2763 or placebo (Day 1; 1 unit is defined as 200 to 350 ml of transfused packed RBCs and last RBC transfusion must have been received ≥14 days prior to randomisation).

   Note: Subjects who are supposed to receive RBC transfusions after randomisation in the Investigator's opinion, and according to local practise, and having received at least 1 dose of VIT-2763, may be considered to stay on study treatment for safety reasons, and in case there are no tolerability concerns. Subjects will be censored for secondary efficacy.

3. Male and female adult* NTDT subjects, 18-65 years of age inclusive (Cohort I only) at time of screening.

* Following section in italics is applicable for dedicated Thailand site(s) as per local EC/IRB guidance:

3. *Male and female adult NTDT subjects, 20-65 years of age inclusive (Cohort I only) at time of screening.*

4. Male and female adolescent* NTDT subjects, 12-17 years of age inclusive (Cohort II only) at time of screening.

* Following section in italics is applicable for dedicated Thailand sites(s) as per local EC/IRB guidance:

4. *Male and female adolescent NTDT subjects, 12-19 years of age inclusive (Cohort II only) at time of screening.*

5. Subjects must have a mean baseline Hb ≤11 g/dl, based on at least 2 consecutive measurements ≥1 week apart within 6 weeks prior to randomisation/baseline.

   Note: If obtained Hb values show more than 10% relative difference and more than 1.0 g/dl absolute change between the highest and lowest value, the subject must be excluded. If there is 1 retrospective Hb value available for the subject at maximum of 2 weeks prior to screening (Day -28), the Hb value can be taken into consideration. A subject not meeting this criterion would be excluded but can be rescreened at maximum 2 times at a later time point.

6. Ability to understand the requirements of the study and abide by the study restrictions, and agreement to return for the required assessments.

7. Ability to swallow a capsule Size 0, to be assessed during the screening visit.

8. Subject and/or legally acceptable guardian has provided the appropriate written informed consent/assent. Subject and/or legally acceptable guardian must provide written informed consent/assent before any study specific procedures are performed including screening procedures, see Section 13.2.

9. Female subjects of childbearing potential, must have a negative pregnancy test at screening, 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). Female subjects must agree to use adequate contraception during the study and for 1 month after the last dose of study medication 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, intra-uterine 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 by the male partner; the condom should then be used together with a spermicide or adequate and approved alternatives.

10. Male subjects must practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, and for at least 1 month (sufficiently exceeding 5 times the mean $t_{1/2}$ of VIT-2763 based on multiple dose human PK data) following investigational product discontinuation, even if he has undergone a successful vasectomy.

5.3 Exclusion Criteria

Note: Assessment of laboratory parameters and other baseline exclusionary characteristics apply at screening Visit V1, if not indicated otherwise.

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

1. Documented diagnosis of TDT, including a beta-thalassaemia major phenotype (including β0/β0, β+/β+, β0/β+ genotype), and mixed compound heterozygous for sickling phenotype variants such as Hb S/β-thalassaemia, or transfusion dependent non-deletional Hb H disease (i.e., Hb constant spring) or Hb C disease.

2. Subjects on concomitant ICT or subjects on prior ICT which was discontinued less than 4 weeks prior randomisation. If ICT was discontinued >4 weeks prior randomisation the subject is eligible.

3. Subjects with either serum ferritin <150 ng/ml or a documented LIC ≤1.5 mg/g liver dry weight assessed through MRI.

   Note: If documented LIC MRI scans retrieved within 24 months prior to randomisation are not available per local practice, serum ferritin will be used only to document iron overload status.

4. Subjects with TSAT <30%.

5. Subjects with documented LIC >15 mg/g liver dry weight assessed through MRI, or a documented myocardial T2* <20 ms, if available per local practice and retrieved within 24 months prior to randomisation.

6. Adult or adolescent subjects with body weight <40.0 kg or >100 kg at screening.

7. Chronic liver disease and/or ALT, AST or GGT above 3-fold the ULN range at screening.

   Note: A subject fulfilling this criterion will be excluded but can be rescreened at a later time point (in order to fulfil eligibility, ≥2 values within ≥1 week should be assessed and be within eligibility limits).

8. eGFR <30 ml/min/1.73 m^2 (according to chronic kidney disease classification Stage 4 or higher), and/or significant albuminuria >30 mg/mmol. eGFR should be estimated according to Chronic Kidney Disease Epidemiology Collaboration formula (CKI-EPI) in adults, and Schwartz formula in adolescents.

9. Newly diagnosed folate deficiency anaemia and/or Vitamin B_{12} megaloblastic anaemia. Subjects with known folate deficiency anaemia and/or Vitamin B_{12} megaloblastic anaemia who are on ≥12 weeks stable replacement therapy are eligible.

   Note: A subject fulfilling this criterion will be excluded but can be rescreened at a later time point.

10. Any history or clinically important finding of cardiac disorders, such as clinically relevant cardiac arrhythmia, cardiomyopathy, coronary disease, valve disorder, or heart failure according to New York Heart Association classification 3-4.

11. Subjects with history of partial or total splenectomy within 6 months prior to screening.

12. 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).

13. Known history, and/or positive result on screening for HBsAg, HBV, HCV or HIV infection, or AIDS. Note: Subjects with known HBsAg positivity and/or anti-HCV antibody positivity will be allowed to participate only if the disease has been treated efficiently/is not active.

14. Any infection requiring hospitalisation or intravenous antimicrobial therapy within 6 months prior to randomisation, or any infection requiring antimicrobial therapy in the 2 weeks prior to randomisation.

15. Use of any prohibited medication(s) as per protocol section “Prohibited Therapy and Concomitant Treatment”, including but not limited to:

    - Prior or concomitant use of any medication that is known to prolong the QT/QTc interval or the PR/QRS interval, within 3 weeks prior to screening or during the treatment phase and until EOS.

- Previous treatment with activin receptor ligand traps (e.g., luspatercept, sotatercept) or JAK2 inhibitors (e.g., ruxolitinib) in the 24 weeks prior to randomisation.

- Previous hydroxyurea treatment <6months prior to randomisation, and previous ESA treatment in the 12 weeks prior to randomisation, or any prior gene therapy. Concomitant hydroxyurea treatment with stable doses ≥6 months is allowed.

- Previous iron therapy as of 4 weeks prior to screening and until EOS.

- Any investigational drug, as of 30 days prior to screening and until EOS.

16. Known sensitivity to any of the components of the study medication to be administered.

17. Participation in any other investigational medicinal device or drug study within 30 days prior to screening.

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

19. History of drug or alcohol abuse within 2 years prior to screening, positive screen for drug abuse or alcohol at screening.

20. History or concomitant solid tumours and/or haematological malignancies unless resolved in the ≥5 past years. Basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, incidental histologic finding of prostate cancer (T1a or T1b according to the Classification of Malignant Tumours clinical staging system).

21. 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. Note: A subject tested positive using nucleic acid amplification testing, antigen or antibody detection for SARS-CoV-2 test within 2 weeks preceding screening or during screening will be excluded but can be rescreened once at a later time point as per Investigator's judgement and if confirmation of a negative SARS-CoV-2 test is being available based on standard of care.

22. 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.

23. Any employee or their close relatives of Vifor Pharma Group, or of the CRO involved or of a study site involved in the study.

5.4 Withdrawal of Subjects

5.4.1 Withdrawal of Subjects from Study

Subjects may voluntarily withdraw their participation from the trial at any time without having to provide a reason or a subject 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 should undergo all end of treatment assessments, if possible.

It is important 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. 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 or stabilisation, unless 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 a subject is not obliged to give her/his reason(s) for discontinuing trial participation prematurely, the Investigator will make every effort to obtain the reason, while fully respecting the subject's rights. If the subject does not wish to provide 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

Study drug must be stopped if there is any clinically relevant AE, laboratory abnormality, inter-current illness or health condition requiring medical treatment, or significant worsening of inter-current illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject. The subject concerned will remain under follow-up and the subsequent visits should be performed in accordance with the protocol schedule. Whether the subject should receive additional doses of study treatment will be discussed with the Medical Monitor and will be decided on a case by case basis. If study drug is stopped prematurely for any one subject, the subject concerned will not be replaced.

Subjects may be withdrawn from the study drug if in the opinion of the Medical Monitor or the Investigator there would be a risk to the subject's safety if they received any further dose of study drug.

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

- A potentially life-threatening (Grade 4) anaemia according to FDA toxicity grading scale for healthy adult and adolescent volunteers including Hb <8.0 g/dl (5.0 mmol/l) for female subjects or <8.5 g/dl (5.3 mmol/l) for male subjects, and with an absolute Hb drop from baseline >2 g/dl for males and females, and confirmed by subsequent repeat ≥24 hours apart [14].

- Serum transaminases (ALT or AST) >3x ULN range and total bilirubin >2x ULN (confirmed by subsequent repeat ≥24 hours apart).

- ALT or AST >3x ULN (confirmed by subsequent repeat ≥24 hours apart) with the appearance or worsening of symptoms felt by the Investigator to be potentially related to hepatic inflammation, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.

- Major protocol deviations, including noncompliance or lost to follow-up.

- Use of a non-permitted concomitant medication.

- 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.

5.4.3 Study Stopping Rules

In case any of the following safety stopping criteria are met in at least 2 subjects after IMP intake, based on treatment stopping rules for individual subjects and considered to be at least possibly related to active VIT-2763 administration, no further dosing of subjects will occur:

[redacted]

[redacted]

5.5 Rescreening of Subjects

A subject can only be randomised once in the trial. If a randomised subject withdraws consent for further follow-up, the subject concerned cannot be rescreened. However, a subject who fails to meet the protocol selection criteria of Hb during baseline, i.e., obtained Hb values show more than 10% relative difference and more than 1.0 g/dl absolute change between the highest and lowest value the subject can be rescreened at maximum 2 times at a later time point. Note: A subject tested positive using nucleic acid amplification testing, antigen or antibody detection for SARS-CoV-2 test within 2 weeks preceding screening or during screening will be excluded but can be rescreened once at a later time point as per Investigator's judgement and if confirmation of a negative SARS-CoV-2 test is being available based on standard of care.

The subject must sign a new written informed consent and will be allocated a new screening number.

6. RANDOMISATION, BLINDING AND UNBLINDING PROCEDURES

6.1 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.

After obtaining informed consent, subjects will be screened according to the inclusion and exclusion criteria. The subjects receive a screening number, as allocated by the EDC system. Once the subject is randomised, a randomisation number will be allocated via a validated centralised procedure (IWRS) to receive VIT-2763 or placebo according to the randomisation scheme (Cohort I and II).

Numbered study treatment will contain either VIT-2763 capsules or placebo according to a computer generated medication number list.

Subjects who have met all eligibility criteria will be randomised to either VIT-2763 or placebo and will receive a randomisation number using a validated centralised procedure (IWRS) that automates the random assignment of treatment groups to randomisation numbers. A randomisation list will be generated separately for each cohort, to active or placebo respectively in an 8:8:4 distribution for NTDT adult subjects and in a 4.4:2 distribution for NTDT adolescents. For the purpose of the safety review in each cohort, randomisation algorithm should ensure that the first 10 subjects in Cohort I and the 5 subjects in Cohort II will match a 4:4:2 and a 2:2:1 distribution, respectively. The randomisation number will ensure identification throughout the study.

Randomised subjects, according to their body weight and randomisation will receive:

- Body weight of 40 kg to 59 kg: VIT-2763 dose of 60 mg QD or 60 mg BID, or placebo.
- Body weight of 60 kg to 100 kg: VIT-2763 dose of 120 mg QD or 120 mg BID, or placebo.

No stratification for body weight will be considered for the randomisation generation.

