SPONSOR: Vivet Therapeutics, SAS
PROTOCOL NUMBER: VTX-801_CLN_001
STATISTICAL ANALYSIS PLAN

Author:	[redacted]

Sponsor:	Vivet Therapeutics, SAS
Protocol Number:	VTX-801_CLN_001
Study Title:	A Phase I/II, Multicenter, Non-randomized, Open Label, Adaptive Design, 5-year Follow-up, Single Dose-escalation Study of VTX-801 in Adult Patients with Wilson's Disease

We, the undersigned, confirm that we have read, understood and agree to the content of this document and hereby authorize its approval.

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	[redacted]		[redacted]

Client Representative

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	[redacted]		[redacted]

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1 Document History

Date	Version	Author(s)	Brief details of changes made
19Dec2024	V0.1	[redacted]	Initial draft version sent to Vivet
17Jan2025	V0.2	[redacted]	Implementing sponsor feedback
24Jan2025	V1.0	[redacted]	Final version 1.0

2 List of Abbreviations

AE	Adverse Event
AESI	AEs of Special Interest
AAV3B	Adeno-Associated Virus serotype 3B
ANCC	Accurate Non-Ceruloplasmin-bound Copper
APRI	AST to platelet ratio index
AST	Aspartate Aminotransferase
ATP7B	Copper-transporting P-type ATPase
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
BQL	Below Quantification Limit
CM	Concomitant medications
Cm	Centimeter
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
Cu	Copper
CuEXC	Exchangeable Copper
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked ImmunoSorbent Assay
ELISpot	Enzyme-Linked ImmunoSpot
CRO	Clinical Research Organization
DILI	Drug Induced Liver Injury
DLT	Drug Limiting Toxicity
DMC	Data Monitoring Committee
EC	Ethic Committee

FAS	Full Analysis Set
FIB4	Fibrosis-4 Index for Liver Fibrosis
HAC	Hepatic Adjudication Committee
IA	Interim Analysis
IAR	Infusion-Associated Reactions
IFN	Interferon
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Boards
IV	Intravenously
Kg	Kilogram
m	Meter
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
M.I.N.I.	Mini International Neuro-psychiatric Interview
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PD	Pharmacodynamic
PDCF	Protocol Deviation Criteria Form
[redacted]	[redacted]
PT	Preferred Term
RAC	Relative Accurate Non-Ceruloplasmin-bound Copper
REC	Relative Exchangeable Copper
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDMT	Symbol Digit Modality Test
SoC	Standard of care
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures and Listings
UWDRS	Unified Wilson's Disease Rating Scale
WD	Wilson's Disease
WHO	World Health Organization
WHOHD	WHO Herbal Dictionary

3 Introduction

The purpose of this document is to describe the statistical outputs to be generated for Vivet Therapeutics, SAS for interim and final analyses of the Phase I/II study titled "A Phase I/II, Multicenter, Non-randomized, Open Label, Adaptive Design, 5-year Follow-up, Single Dose-escalation Study of VTX-801 in Adult Patients with Wilson's Disease".

This statistical analysis plan (SAP) covers the interim and final analyses for the study. The list of tables, figures and listings (TFLs) to be developed for each analysis, as well as the shells for each TFL, are described in a separate document.

The preparation of this document has been based upon the Protocol Version 9.0 from the 07Aug2023, Protocol Version 9.1 from 25SEP2023 (applicable for UK), Protocol Version 9.3 (applicable for Germany and Denmark) from the 25Sep2023, and the latest eCRF version.

This document is developed in the context of an early termination of the treatment phase of the study, leading to the writing of an abbreviated CSR. When the treatment phase was early terminated, only 4 patients from US sites were dosed. Patients will remain in the study for a reduced safety follow-up.

4 Study Description

4.1 Study Objectives and Endpoints

Below are the primary, secondary and exploratory objectives along with the associated endpoints as per the study protocol.

Primary objective:

- Assessing, for up to 5 years, the safety and tolerability of single ascending doses of VTX-801 administered intravenously (IV) to adult patients with Wilson's Disease prior to and following background Wilson Disease (WD) therapy withdrawal.