The system will allocate study treatment pack number(s) which should be used for the subject concerned. Details on how to randomise a subject will be found in the respective user manual. The randomisation plan will be kept strictly confidential, accessible only to authorised persons, until the time of unblinding. If a subject discontinues from the study, neither the randomisation number nor the allocated study treatment pack numbers will be reused, and the subject will not be allowed to be re-randomised in the study.

6.2 Treatment Blinding

This study is conducted in a double-blind fashion. The IMPs (VIT-2763 or placebo) are provided in identical white opaque hypromellose Size 0 hard capsules in packaging of identical appearance. The appearance of the placebo capsules is identical to the VIT-2763 dosage strength 60 mg expressed as drug substance base. During the study, the blind will only be broken under particular conditions that are specified in Section 6.2.1.

6.2.1 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 administered 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 10.7.3).
- If a subject becomes pregnant during the study, the knowledge of the treatment arm is therefore necessary (see Section 10.8.3.2).

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 in the safety reporting to external regulatory bodies (e.g., in case of a SUSAR or a pregnancy). Unblinding must always be performed according to the procedures that are specified in applicable CRO Standard Operating Procedures.

6.3 Dosage Forms/Formulation

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

6.3.1 Study Drug

The active ingredient VIT-2763 will be provided by Vifor Pharma 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: A 60 mg dosage strength of VIT-2763 is used

[redacted]

Dosage Form: Capsules

[redacted]

Storage: VIT-2763 capsules are packed in [redacted] high density polyethylene (HDPE) bottles [redacted] and should be stored according to the instructions on the label

6.3.2 Placebo

[redacted]

Dosage Form: Capsules

[redacted]

Storage: Placebo capsules are packed in [redacted] HDPE bottles [redacted] and should be stored according to the instructions on the label

6.3.3 Devices for Administration

Not applicable.

6.4 Drug Dosage and Administration

6.4.1 Treatment Arms

Cohort I:

- Adult NTDT subjects with a body weight of ≥60 kg and ≤100 kg (assessed at screening) will be randomised to receive either 120 mg VIT-2763 QD, 120 mg VIT-2763 BID, or matching placebo.

- Adult NTDT subjects with a body weight of <60 kg will be assigned in the same manner to receive 60 mg VIT-2763 QD or 60 mg VIT-2763 BID or placebo.

Cohort II:

- Adolescent NTDT subjects with a body weight of <60 kg (assessed at screening) will be randomised to receive either 60 mg VIT-2763 QD, 60 mg VIT-2763 BID, or matching placebo.

- Adolescent NTDT subjects with a body weight of ≥60 kg and ≤100 kg (assessed at screening) will be randomised to receive either 120 mg VIT-2763 QD, 120 mg VIT-2763 BID, or matching placebo.

6.4.2 Dosing and Administration Guidelines

Upon completion of the baseline visit procedures/assessments eligible subjects will be randomised using a validated centralised procedure (IWRS) to receive VIT-2763 or placebo according to the randomisation scheme (Cohort I and II).

The first dose of study treatment must be administered on the same day as randomisation.

6.4.2.1 VIT-2763

Total daily dose of 60 mg, 120 mg or 240 mg VIT-2763, to be taken orally from Day 1 to Day 84 as per randomisation scheme and schedule. Capsules are to be taken in the morning in conjunction with water approximately 1 hour after meals between 08:00 to 10:00 a.m. At study visits, subjects are asked to stay in the hospital until up to 4 hours at selected visits for PK sampling. At 2-3 hours post administration a 12-lead ECG will be conducted. To maintain the BID dosing schedule, i.e., after having received a dose in the morning at the hospital, the subjects will be advised to take the study medication in the evening approximately 1 hour after meals and with water at approximately the same clock time each day between 08:00 p.m. and 10:00 p.m. in the evening.

One dosage strength (60 mg) is available and will be used accordingly to achieve the specified doses.

6.4.2.2 Placebo

Daily dose of placebo matching to VIT-2763, to be taken orally from Day 1 to Day 84 as per randomisation scheme and schedule. Capsules are to be taken in the morning in conjunction with water approximately 1 hour after meals between approximately 08:00 to 10:00 a.m. At study visits, subjects are asked to stay in the hospital until up to 4 hours at selected visits for PK sampling. At 2-3 hours post administration a 12-lead ECG will be conducted. To maintain the BID dosing schedule, i.e., after having received a dose in the morning at the hospital, the subjects will be advised to take the study medication in the evening approximately 1 hour after meals and with water at approximately the same clock time each day between 8:00 p.m. and 10:00 p.m. in the evening.

The placebo will match the VIT-2763 dosage strength (60 mg) used.

6.5 Package and Labelling

VIT-2763 60 mg and matching placebo capsules in HDPE bottles will be supplied to the investigational site as double-blind medication.

Medication labels will comply with local requirements.

6.6 Study Treatment Allocation

Each eligible subject will be randomly assigned to 1 of the 3 treatment arms (VIT-2763 QD or BID, or placebo) through a secure and validated centralised IWRS as described in Section 6.4.1. The IWRS will specify the unique medication number(s) for the study drug to be dispensed to the subjects.

6.7 Site Supply, Storage, Accountability

6.7.1 Site Supply

Once the site has been approved to receive study drug, the site will be supplied with an initial stock of VIT-2763 (dosage strength 60 mg and placebo). The need for IMP resupply will be assessed on a regular basis taking into account the number of subjects enrolled or randomised, and the number of subjects in screening at the site. If a subject is not able to visit the site for IMP resupply due to COVID-19 pandemic, a direct shipment of the study drug to the patient 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 temperature-controlled manner and will be documented adequately. Written information on the dose regimen will be provided to the patient along with contact information to site for any questions patient may have. The subject will return any unused IMP and empty IMP packages with a logistics provider or during the next on-site visit as instructed by the Investigator.

6.7.2 Storage

Upon receipt, all IMPs should be stored according to the instructions specified on the drug labels and accessible to authorised personnel only. The site should have a calibrated thermometer that records minimum and maximum temperatures daily, or the temperature should be monitored continuously using a continuous temperature monitoring system. Maintenance of a temperature log is mandatory. The log should be updated by site personnel daily. 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 medication must be quarantined immediately and the Sponsor contacted for guidance.

[redacted]

6.7.3 Accountability

The Investigator is responsible for the storage and accountability of the IMP supplies. The Investigator will ensure that adequate records of the receipt, dispensation and return of the IMP are kept and that the study drug is used only for subjects enrolled in the study. Subjects should be instructed to return all used and unused IMP dispensed to them at each scheduled visit. All data regarding the study drug (including medication (kit) and batch numbers) must be recorded in the eCRF and on any other relevant forms provided.

The study site will maintain a drug inventory/dispensing record for all IMP dispensed and returned. At the end of the study, a 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 material will be returned to Vifor Pharma. 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 study medication at site must be made by Vifor Pharma. If the study medication is destroyed at site, the Investigator will forward the certificate of destruction to Vifor Pharma.

6.7.4 Procedures for Overdose

Based on the mode of action of VIT-2763, excessive doses of VIT-2763 could cause acute hypoferraemia. In addition it theoretically may warrant acute medical management following transient changes in serum iron parameters, in particular if concurrent (additional) blood loss or haemolysis is suspected or if Hb measurements are low enough to cause symptoms of decreased oxygen delivery. Whilst 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 subjects, 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 or QRS intervals 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 include the following treatments:

- Previous hydroxyurea treatment <6 months prior to randomisation, and previous ESA treatment in the 12 weeks prior to randomisation and until EOS, or any prior gene therapy and until EOS. Concomitant hydroxyurea treatment with stable doses >6 months is allowed.

- Treatment with activin receptor ligand traps (e.g., luspatercept, sotatercept) or JAK2 inhibitors (e.g., ruxolitinib) in the 24 weeks prior to randomisation and until EOS.

- Subjects on concomitant ICT or subjects on prior ICT when discontinued less than 4 weeks prior randomisation. Note: If ICT was discontinued ≥4 weeks prior randomisation the subject is eligible.

- Iron therapy as of 4 weeks prior to screening and until EOS.

- Blood transfusion in the form of RBC packs during the study and until EOS are not allowed. Note: Subjects need to have received <5 units of RBCs during the 24 week period prior to randomisation/first drug administration of VIT-2763 or placebo (1 unit is defined as 200 to 350 ml of transfused packed RBCs and last RBC transfusion must have been received ≥14 days prior to randomisation). Note: Subjects who are supposed to receive RBC transfusions after randomisation in the Investigator's opinion, and according to local practise, and having received at least 1 dose of VIT-2763, may be considered to stay on study treatment for safety reasons, and in case there are no tolerability concerns. Subjects will be censored for secondary efficacy.

- Any medication that prolongs the QT/QTc interval or the PR/QRS interval (including but not limited to antipsychotics, antiarrhythmics, tricyclic and other antidepressants, antihistamines and macrolides), as of 3 weeks prior to screening and until EOS.

- Any investigational drug, as of 30 days prior to screening 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 his/her 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 and tolerability and preliminary efficacy of multiple doses of VIT-2763 in adult and adolescent patients with NTDT and documented iron overload will be investigated in this Phase 2a clinical trial.

The results of a Phase 1 clinical trial in healthy subjects revealed 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 were reported and no discontinuations due to AEs were reported. There were also no findings of clinical relevance with respect to vital signs, 12-lead ECG, telemetry or physical examination. 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 SUSARs and annual/aggregate safety reporting though.

Based on the known pharmacology, nonclinical studies including repeated dose toxicity data, and the available clinical data in adult healthy volunteers to date with VIT-2763, no safety concern is expected for the intended use in a paediatric population of adolescents (12 years and above) for a 3-month treatment duration.

Excessive doses of VIT-2763 could cause acute hypoferraemia. Based on nonclinical data, ECG monitoring is recommended, and standard emergency treatment should be applied. Caution should be exercised in subjects with:

- Developing iron deficiency during treatment.
- A Grade 4 anaemia including Hb <8.0 g/dl (5.0 mmol/l) for female subjects or <8.5 g/dl (5.3 mmol/l) for male subjects, and with an absolute Hb drop from baseline >2 g/dl for males and females, according to FDA toxicity grading scale for healthy adult and adolescent volunteers [14].

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.

Due to the lack or limited data of nonclinical studies of the effect of VIT-2763 on pregnancy, fertility, and lactation at this stage of development, women of childbearing potential and male subjects must use highly effective methods of contraception whilst taking VIT-2763 and for 1 month after the last dose of VIT-2763. Breastfeeding must be

discontinued during treatment with VIT-2763 and for 3 months after the last dose of VIT-2763.

7.1.1 Contraception and Lactation

Due to the lack of nonclinical studies of the effect of VIT-2763 on pregnancy, fertility and lactation at this stage of development, women of childbearing potential and male subjects must use highly effective methods of contraception, as defined below, whilst participating in this study and for 1 month after the last dose of study medication, and breastfeeding must be discontinued during the study as of the first dose of the study medication.

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

- Intra-uterine device
- 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.

Highly effective methods of contraception for men participating in this study are:

- Partner using highly effective method of contraception for women as listed above
- Partner using continuous hormonal contraception
- Surgical sterilisation
- Sexual abstinence

Male subjects must practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, and for at least 1 month (sufficiently exceeding 5 times the mean $t_{1/2}$ of VIT-2763 based on multiple dose human PK data) following investigational product discontinuation, even if he has undergone a successful vasectomy.

[redacted]

8. STUDY PROCEDURES

8.1 Description of Study Assessments

The following description of the assessments performed in this trial refers to the study days when the assessments are carried out. Prior to SIV the monitor had collected as much information as possible regarding the current impact of COVID-19 pandemic on site's ability to conduct the clinical trial and about the capacity of the site to face the reoccurrence of COVID-19 restrictions when managing enrolled subjects. The information for their site is documented in the 'VIT2763_THAL-201: COVID-19 mitigation plan_site specific information' tracker. An overview of the assessments with the visit numbers are displayed in Table 1.

8.1.1 Demographics and Medical History

Subject's demographics (gender, age, race, and ethnicity) and baseline characteristics including body weight, body mass index, and a medical history will be taken during the baseline visit. Information to be collected will include the aetiology and clinical presentation of β-thalassaemia, and the date when β-thalassaemia was first diagnosed, and other clinically relevant past and present medical conditions which were diagnosed/occurred up to at least 12 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 12 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.

8.1.2 Symptoms and Signs of Anaemia

The Investigator must assess signs and symptoms associated to anaemia in β-thalassaemia:

- Fatigue, weakness
- Shortness of breath
- Pale or yellowish skin
- Deformities of the facial bones
- Slow growth, growth retardation
- Abdominal swelling
- Dark urine

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

The β-thalassaemia 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).

8.1.3 Physical Examination and Vital Signs

The body systems to be assessed in the physical examination include general appearance, head (eyes, ears, nose and throat), cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymph nodes, and skin. In the study, physical examination is performed at screening Visit V1 (i.e., Day -28 to -1) and on Visit V3 (Day 1), and V8 (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 screening Visit V1 and on Visits V3 to V8. Vital signs should be performed at V3 to V8 before IMP dosing, 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).

8.1.4 Electrocardiogram

Computerised single 12-lead ECG recordings will have to be obtained locally according to Table 1. 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).

8.1.5 Body Height, Weight

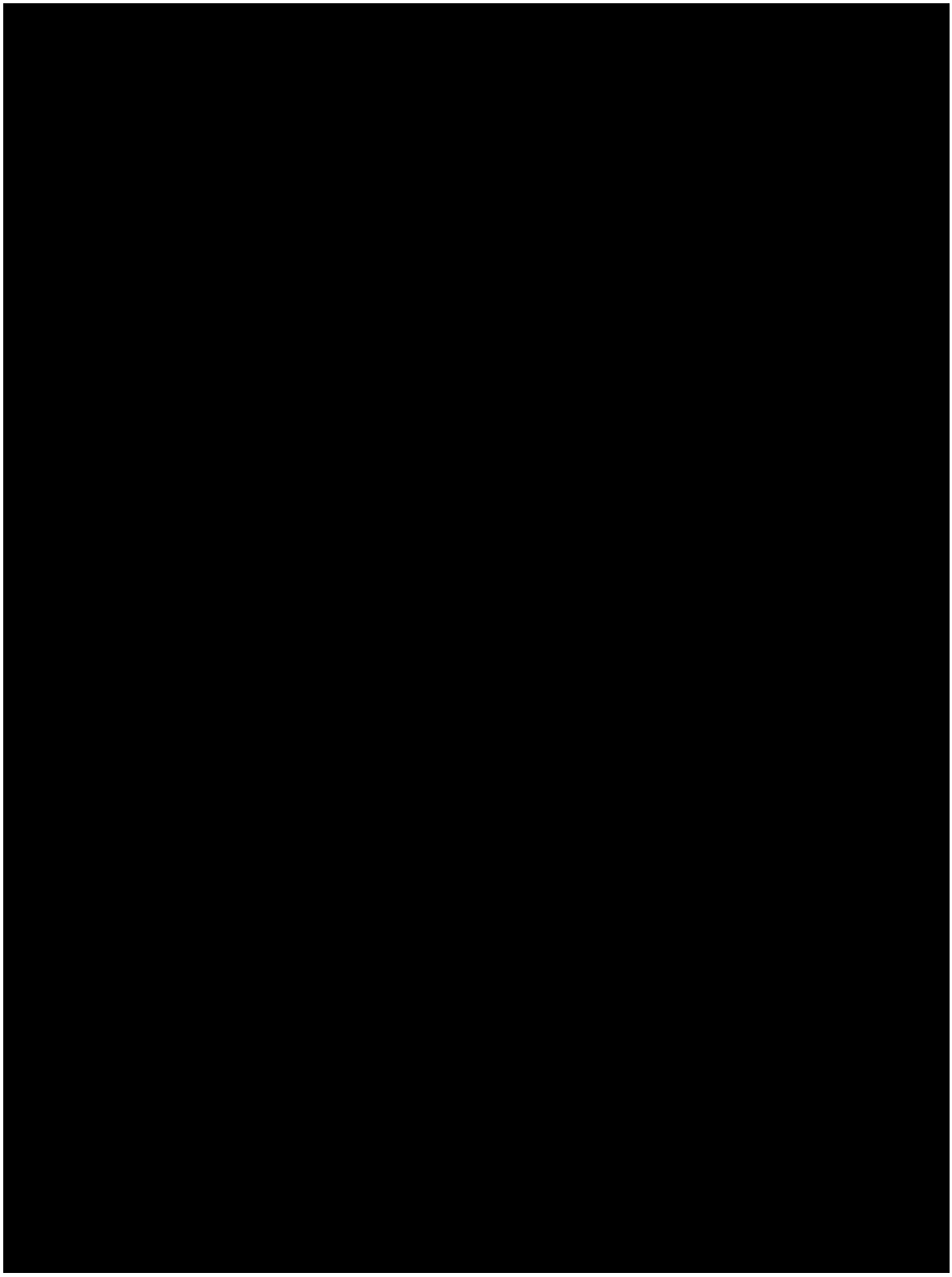
Body height (in cm, without shoes) must be measured at the screening visit only. Body weight must be measured in underwear or light clothing without shoes. The same calibrated scale must be used throughout the trial. Any new clinically relevant change in body weight must be reported as an AE (see Section 10).

8.1.6 Documentation of 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

[redacted]

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).



[redacted]

[redacted]

8.1.9 Local Laboratory Parameters

The laboratory tests to be assessed and analysed locally according to Table 1 results will be transferred into the eCRF.

8.1.9.1 Haemoglobin

Hb levels to be assessed locally at each study visit V3 to Visit V8.

8.1.9.2 Urine Tests

- Urine pregnancy test: human chorionic gonadotropin for females of childbearing potential to be assessed at baseline and study visits V3-V8.
- Urinalysis: pH, protein, glucose, ketone, blood, spot urine for assessment of protein/creatinine and albumin/creatinine ratio (may be done centrally).
- Urine drug screening: alcohol, amphetamines, cannabinoids, cocaine, opioids, phencyclidine.

8.1.10 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 during the study according to Table 1.

Although the assessments should preferably be performed centrally, due to COVID-19 pandemic, assessment may be performed in a local laboratory at site or at a laboratory near to subject's home in case shipment of samples to the central laboratory is no longer

possible. This would notably concern key safety laboratory parameters which should at minimum include haematology panel (RBC, Hb, haematocrit, mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration, white blood cell count with differential, platelets count), coagulation (prothrombin time, activated partial thromboplastin time, thrombin time) and liver function tests (ALT, AST, GGT total bilirubin, alkaline phosphatase).

8.1.10.1 Haematology, Biochemistry, Blood Clotting and Serology

-

- Electrolyte status (sodium, potassium, magnesium, calcium, chloride), total bilirubin, urea, uric acid, creatinine, total protein, alkaline phosphatase, AST, ALT, GGT, glutamate dehydrogenase, LDH, haptoglobin, amylase, bicarbonate, eGFR, unconjugated bilirubin, creatine phosphokinase, folic acid, Vitamin B_{12}, albumin, glucose, total cholesterol, and triglycerides. Total serum iron, serum ferritin, unsaturated iron binding capacity, calculated TSAT (screening visit only).

- Prothrombin time, activated partial thromboplastin time, thrombin time.

- Beta-human chorionic gonadotropin in serum.

- HIV 1/2 antibodies, HCV antibodies and RNA, HBsAg, hepatitis B core antibodies and optional HBV DNA.

8.1.10.2 PD Iron

- PD iron: Total serum iron, serum ferritin, serum transferrin, unsaturated iron binding capacity, calculated TSAT,

-

-

- Biomarker/genotyping.

In subjects consenting for additional biomarker samples and genotyping, blood samples will be taken. The baseline biomarker blood sample will be drawn prior to the first administration of study treatment. Blood samples will be stored for up to 3 years after the end of the trial for future analyses of biomarkers of scientific interest. Details concerning the blood samples storage will be provided in an instruction manual and results of these exploratory analyses will be not part of the clinical study report of the main study.

[redacted]

8.1.10.3 Pharmacokinetics

Blood samples for the determination of VIT-2763 plasma concentrations (sparse sampling) are collected on Visit 3 and Visit 7 at pre-dose trough and at approximately 1 hour and 4 hours post-dose, and on Visits 6 and 8 at pre-dose trough and approximately at 1 hour and 3 hours post-dose.

8.1.11 Blood Volumes Drawn for Each Subject

The approximate total volume of blood drawn during the study for each subject is shown in Table 3.

[redacted]

Table 3 Approximate Blood Volumes Drawn for Each Subject in the Study

Visit	Screen V1	Screen V2 (Optional)	Baseline V3	V4	V5	V6	V7	V8	
Study Day	**-28**	**-15**	**1**	**7**	**14**	**28**	**56**	**84**	
Visit Window (±d)	**N/A**	**±3**	**N/A**	**±1**	**±2**	**±3**	**±3**	**±3**	
Laboratory sample									**Total (ml)**
Haematology	X	–	X	–	X	X	X	X	
Biochemistry	X	–	X	–	X	X	X	X	
Coagulation	X	–	X	–	–	X	–	X	
Biomarker/genotyping(1)	–	–	X	–	–	–	–	X	
Pregnancy test	X(2)	–	–	–	–	–	–	X(2)	
Serology(3)	X(3)	–	–	–	–	–	–	–	
VIT-2763 PK(4)	–	–	x3			x3	x3	x3	
Hb local(5)	–	X	X	X	X	X	X	X	
[redacted]									
PD iron [redacted]	–	–	X	X	X	X	X	X	
[redacted]									
Approximate total volume (ml) per visit (adults)	30	3	57	30	34	42	44	52	**292 ml**
Approximate total volume (ml) per visit (adolescents)	26	3	52	24	29	36	40	52	**262 ml**

1 Taken in subjects consenting to genotyping/biomarker sampling.
2 For women only. Samples will be derived from serum biochemistry tube.
3 Including HCV RNA and HBV DNA.
4 PK samples will be collected on Visits 3 to 8 at pre-dose trough and approximately up to 1 hour to 4 hours post-dose.
5 Local haematology sample to assess Hb will be taken locally at study site and results must be available at day of dosing (sample at optional Visit V2).
6 [redacted]
7 PD measurements including serum iron, serum ferritin, serum transferrin, unsaturated iron binding capacity, calculated TSAT, [redacted] will be assessed centrally. Samples will be collected on Visits 3 to 8 approximately 2 hours post-dose.
8 Approximately 2 hours post-dose.
Notes: [redacted] Hb=Haemoglobin; [redacted] N/A=Not applicable; [redacted] PD=Pharmacodynamics; PK=Pharmacokinetics; [redacted]

8.2 End of Treatment (or Early Discontinuation) Procedures

A visit will take place on completion of the treatment or early discontinuation/withdrawal (i.e., at Week 12 (Visit 8)). All assessments should be performed as detailed in Table 1 end of treatment, V8.

Visit window for end of treatment visit is ±3 days.

8.3 Safety Follow-up (EOS) Procedures

All subjects, whether completing the treatment or who have withdrawn prematurely, will be followed up 4 weeks (28 days) after their last administration of study treatment to collect any new AEs and concomitant medications (i.e., at Week 16 (Visit 9)). This visit may be conducted by telephone call or as an in-clinic visit. If the Investigator has not seen the subject at a clinic 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”.

[redacted]

9. STUDY ASSESSMENTS

9.1 Description of Study Assessments

9.1.1 Screening Visit

9.1.1.1 Screening Visit V1 Days -28 to Day -1 – Performed In-hospital

- Subjects who have a documented diagnosis of β-thalassaemia will be screened within 4 weeks prior to the baseline/randomisation visit to determine potential eligibility to participate in the VIT-2763-THAL-201 trial.