Primary endpoint:

- Safety and tolerability profile, including treatment-emergent adverse events (TEAE), clinical examination, changes in laboratory parameters, vital signs, ECG, brain and abdominal MRI.

Secondary objectives:

- Exploring VTX-801 pharmacodynamics and efficacy,

- Assessing humoral and cellular immune responses to VTX-801,
- Providing data to support VTX-801 dose level selection.

Secondary endpoints:

- Free serum Cu [may include measurement by assay for CuEXC (exchangeable Cu) and/or ANCC (Accurate non-ceruloplasmin-bound Cu)],
- REC (relative exchangeable Cu), RAC (relative ANCC), total serum Cu and 24-hour urinary Cu,
- Serum ceruloplasmin activity (enzymatic assay),
- VTX-801 Responder status [redacted]
- Time to SoC withdrawal,
- Need for SoC adjustments,
- Need for reinstatement of SoC after withdrawal and whether response occurs at the pre-study SoC dose,
- Time to copper deficiency and whether correction occurs,
- Humoral and cellular immune response to VTX-801:
    - In vitro neutralizing antibodies (Nab) anti-AAV3B capsid assay,
    - ELISA: antibodies against AAV3B capsid and miniATP7B transgene,
    - IFN-gamma ELISpot to AAV3B capsid and miniATP7B transgene

Exploratory endpoints:

- Hepatic Cu and histology from liver biopsy,
- Ceruloplasmin level determination by nephelometry,
- Unified Wilson's Disease Rating Scale (UWDRS),
- Liver Magnetic Resonance (MR) elastography,
- Hepatic synthetic function (INR, platelet count, albumin),
- Model for End-Stage Liver Disease (MELD), AST to platelet ratio index (APRI), Fibrosis-4 Index for Liver Fibrosis (FIB4),
- Mini International Neuro-psychiatric Interview (M.I.N.I.),
- Symbol Digit Modality Test (SDMT) and Stroop test,

- Other biomarkers that may inform long term disease outcomes or responses to treatment with VTX-801.

Given the early termination of the treatment phase of the study, the following endpoints will not be analysed, summarized or tabulated:

- Time to SoC withdrawal – did not occur,
- Need for SoC adjustments – did not occur,
- Need for reinstatement of SoC after withdrawal and whether response occurs at the pre-study SoC dose – did not occur,
- Time to copper deficiency and whether correction occurs – did not occur,
- Radiocopper-related parameters [redacted],
- Other biomarkers, than the ones listed in section 7.8, that may inform long term disease outcomes or responses to treatment with VTX-801.

4.2 Study Design and Target Population

Up to approximately 16 Wilson's Disease male and female adult patients will be administered VTX-801 in 3 dose-escalation cohorts each consisting of up to approximately 4 patients and one expansion cohort consisting of approximately 4 patients treated at the selected VTX-801 dose.

Only if and when an optimal VTX-801 dose level has been selected from the escalation phase based on pharmacodynamic studies with radiocopper and other biomarkers of copper metabolism, four patients will be enrolled in the additional cohort and will receive one infusion of VTX-801 at the Selected Dose level.

The adaptive nature of the study intends to minimize the number of patients exposed to a sub optimal VTX-801 dosing regimen, since for them re-treatment with a therapeutic dose might not be possible due to seroconversion to the AAV3 capsid.

About treatments, radiocopper and follow-up scheme for each patient:

- After inclusion, each patient of each cohort will (i) initiate the immunosuppressive regimen, (ii) complete the radiocopper-related assessments, (iii) receive a single VTX-801 infusion without interrupting their background WD therapy (except for planned wash-out periods in patients on chelators or dual chelator and zinc therapy).
- At Week 12, each patient will undergo a second set of radiocopper-related assessments, and their Responder status will be determined.
- At Week 36, patients will receive a third radiocopper injection and the Responder status

will be assessed again, in order to evaluate the sustainability of the effects in Responders and to detect possible late Responders.