- The Investigator will obtain written informed consent from potentially eligible subjects before any trial related procedure is performed. In case of extraordinary events (e.g., COVID-19 pandemic) it is acceptable to have the informed consent via e-mail, SMS or a verbal consent (a witness is required) if allowed per local country guidance. Written consent has to be provided as soon as possible and must be properly recorded in the source documentation.

- Protocol required procedures according to Table 1, including medical/medication history, physical examination, weight and height, vital signs.

- As of the date of informed consent for each subject, the sites will document in the eCRF all AEs and changes/additions made to concomitant medications. SAEs will be reported as they occur but no later than 24 hours after the Investigator's awareness of the event.

- Subject demographics and baseline characteristics will be assessed.

- A single 12-lead ECG will be conducted.

- A blood test will be drawn, which will be analysed centrally, to determine if the subject is eligible according to the main inclusion and exclusion criteria and Table 1.

- Urine will be taken for urinalysis (pH, protein, glucose, ketone, blood, spot urine for assessment of protein/creatinine and albumin/creatinine ratio) and urine drug and alcohol screen.

- During the same blood draw, a serum pregnancy test will be taken for female subjects of childbearing potential.

- A serology test will be conducted to determine HBsAg, HBV, HCV, and HIV.

9.1.1.2 Screening Visit V2 (Day -15±3 Days) - Performed In-hospital - Optional

- If subjects did fulfil the main inclusion criteria and did not meet any exclusion criteria observed at Visit V1, they will be asked to attend a second screening Visit V2 in order to determine the Hb level. Note: If there is 1 retrospective Hb value available from the subject at maximum of 2 weeks prior to screening (Day -28), the Hb value can be taken

into consideration in order to verify if the inclusion criterion is met (mean baseline Hb ≤11 g/dl, ≥2 consecutive measurements ≥1 week apart within 6 weeks prior to randomisation). If obtained Hb values show more than 10% relative difference and more than 1.0 g/dl absolute change between the highest and lowest value, the subject must be excluded.

- In addition, other eligibility criteria including changes in AEs and changes/additions made to concomitant medications will be re-assessed and it will be determined whether the subjects are still eligible.

- In case there is no retrospective Hb value, it is allowed to schedule an optional screening Visit V2 and baseline V3 the same day providing that local Hb result can be obtained on the day of combined V2/V3 visit and that there should be at least 1 week between screening Visit V1 and the combined V2/V3 visit. If V2 and V3 are done the same day, site should only complete V3 in EDC.

9.1.2 Baseline Visit V3 (Day 1) – Performed In-hospital

To accommodate local hospital practice, the subject may attend the V3 visit either at the day of the first dose of study treatment, or the day before the planned randomisation day. Note that a planned overnight stay prior study treatment administration does not fulfil the criteria of an SAE unless there is a medical reason for doing this.

- If subjects did fulfil the main inclusion criteria and did not met the exclusion criteria observed from the Visit V1 and optional V2, they will be asked to attend baseline Visit V3. The Investigator will perform/complete the baseline procedures/assessments as shown in Table 1.

- Eligibility criteria including changes in the medical history, AEs and changes/additions made to concomitant medications will be re-assessed and it will be determined whether the subject is still eligible.

- Physical examination will be done and vital signs will be checked.

- 12-lead ECG.

- Determination of Hb level will be processed locally. Subjects must have a mean baseline Hb ≤11 g/dl, based on at least 2 consecutive measurements ≥1 week apart within 6 weeks prior to randomisation/baseline. If obtained Hb values show more than 10% relative difference and more than 1.0 g/dl absolute change between the highest and lowest value, the subject must be excluded. Note: If there is 1 retrospective Hb value available for the subject at maximum of 2 weeks prior to screening (Day -28), the Hb value can be taken into consideration. A subject not meeting this criterion would be excluded but can be rescreened at maximum 2 times at a later time point.

- In addition, for females of childbearing potential, the urine pregnancy test must be negative.

- Further baseline laboratory blood draws will be taken according to Table 1:

  - Baseline PK sample for determination of VIT-2763 concentrations.

  - Blood draws for haematology, biochemistry, coagulation.

  - PD iron, [redacted]

  - Genotyping/biomarker sampling in subjects consented.

  - Urine will be taken for urinalysis (pH, protein, glucose, ketone, blood, spot urine for assessment of protein/creatinine and albumin/creatinine ratio).

  - [redacted]

9.1.3 Randomisation and Administration of the First Dose of Study Treatment

- Upon completion of the baseline visit procedures/assessments eligible subjects will be randomised using a validated centralised procedure (IWRS) to receive VIT-2763 or placebo according to the randomisation scheme (Cohort I and II).

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

- The assignment of subjects to either active treatment dose or matching placebo will be based on body weight at screening, according to Section 6.4.

- The first dose of study treatment must be administered on the same day as randomisation.

- The medication (VIT-2763 or placebo) will be administered in the morning in conjunction with water approximately 1 hour after meals between approximately 08:00 a.m. and 10:00 a.m. in the morning. Subjects are asked to stay in the hospital until up to 4 hours at selected visits for PK sampling. At 2-3 hours post study drug administration a 12-lead ECG will be conducted. To maintain the BID dosing schedule, i.e., after having received a dose in the morning at the hospital, the subjects will be advised in taking the study medication in the evening approximately 1 hour apart from meals and with water at approximately the same clock time each day (between 08:00 p.m. and 10:00 p.m. in the evening).

Study medication will be given to the subject to administer at home until the next visit.

9.1.4 Post-randomisation Visits V4 (Week 1) to V8 (Week 12 or Early Discontinuation)

- Subjects will return to the out-patient clinic at 1 (±1 day), 2 (±2 days), 4 (±3 days), 8 (±3 days) and 12 weeks (±3 days) after randomisation.

- If a subject cannot return to the site for a study visit due to COVID-19 pandemic, the Investigator will conduct a remote visit (e.g., telemedicine, phone call), a visit at the subject's 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.

- At the remote/home visits the Investigator should at minimum perform the following: evaluation of the subject's general condition, collection of information on any new and ongoing adverse events, collection of information on the IMP intake and concomitant medications use. Scheduled urine samples may be collected at a home visit, or in laboratories near to the subject's home and should be processed locally. Scheduled blood samples may also be collected at home visit or laboratories near to the subject's home and sent to the central laboratory if possible, otherwise processed locally. Safety analyses such as haematology panel (RBC, Hb, haematocrit, mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration, white blood cell count with differential, platelets count), coagulation (prothrombin time, activated partial thromboplastin time, thrombin time) and liver function tests (ALT, AST, GGT, total bilirubin, alkaline phosphatase) should be done at the minimum.

- Subjects will have to come in the morning of the visit before taking the study medication, and have to come on an empty stomach. Drinking of water ad libitum is allowed. If a subject is not able to visit the site for IMP resupply due to COVID-19 pandemic, a direct shipment of the study drug to the patient 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 temperature-controlled manner.

[redacted]

- During the out-patient visits, the Investigator will check the vital signs (including weight at V8 only), also for AEs, check concomitant medication. On Visit 8 also a physical examination will be done.

- At Week 1 (Visit 4), Week 2 (Visit 5), Week 4 (Visit 6), Week 8 (Visit 7) and Week 12 (Visit 8), a blood test to assess Hb will be performed and analysed locally. The Hb value needs to be available at the day of dosing before the subject is leaving the hospital, and will be documented in the eCRF. In addition, a urine pregnancy test will be drawn.

- Urine will be taken for urine pregnancy and test urinalysis (pH, protein, glucose, ketone, blood, spot urine for assessment of protein/creatinine and albumin/creatinine ratio), blood samples for haematology and clinical chemistry (all visits) and coagulation (Visits 6 and 8).

- Dosing will only be done in subjects for whom the urine pregnancy test is negative in females of childbearing potential. In case of a Grade 4 including Hb <8.0 g/dl (5.0 mmol/l) for female subjects or <8.5 g/dl (5.3 mmol/l) for male subjects, and with an absolute Hb drop from baseline >2 g/dl for males and females, and confirmed by subsequent repeat ≥24 hours apart, study drug will not be re-dispensed.

- Subjects will bring back the study medication dispensed to them at the previous visit and returned drug will be documented. Subjects will be dispensed new study drug and will take the first morning dose in the hospital as described in the 'Treatment' section. Approximately 2-3 hours after dosing a 12-lead ECG will be done, blood will be taken for PK (selected visits) and PD measurements (all visits), [redacted]

- In subjects that have consented for genotyping and biomarker sampling an additional blood sample will be taken on Visit 8 only.

- [redacted]

If subject withdraws prematurely, all assessments at V8 should be performed, if possible.

[redacted]

9.1.5 Safety Follow-up Visit V9 (EOS Visit)

- All subjects, whether completing the treatment or who have withdrawn prematurely, will be followed up 4 weeks (28±4 days) after their last administration of study treatment to collect any new AEs and concomitant medications. This visit may be conducted by telephone call or as an in-clinic visit.
- [redacted]

10. EVALUATION, RECORDING AND REPORTING OF AEs

10.1 Definition of AEs

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 medicinal (investigational) product.

10.2 AE Reporting Period

The AE reporting period begins at the time the Informed Consent Form (ICF) is signed by the subject. The AE reporting period ends at the last study contact Visit 9/Week 16.

10.3 Eliciting AEs

If the subject reports an AE, it is the Investigator's responsibility to acquire sufficient information in order to assess causality. 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 AEs

10.4.1 Intensity/Severity

The medical assessment of intensity of AEs, except changes in laboratory parameters, will be determined using the following definitions:

- Mild: The AE is easily tolerated and does not interfere with usual activity.
- Moderate: The AE interferes with daily activity, but the subject is still able to function.
- Severe: The AE is incapacitating and the subject is unable to work or complete usual activity.

The intensity of a particular AE to be recorded is the worst intensity experienced by the subject during the course of the event.

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, however, 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 investigational product 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.

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 • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ likely	Yes	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	Yes	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • 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 investigational product is determined to be “certain", "probable/likely", or "possibly" related, the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting. In circumstances where the causal relationship has not been provided, the event will be considered as related and qualify for 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 kind 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 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 AEs

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.

[redacted]

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

The intensity of changes in clinical laboratory parameters should be determined according to the FDA guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [14] provided in Appendix 2.

Not every laboratory abnormality qualifies as an AE. It is the Investigator’s responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. When evaluating such changes, the criteria below and the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration:

- 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 FDA Toxicity grade [14], 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 end of treatment with the investigational product, 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.

[redacted]

10.5.5 Worsening of the Disease Under Study

Symptoms and signs of the disease under study should not be considered AEs as long as they are not regarded as worsening of the clinical features of the disease under study. If a sign or symptom of the disease has unexpectedly worsened in severity or frequency or changed in nature at any time during the study, the symptoms and signs should be recorded as AEs, 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 any of the following criteria:

- Accompanied by clinical symptoms or lead 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 RSI

10.6.1 Adverse Drug Reaction

An adverse reaction is an untoward and unintended response to an IMP related to any dose administered. This definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

All AEs judged as having a reasonable causal relationship to a medicinal (investigational) product will be designated as ADRs.

10.6.2 Reference Safety Information

The Reference Safety Information (RSI) presents the basis for expectedness assessment of an adverse reaction for expedited 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 that at any dose:

- 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 inpatient 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 CRO/Sponsor 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 during the study.

- 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 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 lasts until 4 weeks (28±4 days) following the last study drug administration. 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.

A death occurring during the study or which comes to the attention of the Investigator within 30 days after the last study drug administration, whether considered treatment-related or not, must be reported to the CRO/Sponsor.

Any SAE considered to have a causal relationship (i.e., related) to the investigational product 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 database lock of the clinical database 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 EDC system. The Investigator must verify the accuracy of the information recorded.

At a minimum, the following information should be provided at the time the initial SAE report is completed:

- Study name and/or number

- Subject number (i.e., screening number), age and gender/sex

- Event description/verbatim (including onset date of the SAE, outcome and reason for it being considered serious)

- Relationship to the IMP (i.e., causality)

- Name of the IMP (including drug dose and administration dates)

[redacted]

- Investigator name and address
- Name of the reporter (including site name or number and country)
- Dated signature of the Investigator or Sub-/Co-investigator (for paper reports)

Additional follow-up information, if required or available, must be provided within 24 hours of awareness.

Preliminary reports will be followed by detailed descriptions, which will include copies of hospital case reports, autopsy reports/certificates (in case of death) and other documents when requested and applicable.

Any supporting information provided should not reveal a subject's identity beyond the agreed study identifier. The Investigator should ensure that information reported is accurate and consistent.

The onset date of the SAE is defined as the date the signs and symptoms/diagnosis became serious (i.e., met at least 1 of the criteria for seriousness). 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 RSI; see Section 10.6.2) that is felt to have a reasonable suspected causal relationship to a medicinal product.

10.7.3.1 SAE Expedited Reporting

Prompt notification by the Investigator to the Sponsor or CRO of all SAEs occurring during a clinical trial is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical trial investigation are met.

Vifor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies regarding the safety of a product under clinical investigation. Vifor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRB/Independent Ethics Committee (IEC) and Investigators.

Investigator safety reports are prepared for SUSARs (those not listed in the Investigator's Brochure) according to local reporting requirements/Vifor policy and are forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Vifor will file it with

the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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. The blind should be maintained for individuals responsible for the ongoing conduct of the study (e.g., management, monitors and Investigators) and those responsible for data analysis and interpretation of results at the conclusion of the study (e.g., biometrics personnel).

Unblinded information should only be accessible to those who need to be involved in the safety reporting to pertinent Regulatory Authorities, ECs.

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 overdose: the administration of a quantity of study medication given per administration or per day which is above the protocol maximum permitted dose
- Drug interaction involving study medication

Special situations including medication errors impacting patient'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.

Special situations shall not be assessed as per accidentally missed/omitted individual doses or subsequent single dose substitutions.

Any deviation from study protocol procedures (including e.g., study drug storage, prescription, administration), which will come to the awareness of the Investigator, or may be identified during study conduct by any site personnel, shall be recorded via the study-specific protocol deviation list.

[redacted]

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 should be reported within 24 hours of awareness to the Sponsor/CRO, following the same procedure as for SAEs (Section 10.7.2).

If any special situation leads to an SAE the steps outlined in Section 10.7.2 should also be followed.

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, should have a negative serum pregnancy test prior to randomisation. Study medication 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 both male and female subjects before beginning study medication, during study dosing, and for 30 days following discontinuation of study medication or according to local requirements, whichever is longer, even when there has been a history of infertility, unless due to hysterectomy.

Highly effective contraception must be used (refer to Synopsis and Section 7.1.1) unless abstinence is the chosen method 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 study medication. The Medical Monitor must be contacted immediately to break the blind (if applicable). 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

[redacted]

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 CRO/Sponsor within the same timelines as a SAE, i.e., immediately (within 24 hours of awareness). The Investigator should complete a Vifor Pharma Report on Exposure to Medicines during Pregnancy form (see Appendix 3) and forward to the CRO/Sponsor. 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 same method outlined in Section 10.7.3.1.

All pregnancies occurring in a female subject or the female partner of a male subject within 90 days after discontinuation of investigational product should be reported within the same timelines as a SAE to the CRO/Sponsor.

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. STUDY COMMITTEES

11.1 SRT Procedures

To ensure an appropriate review of safety information of all subjects, blinded preliminary safety and preliminary efficacy data will be reviewed by an SRT. The SRT will be comprised at minimum of the Co-ordinating Investigator, 2 independent haematologists, the Vifor Medical Monitor, and the Vifor Drug Safety Representative or their designee. Additional subject matter experts, including additional external advisors, may be invited if deemed appropriate.

The SRT will make recommendations to enrol adolescent NTDT subjects into Cohort II, or proceed to the expansion of the Cohort I by enrolment of additional adult NTDT subjects. The SRT may also make recommendations to reduce the dose level at any given interim steps, or to unblind any subject due to safety concerns, or to stop the trial. Further details will be described in the SRT charter.

11.2 Steering Committee

The SC, chaired by the Co-ordinating Investigator, will be responsible for maintaining the scientific integrity of the trial. Members will be selected Investigators from the participating countries/regions, or advisors who contributed to the concept of the study design and/or attended 1 or more scientific advisory committees.

The Co-ordinating Investigator will review and approve the trial protocol and subsequent protocol amendments, taking into account also feedback from other SC members, if applicable. The SC will be blinded to study treatment allocation while the trial is ongoing. Each SC member is expected to discuss with the SC Chairman any activities that might constitute a conflict of interest for the VIT-2763-THAL-201 trial. SC meetings will be attended by, in addition, representatives of the Sponsor and coordinating personnel (if applicable), in a non-voting capacity.

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). 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.

The two cohorts will be analysed the same way into 2 separated analyses.

Summary statistics will include the number of subjects, the mean, the standard deviation, the quartiles and the minimum and maximum for continuous parameters, and counts and percentages in each category for categorical parameters. Summary statistics will be provided on overall subjects receiving VIT-2763 and by dose daily frequency and for all subjects receiving placebo.

No inferential statistics will be performed to compare treatment groups.

12.2 Sample Size and Power Calculations

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

It is planned to randomise at least 20 subjects in Cohort I and up to 10 subjects in Cohort II.

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 study drug using a validated centralised procedure (IWRS). Randomisation will be performed based on pre-defined randomisation list for each cohort.

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

The subjects will be randomised according to the following scheme:

- In Cohort I, at least 20 subjects will be randomised into a 8:8:4 distribution to VIT-2763 QD or VIT-2763 BID, or placebo respectively.

- In Cohort II, up to 10 subjects will be randomised into a 4:4:2 distribution to VIT-2763 QD or VIT-2763 BID or placebo, respectively.

VIT-2763 dose will be adapted to the body weight of the subject:

- Body weight of 40 kg to 59 kg: VIT-2763 dose of 60 mg QD or 60 mg BID, or corresponding placebo.
- Body weight of 60 kg to 100 kg: VIT-2763 dose of 120 mg QD or 120 mg BID, or corresponding placebo.

The randomisation list in each cohort will be generated using an algorithm that will ensure that for Cohort I and Cohort II, the first 10 and 5 subjects will be randomised with a 4:4:2 and 2:2:1 distribution, respectively, for the safety review of each cohort.

12.4 Analysis Sets

12.4.1 Full Analysis Set

The FAS consist of all subjects who satisfy the following criteria:

- Randomised to treatment
- Received at least 1 dose of randomised treatment
- Had at least 1 post-baseline PD assessment

The subjects in this data set 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 FAS criteria, had no major protocol deviations (as defined in the SAP and finalised during the blind data review meeting).

The subjects in this data set will be analysed based on the treatment they were randomised to.

12.4.3 Safety Set

The safety set (SS) consists of all randomised subjects who have taken at least 1 dose of study medication. 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, iron parameters (total serum iron, ferritin, transferrin, calculated TSAT) will be summarised on overall subjects receiving VIT-2763, subjects receiving VIT-2763 by dose daily frequency and on subjects receiving placebo within each cohort.

[redacted]

Demographic characteristics and baseline characteristics including baseline weight, body mass index, iron and iron related parameters and blood transfusion history will be summarised on overall subjects, overall subjects receiving VIT-2763, subjects receiving VIT-2763 by dose frequency group and on placebo subjects within each cohort. If at least 1 subject is randomised in each body weight category, summary statistics will be repeated in each body weight category.

Analyses will be performed on the 3 analysis sets. In case some analyses sets are identical, analyses will not be repeated.

12.6 Study Medication

The total amount of study drug 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, subjects receiving VIT-2763 by dose frequency group and on placebo subjects within each cohort. If at least 1 subject is randomised in each body weight category, summary statistics will be repeated in each body weight category.

It will be provided for the FAS and the SS, if they differ.

12.7 Concomitant Therapy

Concomitant medications will be categorised according to a standard dictionary (World Health Organization Drug Classification). Counts and percentages of subject use for each medication will be computed and summarised on overall subjects, overall subjects receiving VIT-2763, subjects receiving VIT-2763 by dose frequency group and placebo subjects within each cohort.

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

12.8 Safety Evaluations

12.8.1 Primary

All safety analyses will be performed on the SS.

If at least 1 subject is randomised in each body weight category, all safety tabulations will be repeated by body weight category.

Adverse Events

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

A summary table with the counts and percentage of subjects and the number of events will be provided on overall subjects receiving VIT-2763, subjects receiving VIT-2763 by dose daily frequency and on all subjects receiving placebo within each cohort, for any TEAEs, any severe TEAEs, any serious TEAEs, any TEAEs leading to study withdrawal, 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 to study drug on overall subjects receiving VIT-2763, subjects receiving VIT-2763 by dose daily frequency and on all subjects receiving placebo within each cohort.

Same tables according to SOC and PT 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, subjects receiving VIT-2763 by dose daily frequency 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, subjects receiving VIT-2763 by dose daily frequency 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, subjects receiving VIT-2763 by dose daily frequency and on subjects receiving placebo.

Abnormal ECG findings will be listed.

12.9 Iron PD Evaluations

12.9.1 Secondary PD

Values by visit from baseline and changes from baseline by post-baseline visit for the iron parameters (total serum iron, ferritin, transferrin, calculated TSAT) and iron related

parameters will be summarised on overall subjects receiving VIT-2763, subjects receiving VIT-2763 by dose daily frequency and on subjects receiving placebo.

Values at each visit from baseline and changes from baseline at each post-baseline visit of the iron parameters (total serum iron, ferritin, transferrin, calculated TSAT) will be summarised on the same treatment groups.

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

If at least 1 subject is randomised in each body weight category, the summary statistics will be repeated by body weight category.

Observations will be treated as right-censored for subjects who complete the study treatment (Week 12) or prematurely withdraw prior to initiation of RBC transfusions, or any iron related pharmacological treatment.

12.10 Interim Analyses

For each cohort, blinded data of the first 10 subjects in Cohort I and the first 5 subjects in Cohort II will be reviewed by an SRT (see Section 11).

Data to be reviewed by the SRT will be defined in the SRT charter. Tabulations and listings will be run by an independent statistical person(s) and sent only to the SRT members, to ensure that the study statistical members remain blinded.

12.11 Secondary Evaluations

12.11.1 Pharmacokinetics

PK concentrations will be listed by subject for each sampling time point by visit 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 on VIT-2763 subjects by dose frequency group.

A population PK approach in adult and adolescent subjects combined with suitable mathematical/statistical analysis, using nonlinear mixed-effects modelling will be applied. Details will be specified in the SAP. PK parameters i.e., individual estimated C_{max}, clearance, distribution volume, AUC will be listed by subject and visit for all subjects who received VIT-2763. Summary level statistics (means and variability) will be generated by dose frequency group. The results of the population PK analysis will be reported separately in a modelling and simulation report.

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

If at least 1 subject is randomised in each body weight category, the summary statistics will be repeated by body weight category.

If at least 1 subject is randomised in each body weight category, PK analyses will be repeated in each body weight category.

12.12 Other Evaluations

12.12.1

Values by visit from baseline and changes from baseline by post-baseline visit for Hb, reticulocytes, amylase, bicarbonate, eGFR, will be summarised on overall subjects receiving VIT-2763, subjects receiving VIT-2763 by dose daily frequency and on all subjects receiving placebo.