- Patients will be followed up for a total of 5 years from the time of VTX-801 administration (10 years in Germany only – although no patients recruited in Germany therefore this is not applicable).

The detailed study design plan is presented in Section 4 of the protocol.

4.3 Study Treatments and Procedures

Study Treatment

The IMP will be administered as a single dose intravenous (IV) administration per patient, at up to 3 different dose levels.

VTX-801 dose will be incremented by a factor of 3 between escalation cohorts 1 and 2 and by a factor of 2 between escalation cohorts 2 and 3. The following will be used:

- Cohort 1: 5E12 VG/kg
- Cohort 2: 1.5E13 VG/kg
- Cohort 3: 3E13 VG/kg

The Selected Dose for the expansion cohort will be one of the previously tested doses.

Procedures

Schedule of assessments and procedures are presented in table 1, table 2, table 3 and table 4 of the protocol.

Given the study was terminated early, only Cohort 1 and Cohort 2 were investigated to subjects.

4.4 Randomization and Blinding

NA.

4.5 Sample Size Determination

Sample size has not been determined based upon statistical calculations. The sample size of up to approximately 16 patients, with approximately 4 patients per cohort, was chosen based on scientific judgment to have sufficient replication to meet the study objectives.

The best efforts will be made to enrol at least 1 patient of each gender in each cohort of 4.

5 Considerations for Statistical Analysis

The SAS Viya 3.5 (or higher) will be used for all analysis, unless otherwise specified.

5.1 Analysis Periods

Analysis Periods

When Visit data is to be displayed, the following abbreviations in the 'Table Display' column will be used for Tables, Figures and Listings (TFL):

Table 1: Visit and study periods

Visit Number	Study Period (Day or Month)	Table Display
Screening V1A	Minimum 6 to 8 weeks before Screening V2	SCR1
Screening V1B	Day -49 to Day -14	SCR2
Baseline V2	Day -7	BAS D-7
Baseline V3	Day -3	BAS D-3
Baseline V4	Day -2	BAS D-2
Baseline V5	Day -1	BAS D-1
Treatment V6	Day 1	TRT
Follow-up V7	Day 2	FUP D2
Follow-up V8	Week 2	FUP W2
Follow-up V9	Week 3	FUP W3
Follow-up V10	Week 4	FUP W4
Follow-up V11 to V17*	Week 4 to Week 7	FUP W4 to W7
Follow-up V18	Week 8	FUP W8
Follow-up V19 to V25*	Week 8 to Week 11	FUP W8 to W11
Follow-up V26 to V29*	Week 12	FUP W12
Follow-up V30 and V31	Week 12 to Week 13	FUP W12 and FUP W13
Follow-up V32	Week 14	FUP W14
Follow-up V33	Week 15	FUP W15
Follow-up V34	Week 16	FUP W16
Follow-up V35	Week 20	FUP W20
Follow-up V36	Week 24	FUP W24
Follow-up V37	Week 28	FUP W28
Follow-up V38	Week 32	FUP W32
Follow-up V39 to V42*	Week 36	FUP W36

Follow-up V43	Week 38	FUP W38
Follow-up V44	Week 40	FUP W40
Follow-up V45	Week 44	FUP W44
Follow-up V46	Week 52	FUP W52
Follow-up V47	Month 15	FUP M15
Follow-up V48	Month 18	FUP M18
Follow-up V49	Month 21	FUP M21
Follow-up V50	Month 24	FUP M24
End of Study	End Of Study Visit	EOS
FUP (safety) call	Phone call following treatment early termination	FUP call

*Multiple assessments within a given visit will be averaged for summary tables, and individual assessments will be provided in listings.

For visits where assessments occur at multiple timepoints within a visit (e.g. Radiocopper Assessments), the appropriate timepoint description will be added in the format Visit – Timepoint (e.g. Treatment – 4 hours post-dose).

Visit Windowing

All data will be analyzed according to the planned visit as collected in the eCRF.

Unscheduled visits

All data from unscheduled visits will not be included in summaries and will only be presented in data listings, if not otherwise specified.

5.2 Data Handling Rules

Missing Data

No imputation for missing data will be carried out.