The counts and percentages of subjects achieving an increase in Hb ≥1.0 g/dl and the ones achieving an increase in Hb ≥1.5 g/dl will be provided by visit on the same treatment groups.

If at least 1 subject is randomised in each body weight category, the summary statistics will be repeated by body weight category.

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

Values by visit from baseline and changes from baseline by post-baseline visit for will be summarised on overall subjects receiving VIT-2763, on subjects receiving VIT-2763 by dose daily frequency and on all subjects receiving placebo.

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

If at least 1 subject is randomised in each body weight category, the summary statistics will be repeated by body weight category.

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 [16], and the ICH guidelines for Good Clinical Practice [17] as amended. Vifor Pharma 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/EC/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 or their legally acceptable guardian 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. Also, consent from parent in case of adolescent subjects will be required as applicable.

13.3 IRB or EC/IEC

The protocol, any protocol amendments and consent form for the proposed clinical study and any other documents required by the local IRB/EC/IEC must be submitted by the Investigator for review and approval to the IRB/EC/IEC. The Investigator must also ensure that the IRB/EC/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 Vifor Pharma before the study is implemented.

14. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator must ensure that all trial related site source data, study related documents and reports will be available, and that the provision of direct access for monitoring and auditing by Vifor Pharma 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/EC/IEC.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the Monitor (source document verification), and the maintenance of a drug dispensing log by the Investigator. The data collected will be entered (EDC) into the study database. A comprehensive validation check program will verify the data and queries will be generated for resolution by the Investigator. Throughout the study, Vifor Pharma or its designates may review data as deemed necessary.

[redacted]

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
- 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 study visits and reference to the trial identifier

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

15.1.1 Records Retention

The Investigator must arrange for the retention of all study documentation (such as 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.

[redacted]

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 Vifor Pharma immediately if any documents are lost, to be transferred to a different facility, or to be transferred to a different owner.

15.1.2 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.

15.2 Other Services

Not applicable.

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 Vifor, 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 Vifor Pharma. Each applicable Regulatory Authority/IRB/EC/IEC will review and approve amendments prior to their implementation. Regulatory Authority/IRB/EC/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/ECs. 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

Vifor Pharma is committed to the timely communication of data from clinical research trials, following the Pharmaceutical Research and Manufacturers of America principles [18]. Where possible, authorship will be agreed at the beginning of the study. The authors will form a publication committee and this committee will propose and develop appropriate scientific manuscripts or abstracts from the study data. Investigators may not present or publish partial or complete study results individually.

Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by Vifor Pharma before submission for publication. Names of all Investigators actively participating in the study will be included in the publication. The publication committee for a study will comprise of authors selected in adherence with the International Committee of Medical Journal Editors criteria [19] for authorship.

That is, all authors must meet each of the following 3 criteria:

1. Substantial contribution to conception and design or acquisition of data, or analysis and interpretation of data

2. Drafted the article or revised it critically for important intellectual content

3. Approved the final version for publication

In addition, certain Vifor Pharma employees involved in the design and conception of the protocol, study management and data analysis and interpretation are qualified authors and will be included in the publication committee e.g., the lead physician, statistician and study project manager or their equivalents.

18. REFERENCES

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[redacted]

Appendix 1 Serious Adverse Event Form (Sample)

VIFOR PHARMA

FORGDS027915: SAE Report Form, V03

Study/Protocol ID: _____ **SUBJECT ID:** |_ _|_ _|_ _|_ _||_ _|_ _|_ _|_ _|_ _|

1. REPORT INFORMATION

Select: ☐ **Initial Report** or ☐ **Follow-up Report** (Enter Date: |_ _|_ _| - |_ _|_ _|_ _| - |_ _|_ _|_ _|_ _|)
DD MMM YYYY

2. SUBJECT INFORMATION:

a) Year of birth: |_ _|_ _|_ _|_ _| or if unknown, enter age at SAE onset: |_ _|_ _| years

b) Gender: ☐ Male or ☐ Female

c) Randomization number: |_ _|_ _|_ _|_ _|_ _|_ _|_ _|_ _|

d) Height: |_ _|_ _|_ _| ☐ cm or ☐ inches

e) Weight: |_ _|_ _|_ _| ☐ kilograms or ☐ pounds

3. STUDY DRUG ADMINISTRATION

Study drug administration: ☐ NOT APPLICABLE or ☐ STUDY DRUG 1 or ☐ STUDY DRUG 2 (COMPARATOR) or ☐ PLACEBO or ☐ BLINDED STUDY

Has the subject taken/received at least one dose of study drug? ☐ NO or ☐ YES. If yes, please fill in following details:

Start Date of Administration: |_ _|_ _| - |_ _|_ _|_ _| - |_ _|_ _|_ _|_ _| (DD-MMM-YYYY)

Stop Date of Administration: |_ _|_ _| - |_ _|_ _|_ _| - |_ _|_ _|_ _|_ _| (DD-MMM-YYYY)

Most recent Date of Administration before onset of SAE: |_ _|_ _| - |_ _|_ _|_ _| - |_ _|_ _|_ _|_ _| (DD-MMM-YYYY)

Study drug administration details:

Volume administered (Units) *Optional (Example to be added)*	Dose per administration (Units) *(Example to be added)*	Dose Form	Dose Route	Dose Frequency	Batch number *Optional*	Cumulative total dose of study drug administered until start of event (Units) *Optional*

[redacted]

VIFOR PHARMA

FORGDS027915: SAE Report Form, V03

Study/Protocol ID: _____ **SUBJECT ID:** |__|__|__|__|__|__|__|__|__|__|

4. ACTION TAKEN WITH STUDY DRUG:

- ☐=None/Dose not changed
- ☐=Dose reduced, please record details below if applicable:

  Date of dose reduced : |__|__| - |__|__|__| - |__|__|__|__| (DD-MMM-YYYY)

  New dose details and frequency :
- ☐=Dose increased, please record details below if applicable:

  Date of dose increased : |__|__| - |__|__|__| - |__|__|__|__| (DD-MMM-YYYY)

  New dose details and frequency :
- ☐=Temporary interrupted, please record the Date: |__|__| - |__|__|__| - |__|__|__|__|
  DD MMM YYYY

  Record the Date of study drug administration restart: |__|__| - |__|__|__| - |__|__|__|__|
  DD MMM YYYY
- ☐=Permanently discontinued, please record the Date : |__|__| - |__|__|__| - |__|__|__|__|
  DD MMM YYYY
- ☐=Not applicable
- ☐=Unknown

Did the SAE(s) improve or resolve after stopping or reducing study drug? ☐ No ☐ Not applicable ☐ Unknown

☐ Yes. If yes, please provide the SAE number(s) from section 6: _____

Did the SAE(s) recur after study drug was restarted? ☐ No ☐ Not applicable ☐ Unknown

☐ Yes. If yes, please provide the SAE number(s) from section 6: _____

[redacted]

VIFOR PHARMA

FORGDS027915: SAE Report Form, V03

Study/Protocol ID: _____ **SUBJECT ID:** |__|__|__|__||__|__|__|__|__|

5. SERIOUS ADVERSE EVENT (SAE) DESCRIPTION *(Please describe the clinical course of events, incl. signs, symptoms, most important reactions, final (or working) diagnosis, all relevant laboratory tests and findings. Please provide alternative factors and contributing etiology)*

[redacted]

VIFOR PHARMA

FORGDS027915: SAE Report Form, V03

Study/Protocol ID: _____ **SUBJECT ID:** |_ _|_ _|_ _|_ _||_ _|_ _|_ _|_ _|_ _|_ _|

6. SERIOUS ADVERSE EVENT DETAILS: Please indicate how many pages for describing SAE Details are used for this Report: ☐ **1 or** ☐ **2 or** ☐ **3**

SAE No.	**SAE Term(s)** *(Please provide diagnosis {single illness or syndrome} instead of symptoms)*	**SAE Start date** Add DD-MMM-YYYY	**SAE Stop date** Add DD-MMM-YYYY Or tick "ongoing" ☐ Or "Unknown" ☐	**Severity:** Add 1=Mild 2=Moderate 3 =Severe; **or** **Toxicity:** Add 0=Grade 0 Absent 1=Grade 1 Mild 2=Grade 2 Moderate 3=Grade 3 Severe 4=Grade 4 Life-threatening/disabling 5=Grade 5 Death *(Optional: To be selected as per study – either Severity or Toxicity)*	**Other Action taken** 0=None; 1=Medication given; 2=Procedure given; 3=Early study termination	**Outcome** 1=Recovered/resolved (without sequelae) 2=Recovered/resolved with sequelae, also specify the kind of sequelae 3=Recovering/resolving 4=Not recovered/not resolved 5=Fatal 6=Unknown, also specify the rational for unknown.	**SAE Criteria** 1=Fatal 2=Life threatening 3=Hospitalisation or prolongation of hospitalisation 4=Persistent or significant disability/incapacity 5=Congenital anomaly/birth defect 6=Other important/ significant medical event [If SAE resulted in death, please complete information on the next page in table (a)]. [If hospitalisation, please provide the dates on the next page in table (b)]	**Relationship to study drug** 0=Certain 1=Probable /Likely 2=Possible; 3=Not related/ Unrelated

[redacted]

VIFOR PHARMA

FORGDS027915: SAE Report Form, V03

Study/Protocol ID: _____ **SUBJECT ID:** |__|__|__|__||__|__|__|__|__|

[redacted]

VIFOR PHARMA

Study/Protocol ID: _____ **SUBJECT ID:** |__|__|__|__|__|__|__|__|__|__|

7. SERIOUS ADVERSE EVENT DETAILS - SAE Criteria (continued)

a) If the subject died, record the possible causes of death under SAE term above OR if the cause of death is unknown insert "Death due to unknown cause" as SAE term.

Date of death: |__|__| - |__|__|__| - |__|__|__|__| (DD-MMM-YYYY)

Autopsy done: ☐ Unknown ☐ No ☐ Awaiting result ☐ Yes. If Yes, please provide the official cause of death:

_____

b) Date of hospital admission: |__|__| - |__|__|__| - |__|__|__|__| (DD-MMM-YYYY)

Date of discharge: |__|__| - |__|__|__| - |__|__|__|__| or ☐ Not applicable (check this only for death)
DD MMM YYYY

8. RELEVANT MEDICAL HISTORY and CONCOMITANT MEDICATIONS/PROCEDURES

- Has the subject had any relevant medical and surgical history or any co-existing diseases? ☐ **No** ☐ **Yes.**
  If Yes, please attach a copy of the completed **"Medical History"** CRF page(s).

- Has the subject received any Concomitant Medication(s) or Procedures? ☐ **No** ☐ **Yes.**
  If Yes, please attach a copy of the completed **"Prior or Concomitant Procedures"** and **"Prior or Concomitant Medications"** CRF page(s).

9. REPORTER INFORMATION: **Site number:** |__|__|__|__|

Country: _____ **Reporting Date:** |__|__| - |__|__|__| - |__|__|__|__| (DD-MMM-YYYY)

Reporter:

_____ _____
Print Reporter's Name **Reporter's signature**

Fax number: _____ Phone number: _____

Investigator (if different from Reporter):

_____ _____
Print Investigator's Name **Investigator's signature**

After completion of this Form, please transmit it immediately using the below fax numbers or e-mail:

[redacted]

VIFOR PHARMA

FORGDS027915: SAE Report Form, V03

Study/Protocol ID: _____ SUBJECT ID: |__|__|__|__||__|__|__|__|__|
Country 1 (Fax _____) / Country 2 (Fax _____) / Toll-Free number (_____) / Email: @

[redacted]

Appendix 2 Laboratory Grading Criteria According to FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review at 301-827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2007

[redacted]

Contains Nonbinding Recommendations

Table of Contents

[redacted]

Contains Nonbinding Recommendations

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C. 262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See, for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study). Less extreme observations (e.g., mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

[redacted]

Contains Nonbinding Recommendations

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

III. TOXICITY GRADING SCALE TABLES

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categorize adverse events observed during a clinical trial may assist you in monitoring safety and making required reports. Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate

to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illnes	**Mild (Grade 1)**	**(Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

[redacted]

Contains Nonbinding Recommendations

IV. REFERENCES

1. National Cancer Institute Common Toxicity Criteria, April 30, 1999. (http://ctep.cancer.gov/reporting/CTC-3.html)

2. Division of AIDS Table for Grading Severity of Adult Adverse Experiences; August 1992. (http://rcc.tech-res-intl.com/tox_tables.htm)

3. The Brighton Collaboration. Finalized Case Definitions and Guidelines. (http://brightoncollaboration.org/internet/en/index/definition___guidelines.html)

4. HIV Vaccine Trials Network Table for Grading Severity of Adverse Experiences; September 18, 2002. (http://rcc.tech-res-intl.com/tox_tables.htm)

5. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004. (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf)

6. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory Reference Values. New England Journal of Medicine. 2004;351:1548-1563.