Partial Date Imputation

Detailed rules for partial date imputation are described below.

General rules for Adverse events (AE) and prior and concomitant medications (CM)

- In case of partial dates with missing day:

  For AE and CM, any partial start date during the month of VTX-801 dosing will be imputed to be the date of VTX-801 dosing, taking the worst-case scenario.

  For any AE and CM starting after the month of VTX-801 dosing, the start date will be imputed to be the first day of the month.

  For any AE and CM starting before the month of VTX-801 dosing, the start date will be imputed to be the last day of the month.

  Partial AE and CM end dates will be imputed to be the last day of the month or at the date of study discontinuation/completion, whichever occurs first.

- In case of partial dates with missing day and missing month:

  For AE and CM, any partial start date during the year of VTX-801 dosing will be imputed to be the date of VTX-801 dosing, taking the worst-case scenario.

  For any AE and CM starting after the year of VTX-801 dosing, the start date will be imputed to be the first day of the year (e.g., 01 January).

  For any AE and CM started before the year of VTX-801 dosing, the start date will be imputed to be the last day of the year (e.g., 31 December).

  Partial AE and CM end dates will be imputed to be the last day of year (e.g., 31 December) or at the date of study discontinuation/completion, whichever occurs first.

  Some examples are given below (DDMMMYYYY).

  In most cases, start dates are imputed as first day of the month or first day of the year.

Table 1: Examples of missing dates imputation

Data Type	Start Date	Imputed Start Date	First Study Treatment Dose Date	End Date	Imputed End Date
Adverse Event, Prior/ Concomitant Medication	JAN2017	31JAN2017	11NOV2017	MAR2017	31MAR2017
	MAR2017	01MAR2017	27JAN2017	MAR2017	31MAR2017
	2017	27JAN2017	27JAN2017	2017	16MAR2017£
	MAR2017	01MAR2017	27JAN2017	MAR2017	01MAR2017*
	JAN2017	31JAN2017	27FEB2017	2017	31DEC2017
	2016	01JAN2016	27FEB2017	SEP2016	30SEP2016

£ Patient discontinued on 16MAR2017; * Patient discontinued on 01MAR2017.

Rules for other partial dates

If partial date is present for dates related to disease history, the same rules as for AE and CM will be applied.

5.3 Data Derivations

Baseline and Change from Baseline

Baseline and change from baseline will be calculated for all assessments, including additional assessments (if applicable), as follows:

- Baseline value is defined as the last available value prior VTX-801 dosing, if not defined otherwise in the study protocol. Assessments that occurred on the same day as VTX-801 dosing, when time of assessment is not available, will be assumed to be prior to VTX-801 dosing (unless the assessment is planned after VTX-801 dosing in the study protocol).
- Change from baseline will be calculated for any post-baseline data as the difference between the post-baseline assessment value and the baseline value.

Study Day

Study day will be calculated as (assessment/sample date – date of first study treatment dose) for pre-baseline assessments and [(assessment/sample date – date of first study treatment dose) + 1] for post-baseline assessments, i.e., there will be no study day 0 and study day 1 will correspond to the first study treatment dose.

5.4 Other Data Analyses Considerations

Centre Effect Management

Not Applicable.

Subgroup Analyses

Not Applicable.

Other Strata and Covariates

Not Applicable.

Multiple Comparisons and Multiplicity

Not Applicable.

6 Analysis Sets

Analysis sets to be used for the analyses are described in the table below.

Table 2: Analysis Sets

Analysis Set	Description
Screened set	The Screened set will include all patients who were enrolled (signed informed consent) regardless of whether they received the study drug or not.
Safety set	The Safety set will include all patients who received at least part of the VTX-801 dose. This analysis set will be used for all safety analyses.
Pharmacodynamics set	The Pharmacodynamics set will include all patients who received at least part of the VTX-801 dose and who have at least one post-baseline pharmacodynamics assessment (free serum Cu (CuEXC and ANCC), REC, RAC, total serum Cu, 24-hour urinary Cu and serum ceruloplasmin by enzymatic activity assay and by nephelometry).
Efficacy set	The efficacy set will include all patients who received at least part of the VTX-801 dose and who have at least one post-baseline radiocopper assessment.

Given that the study was early terminated and an abbreviated CSR focusing mostly on safety data will be prepared, Pharmacodynamics Set and Efficacy Set will not be used in any analysis.

7 Methods of Analysis

7.1 General Considerations

N

N will be the number of patients in the specified population and cohort.

Continuous data

Continuous data will be summarized using: the number of patients with non-missing observations (n), mean, median, standard deviation (SD), minimum and maximum.

Continuous variables will be reported with the same number of decimal places as collected in the CRF except for mean and median (+1 decimal place) and standard deviation (+2 decimal places).

Categorical data

Categorical data will be summarized using: the number of patients with non-missing observations (n), count/number of events (if applicable) and percentage of each category.

- All categories will be presented, even if no patients are counted in a particular category, unless otherwise stated.
- In case 1 or more patients have missing data for the summary, the number with missing data will be presented as a separate category, labelled accordingly as 'Missing', if not otherwise stated.
- Counts of zero in any category will be presented without percentage.
- All summary percentages will be calculated using N as the denominator, unless otherwise stated.
- For AEs, medical history, prior and concomitant medications, the counts are based on single counts of patients with multiple events/treatments under the same category, while the percentages are calculated using N. Counts will be displayed by descending order of frequency for the overall group, unless otherwise stated.

Data presentation

- Outputs: generated directly in rtf format using ODS RTF within SAS. Outputs will be delivered in a single combined pdf file.
- Page Orientation: Landscape.
- Font: Courier New font with minimum of 9-point font size.
- Margins: top: 3cm, bottom: 2cm, left: 3.8cm and right: 2cm on A4 paper.
- Column headers will be left aligned.
- Page headers will include the name of the sponsor, and the date of database lock and data extraction.

7.2 Patient Disposition

Patient disposition data will be presented by dose cohort and overall.

The number and percentage of patients belonging to the following categories will be presented along with the reason for discontinuation: enrolled, screened, screening discontinuation, completed the study, discontinuation from the study.

The number and percentage of patients in each analysis set will also be presented.

In addition, information on analysis sets, study completion and discontinuation will be listed.

7.3 Protocol Deviations

The list of potential protocol deviations, including classification (Important/Non-important) for each protocol deviation, will be pre-defined in the Protocol Deviation Criteria Form (PDCF).

Prior to data lock for analysis, a meeting will be held to review protocol deviation classification, and to agree on the analysis sets.

The number and percentage of patients with at least one important deviation will be provided separately for each cohort and overall.

Important protocol deviations will also be summarized (frequencies and percentages) by deviation category and overall, on the Safety Set.

A listing of all important protocol deviations will be provided for all patients.

7.4 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized using descriptive statistics and presented by dose cohort and overall using the SAF:

- Age at baseline (years) – continuous and categorical (18-64, 65-84, >=85),
- Gender,
- Childbearing / Reproductive potential,
- Race,
- Ethnicity,
- Smoking history, and alcohol consumption
- Height at baseline (cm),
- Weight at baseline (kg),

- BMI (kg/m²).

The following disease characteristics will be summarized using descriptive statistics and presented by dose cohort and overall using the SAF:

- Time since Wilson Disease diagnosis,
- Leipzig score at diagnosis,
- ATP7B genotyping performed by CLIA certified laboratory,
- Gene/codon/amino acid change as reported in the eCRF.

All the above will also be provided in listings for all patients.

7.5 Medical History

Medical history and concomitant diseases will be coded using MedDRA dictionary.

Medical histories are defined as events reported on the General Medical History eCRF pages, which ended before the first study treatment date.

Concomitant diseases are defined as diseases which started before the first study treatment date but were ongoing at the first study treatment date, or disease which started on or after VTX-801 dosing.

The number and percentage of patients with a medical history will be tabulated by dose cohort and overall, by System Organ Class (SOC) and Preferred Term (PT), using the SAF. A by-patient listing will be produced.