Appendix 3 Report on Exposure to Medicines During Pregnancy (Sample)

Vifor Pharma Ltd.
[redacted]

VIFOR PHARMA
FORGDS027927 V03: Pregnancy Report

REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 1

Name of Vifor Drug (Trade name / IMP):

Patients Initials / No: Country: Local Reference No:

Details of Mother and Pregnancy

Date / Year of Birth: / / (dd/mmm/yyyy) Age: Occupation:

Previous Pregnancy

Yes ☐ No ☐ Total no. of pregnancies: Normal Deliveries:

Abortions (Spontaneous): Abortions (performed):

Relevant Medical History:
(including pregnancy risk factors, Pre-eclampsia, eclampsia, smoking, alcohol, environmental & occupational exposures etc.)

Relevant Family History:
(hereditary diseases e.g. hypertension, diabetes)

Current Pregnancy

First day of Last Menstruation: / / (dd/mmm/yyyy) Expected Delivery Date: / / (dd/mmm/yyyy)

Gestational age of foetus (specify at time of exposure / time of reporting) :

Ultrasound performed? Yes ☐ No ☐ If yes, findings if any:

Any complications, infections or illnesses during pregnancy? Yes ☐ No ☐

If yes, elaborate:

Drug Exposure during Pregnancy

Mother /Father Exposure	Suspect Drug/ Concomitant medication	Product Name (Trade / IMP) Batch no.	Total Daily Dose (Units)	Therapy Start date	Therapy Stop date	Indication for use	Route of application (oral, infusion, injection)

Reporting Physician: Name: Profession:

Privacy Notification:
The personal data that you provide, such as your name and contact details, will be handled and stored by Vifor Pharma. You can read in detail what information we save and how the information will be handled in our Privacy Notices on the Vifor Pharma website (www.viforpharma.com/dataprivacy) where you also find contact details if you have questions.

NOTE: The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule specifically permits covered entities (such as pharmacists, physicians or hospitals) to use and disclose health information without authorization in order to report adverse events and other information related to the quality, effectiveness and safety of FDA-regulated products both to the manufacturers and directly to FDA. Please submit only that health information which is reasonably necessary to achieve the purpose of the report.

REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 2

Information on Outcome of Pregnancy

Name of Vifor Drug (Trade name/IMP):

Patients Initials / No: Country: Local Reference No:

Outcome of Pregnancy

☐ Full Term — Normal delivery or Caesarean:

☐ Premature Birth — If premature birth, gestational age: weeks

☐ Spontaneous Miscarriage

☐ Elective termination — Medical Reason? ☐ Yes ☐ No

If yes, specify:

Details / Comments (if any):

☐ Healthy Baby ☐ Multiple Births

☐ Sick Baby (e.g. Birth trauma, infection etc.) ☐ Congenital anomaly or Birth defect ☐ Still Birth

Date of Birth / / (dd/mmm/yyyy) Sex ☐ Male ☐ Female

Size: Weight: APGAR scores, if provided (Birth/5/10 mins.)

Details / Comments (if any):

Please comment on any abnormal condition or occurrence regarding outcome of pregnancy and/or birth/delivery.

Is there a suspicion that adverse outcome of pregnancy is related to exposure to Product?

☐ Yes ☐ No

Please elaborate:

Reporting Physician: Name: Profession:

Please provide all available information and send to completed form. Attach any applicable supporting documentation if applicable. (such as pictures, autopsy report, hospital discharge summary, laboratory values)

Privacy Notification:

The personal data that you provide, such as your name and contact details, will be handled and stored by Vifor Pharma. You can read in detail what information we save and how the information will be handled in our Privacy Notices on the Vifor Pharma website (www.viforpharma.com/dataprivacy) where you also find contact details if you have questions.

[redacted]

NOTE: The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule specifically permits covered entities (such as pharmacists, physicians or hospitals) to use and disclose health information without authorization in order to report adverse events and other information related to the quality, effectiveness and safety of FDA-regulated products both to the manufacturers and directly to FDA. Please submit only that health information which is reasonably necessary to achieve the purpose of the report.

Please always send both, Part I and Part II of the form to [redacted]

[redacted]

Appendix 4 Guidelines for Administering Informed Consent

VIFOR PHARMA

Administrating Informed Consent

These guidelines apply to all study site personnel administrating informed consent to a potential subject *or* their legally acceptable representative, which must be done ***prior*** to conducting any study related functions, including verifying eligibility.

These guidelines are to be used when your site IRB does not provide you with an equivalent documented consent process; or when your site does not have an equivalent written process (like an SOP).

1. Present the potential subject or legally acceptable representative with:
   - The most up-to-date version of the IRB/REB/EC approved informed consent form (ICF)
   - The Subject Information Sheet (PIS) (if any)

2. Explain the following to the potential subject:
   - That the trial involves research
   - The purpose of the trial
   - The trial treatments, procedures to be followed and (if randomized) the probability of each treatment
   - Alternative procedures or treatment that may be available
   - The subject's responsibilities
   - All aspects of the trial which are experimental
   - Reasonably foreseeable risks
   - Reasonably expected benefits
   - Compensation and/or treatment available in the event of trial-related injury
   - Anticipated payment to the subject, and expenses (if applicable)
   - The subject's participation is voluntary; the subject may withdraw consent at anytime. In the USA and whenever possible the withdrawal of consent must be done in writing.
   - Monitor(s), auditor(s) and the IRB/EC and Regulatory Authorities may be allowed direct access to the subjects' medical records.
   - Records identifying the subject will be kept confidential
   - If any information becomes available which may be relevant to the subject's willingness to continue in the trial, he/she should be informed in a timely manner
   - The person(s) to contact for further information regarding the trial and the subject's rights
   - The foreseeable circumstances and/or reasons whereby the subject may be withdrawn from the trial
   - The foreseeable circumstances and/or reasons whereby the trial may be terminated
   - The expected duration of the subject's participation in the trial
   - The approximate number of subjects in the trial

3. Throughout the process, ensure that:

- The potential subject is not coerced or unduly influenced to participate in the trial
- There is ample opportunity and time for the subject to ask questions and to receive satisfactory answers.
- If the subject (or representative) is unable to read, an impartial witness is present during the entire consent discussion. By signing the consent form, the witness confirms that the trial was fully explained and verbal consent willingly given.
- The consent form is **signed** and **dated** by the subject (or representative), the person explaining the study and the witness (if applicable).
- The subject (or representative) receives a copy of the signed and dated consent form and all other written subject information.

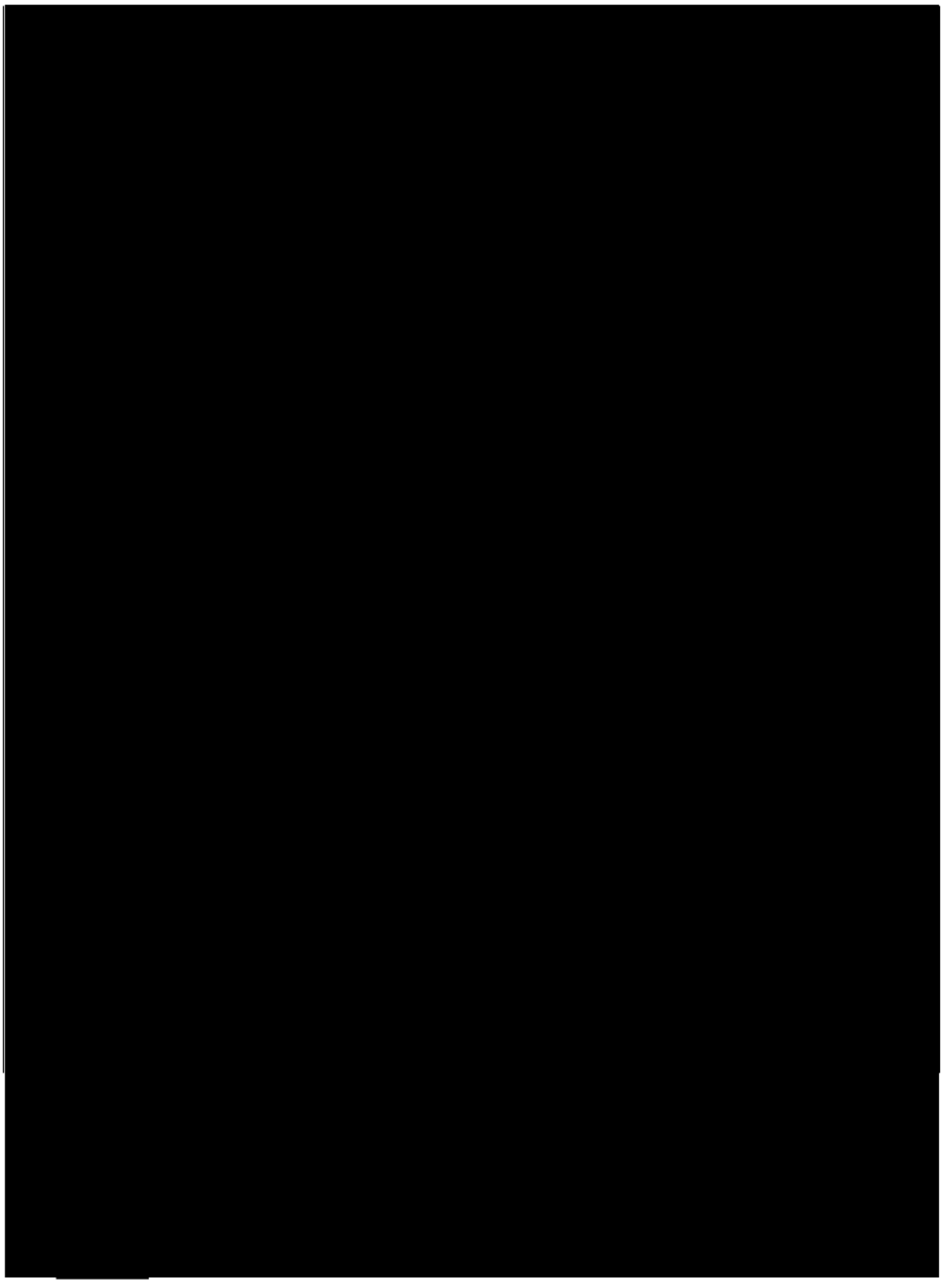
IT IS THE PRINCIPAL INVESTIGATOR'S RESPONSIBILITY TO DOCUMENT THIS PROCESS

4. Tips on documentation of the informed consent process

- There should be a "contextual" statement in the source document to show exactly how and when IC was administered - including the time (even if it is on the ICF).