The number and percentage of patients with a concomitant disease will be tabulated by dose cohort and overall, for each SOC and PT, using the FAS. A by-patient listing will be produced.

7.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHOHD dictionary.

Medications will be defined as follows:

- Prior Medication: any medications with start date before VTX-801 dosing.
- Concomitant Medication: any medications with end date either the same or after VTX-801 dosing or missing.

Any medications with start date before the first study treatment date and end date either after the first study treatment date or missing will be assumed to be both prior and concomitant medication.

The number and percentage of patients with prior and concomitant medications will be tabulated by cohort and overall, by Anatomical Therapeutic Chemical Classification (ATC) and preferred term (PT) on the SAF. A by-patient listing will be produced for prior and concomitant medications as well as for all prior therapies.

Prior and concomitant medications attached to WD will be listed.

Surgery and Medical Procedures:

Surgery and Medical Procedures will be listed on the SAF.

7.7 Treatment Exposure and Compliance

VTX-801 administration and infusion parameters will be reported using listings.

7.8 Efficacy and Pharmacodynamic (PD) Analyses

Unless otherwise specified, the following endpoints will be listed.

Secondary endpoints:

- Free serum Cu [may include measurement by assay for CuEXC and/or ANCC],
- REC, RAC, total serum Cu and 24-hour urinary Cu,
- Serum ceruloplasmin activity (enzymatic assay),
- VTX-801 responder status [redacted]
- VTX-801 Responder status,
- Humoral and cellular immune response to VTX-801:
    - In vitro neutralizing antibodies (Nab) anti-AAV3B capsid assay,
    - ELISA: antibodies against AAV3B capsid and miniATP7B transgene,
    - IFN-gamma ELISpot to AAV3B capsid and miniATP7B transgene

Exploratory endpoints:

- Hepatic Cu and histology from liver biopsy,
- Ceruloplasmin level determination by nephelometry,
- Unified Wilson's Disease Rating Scale,
- Liver Magnetic Resonance elastography,

- Hepatic synthetic function (INR, platelet count, albumin),
- Model for End-Stage Liver Disease, AST to platelet ratio index, Fibrosis-4 Index for Liver Fibrosis,
- Mini International Neuro-psychiatric Interview,
- Symbol Digit Modality Test and Stroop test,

7.9 Safety Analyses

All safety analyses will be performed using descriptive statistics by cohort and overall using the SAF, unless otherwise specified.

7.9.1 Adverse Events

Adverse events (AEs) will be coded using MedDRA dictionary.

AEs will be graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5, based on study protocol.

The following definitions will be used:

- Treatment-emergent AEs (TEAEs): AEs that occurred during on-treatment period, from the day of VTX-801 dosing,
- Related AEs: AEs suspected by the Investigator to have a relationship to study treatment (as recorded on the AE eCRF page, Relationship to VTX-801 = Possibly related, Probably related, Definitely related or missing,
- Serious Adverse Events (SAE): serious AEs (as recorded on the AE eCRF page, Does AE Meet the Definition of an SAE = Yes),
- AEs leading to Death: adverse event leading to death (as recorded on the AE eCRF page, Results in death, or Outcome = Fatal, or Grade = 5),
- Liver function AEs: adverse event meeting the definition of a suspected DILI (as recorded on the AE eCRF page, does AE meet the definition of a suspected DILI event? = Yes).

An overview summary table will present the number and percentage of patients with a TEAE, including:

- TEAEs / TEAEs related to study treatment,
- Serious TEAEs / Serious TEAEs related to study treatment,
- Liver TEAEs / Liver TEAEs related to study treatment,

- Adverse events of special interest (AESI) / AESI related to study treatment,
- Dose Limiting Toxicity / Dose Limiting Toxicity related to study treatment,
- TEAEs leading to death / TEAEs related to study treatment leading to death,
- TEAEs with NCI-CTCAE grade ≥ 3 / TEAEs related to study treatment with NCI-CTCAE grade ≥ 3,
- TEAE meeting any stopping rule,
- TEAE Related to Radiocopper Administration,
- TEAE related to Other Study Procedure.

In addition, the following tables will be produced by SOC and PT:

- TEAEs / TEAEs related to study treatment,
- Serious TEAEs / Serious TEAEs related to study treatment,
- Liver TEAEs / Liver TEAEs related to study treatment,
- TEAEs and maximum CTCAE grade / TEAEs related to study treatment and maximum CTCAE grade,
- TEAEs leading to death / TEAEs related to study treatment leading to death,
- Non-serious TEAE.

A patient with multiple occurrences of an AE will be counted only once in the AE category. SOCs will be sorted by descending order of frequency for the overall group, PTs will be sorted by descending order of frequency for the overall group within each SOC.

All deaths and on-treatment deaths will be listed together with the corresponding reasons.

The following listings will be provided:

- All AEs, identifying events collected during the pre-treatment and on-treatment,
- Serious AE,
- Non-Serious AE.

7.9.2 Clinical Laboratory Evaluation

All laboratory data collected will be reported using standards units.

The continuous numerical measurements of all laboratory tests will be summarized using descriptive summary statistics for each visit, by dose cohort and overall. A listing of laboratory parameters will be created.

Also, results of pregnancy tests will be listed.

7.9.3 Vital Signs

All vital signs parameters collected will be reported in a listing.

7.9.4 Other Safety Data

Electrocardiogram (ECG)

All ECG parameters collected will be reported.

The numerical measurements and change from baseline of ECG parameters will be summarized by timepoint using descriptive summary statistics for each visit, by dose cohort and overall. ECG parameters will also be provided in a listing.

Ophthalmology

A listing of all ophthalmological examination assessments will be created on the SAF.

Sirolimus

Sirolimus assessments will be reported in listings on the SAF.

Radiocopper administration

Radiocopper administration will be reported in a listing on the SAF.

Steroids:

Per protocol steroid treatments will be reported in a listing on the SAF.

[redacted]

Vector shedding:

Vector shedding findings will be reported in a listing on the SAF.

Brain and abdominal MRI:

Brain and abdominal MRI assessments/findings will be reported in a listing on the SAF.

Physical examination:

Physical Examination includes the following parameters: General appearance, Skin, Head and neck, Eyes, ears, nose, throat, Lymph node palpation, Lungs, Chest, Abdomen, Extremities, Neurological function.

A listing of physical examination evaluations will be created on the SAF.

8 Interim Analysis (IA)

8.1 Planning of Analyses

This SAP covers the interim and final analyses for the study.

A separate SAP has been developed specifically for the safety reviews to be conducted by the DMC.

Given that the treatment was early terminated, an abbreviated CSR focusing on safety will be prepared based on the interim analysis. Thus, the SAP is written with focus on safety and other important data for reporting purposes.

The final analysis will occur at the end of the safety follow-up and will support the writing of a CSR addendum.

8.2 Planned Interim Analysis Details

An interim analysis was planned to occur 1 year after the last patient was treated with VTX-801, per protocol. Due to the treatment premature discontinuation, the IA will occur before the 1-year period is reached after the last patient is treated with the study drug. Also, the IA will mainly focus on safety data.

9 Changes from Study Protocol

Due to early termination of the treatment, below is the list of changes from protocol:

- When the decision has been made to early terminate the treatment phase of the study, only 4 patients were dosed from US sites (2 in cohort 1 and 2 in cohort 2),
- The interim analysis will cover the study up to the early termination visit, occurring prior the end of the 1 year period after last patient was treated,
- The final analysis will cover the safety follow-up period after the study was prematurely discontinued,
- Pharmacodynamics Set and Efficacy Set will not be used for any of the TFLs,
- Pharmacodynamics and efficacy analysis will be limited to descriptive statistics,
- SoC withdrawal related data will not be produced,
- Shift tables will not be produced for laboratory evaluations,
- MELD has been calculated with an outdated formula. Footnote will be added to MELD-related outputs for reader's information.

10 References

[1] ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[2] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

11 Appendices

11.1 Tables, Figures and Listings

Tables, figures and Listings (TFLs) shells are presented in a separate document.

11.2 Other

Not Applicable.