[redacted]

[redacted]



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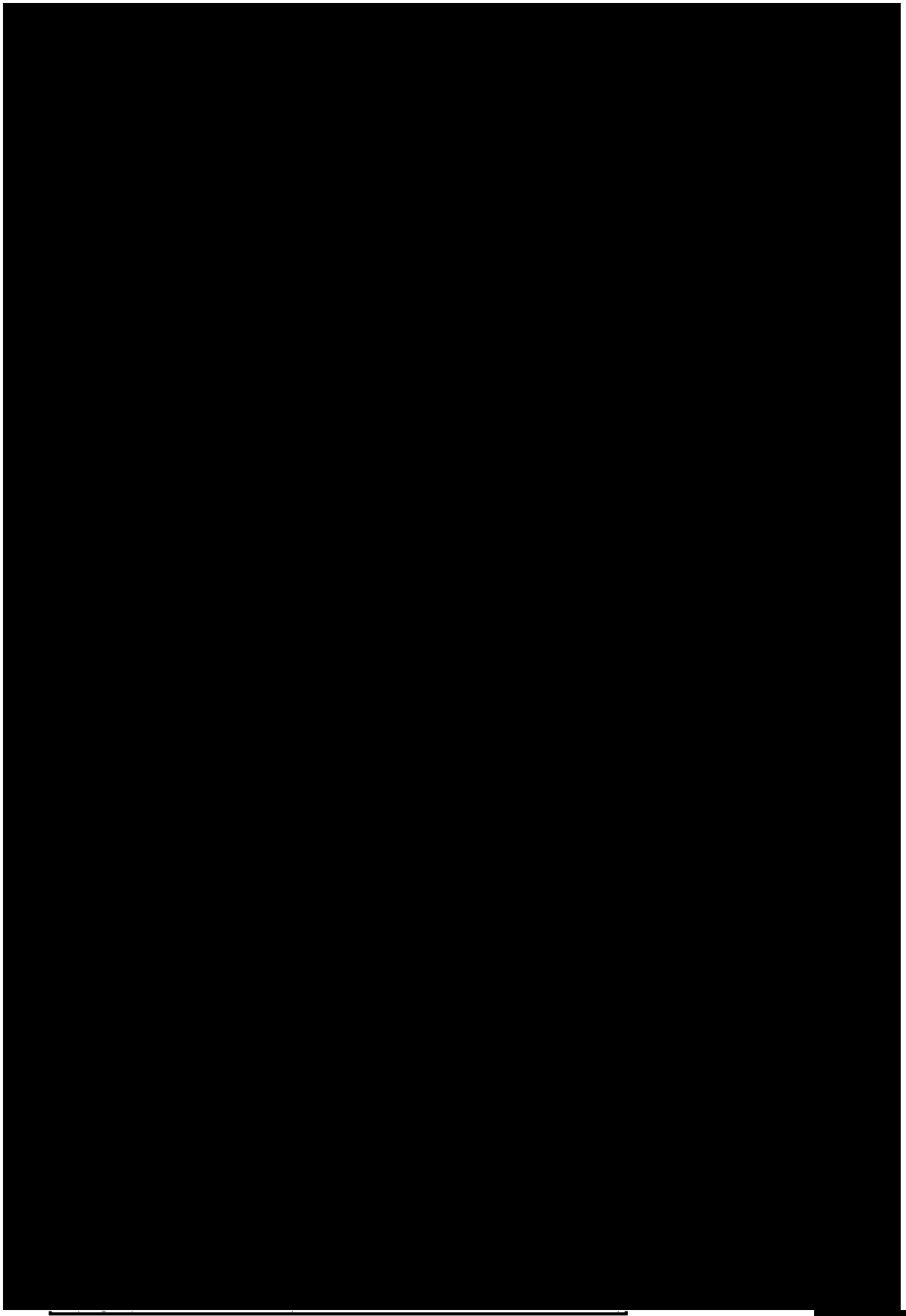

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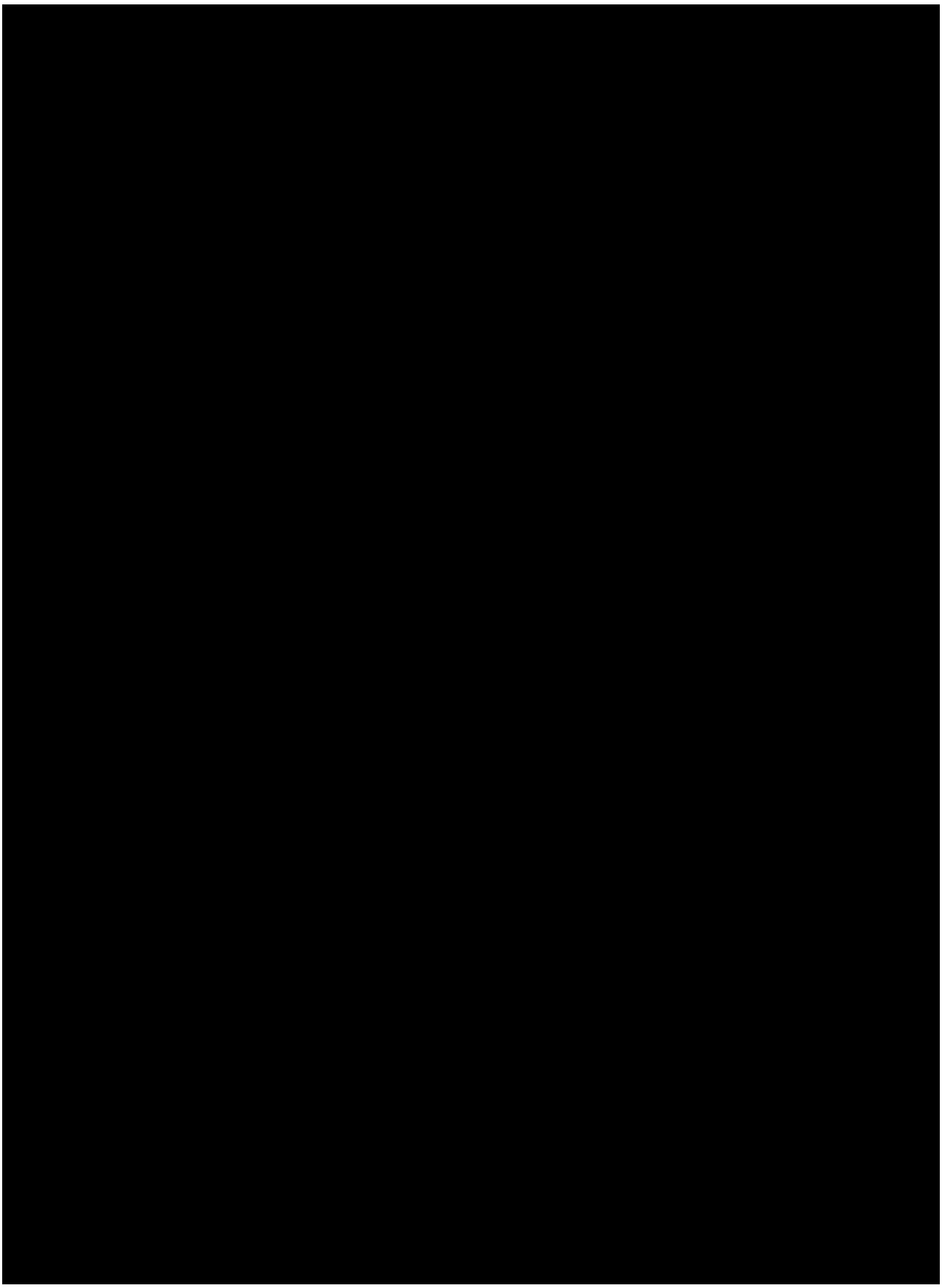

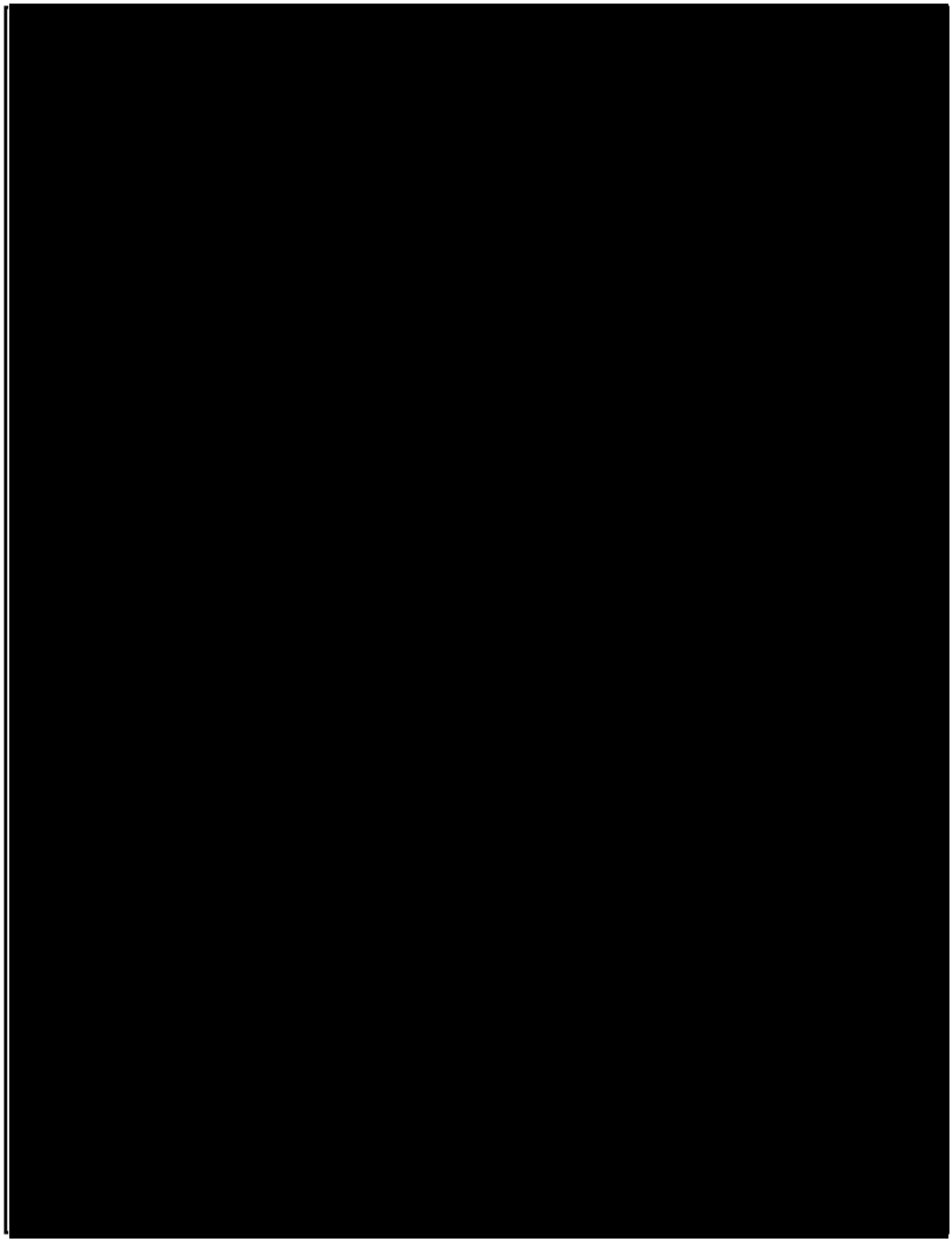

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Certificate Of Completion

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Source Envelope:
Document Pages: 139
Signatures: 1
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
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11-Mar-2022 | 12:24
Holder: [redacted]
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Signer Events	Signature	Timestamp
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Electronic Record and Signature Disclosure: Accepted: 07-Jan-2022 | 15:19 [redacted]		

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	11-Mar-2022 | 12:27
Certified Delivered	Security Checked	11-Mar-2022 | 12:28
Signing Complete	Security Checked	11-Mar-2022 | 12:28
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To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us a [redacted] and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

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ii. send us an email to [redacted] and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

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