Protocol VTX-801_CLN_001	Investigational Product: VTX-801
	Version: 9 dated 07 AUG 2023
	Author: Aixial Group CRO

Clinical Study Protocol

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

Study / IND Sponsor:	Vivet Therapeutics, SAS
Investigational Product:	VTX-801 (Adeno-associated viral vector serotype 3B encoding shortened human ATP7B)
Indication:	Wilson's Disease
Protocol Number:	VTX-801_CLN_001
International Coordinating Investigator:	Prof. Michael Schilsky, MD
Medical Monitoring:	Aixial Group CRO (formerly Cmed)
Final Version Number:	9
Final Version Date:	07 Aug 2023
EudraCT number	2020-000963-22
IND number	026173

COMPLIANCE STATEMENT

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- International Conference on Harmonization (ICH) Guideline on GCP E6; 62 Federal Register 25691 (May 9, 1997)
- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for Good Clinical Practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products
- Regulation (EU) no 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

PROTOCOL SIGNATURES

Sponsor's Chief Medical Officer:

Name:	[redacted]	**Date:**	
Position:	[redacted]		
Signature:			

Clinical Research Organization's Medical Monitor and Safety Physician:

Name:	[redacted]	**Date:**	
Position:	[redacted]		
Signature:			

Coordinating Investigator:

Name:	Professor Michael Schilsky, MD	**Date:**	
Position:			
Signature:			

INVESTIGATOR SIGNATURE

The signature below constitutes the approval of this protocol and its attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations, EU regulations and ICH guidelines.

Name:		**Date:**	
Site Name:			
Site Address:			
Signature:			

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAV3B	Adeno-Associated Virus serotype 3B
ACE	Angiotensin-Converting Enzyme
AE	Adverse Event/Adverse Experience
ALF	Acute Liver Failure
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ANC	Absolute Neutrophil Count
ANCC	Accurate non-ceruloplasmin-bound Cu
APRI	AST to platelet ratio index
aPTT	Activated Partial Thromboplastin time
AST	Aspartate Aminotransferase
ATP7B	Copper-transporting P-type ATPase
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
BQL	Below Quantification Limit
BSL	Biosafety Level
BUN	Blood Urea Nitrogen
CAP	Controlled Attenuation Parameter
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum Plasma Concentration
CMV	Cytomegalovirus
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
$^{64}Cu/[^{64}Cu]CuCl_2$	Radiocopper
Cu	Copper
CuEXC	Exchangeable Copper

Cp-Copper	Ceruloplasmin-bound copper
D	Day
DB	Direct Bilirubin
DILI	Drug-Induced Liver Injury
DL	Dose Level
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-Linked ImmunoSorbent Assay
ELISpot	Enzyme-Linked ImmunoSpot
EMA	European Medicines Agency
ERC	Eligibility Review Committee
ESLD	End-Stage Liver Disease
EU	European Union
FIB4	Fibrosis-4 Index for Liver Fibrosis
FIH	First-in-Human
FDA	Food and Drug Administration
GaTeWay	Gene Therapy in Wilson disease
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practice
H	Hour
HAC	Hepatic Adjudication Committee
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCP	Health Care Provider
HCV	Hepatitis C virus
HDL	High Density Lipoprotein
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HLGT	High Level Group Term

HSV	Herpes Simplex Virus
HTLV	Human T-cell Lymphotropic Virus
IAR	Infusion-Associated Reactions
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICRP	International Commission on Radiological Protection
ID	Injected Dose
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-2,6 or 10	Interleukin-2, 6 or 10, respectively
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
ERC	Eligibility Review Committee
IS	Immunosuppressive Regimen
ISH	*In Situ* Hybridization
ISM	Independent Safety Monitor
IU	International Unit
IUD	Intrauterine Device
IV	Intravenous
KVO	Keep-Vein-Open
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LKM1	Liver-Kidney Microsome Type 1
LLT	Lower-Level Term
LoQ	Limit of Quantification
LS	Liver Stiffness
MBq	Megabecquerel
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
M.I.N.I	Mini International Neuro-psychiatric Interview
MoCA	Montreal Cognitive Assessment

MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
mSv	Millisievert
mTOR	Mammalian target of rapamycin
NAb	Neutralizing Antibody
NCC	Non-ceruloplasmin-bound copper
NHP	Non-Human Primates
NIH	National Institutes of Health
NIMP	Non-Investigational Medicinal Product
P	Pulse
PET	Positron Emission Tomography
PCP	Phencyclidine
PCR	Polymerase Chain Reaction
P-gp	P-glycoprotein
PHI	Protected Health Information
PI	Principal Investigator
[redacted]	[redacted]
PoC	Proof of Concept
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
RAC	Relative ANCC
rAAV	Recombinant Adeno-Associated Viral Vector
RBC	Red Blood Cell
REC	Relative Exchangeable Cu
RNA	RiboNucleic Acid
RR	Respiration Rate
SAE	Serious Adverse Event
SDMT	Symbol Digit Modality Test
SIV	Site Initiation Visit
SMA	Smooth Muscle Antibodies
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected, Unexpected, Serious Adverse Reaction
TB	Tuberculosis

TEAE	Treatment-Emergent AE
Tmax	Time to Maximum Plasma Concentration
ULN	Upper Limit of Normal
US	United States
UWDRS	Unified Wilson's Disease Rating Scale
W	Week
WBC	White Blood Cell
WD	Wilson’s Disease
WHO	World Health Organization
Zn	Zinc

PROTOCOL SUMMARY

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
Phase	Phase I/II
Number of Sites	Approximately 10 sites in Europe and North America
Objectives	Primary: • 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 WD therapy withdrawal. Secondary: • Exploring VTX-801 pharmacodynamics and efficacy • Assessing humoral and cellular immune responses to VTX-801 • Providing data to support VTX-801 dose level selection
Study Duration	Approximately 7 years

Study Design	**General Design** 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 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. **Dose Escalation** Adult male and female WD patients receiving standard of care therapy with either a zinc salt, a copper chelator (D-penicillamine or trientine) or the association thereof and who meet eligibility criteria will be sequentially enrolled and treated with escalating doses of VTX -801 in up to 3 consecutive cohorts of approximately 4 patients each; each patient will receive a single VTX-801 infusion, starting with a potentially therapeutic dose. The best efforts will be made to enroll at least 1 patient of each gender in each cohort of 4. Note: A chelator-wash-out period will be required around each radiocopper injection (starting 3 days before radiocopper injection and continuing until the end of the radiocopper investigations) that will occur during the week preceding the VTX-801 administration and at Weeks 12 and

	36 from VTX-801 administration. The objective of the wash-out period is to prevent any possible interference of chelators with 24-hour urinary copper and radiocopper assessments (no wash-out is required for patients on any zinc-only treatment). Dose escalation will proceed according to the following enrollment scheme [response to VTX-801 will be assessed per pre-defined criteria based upon radiocopper associated assessments at W12 and W36]: • ≥ 6-week intervals will be maintained between the VTX-801 infusion of the first 2 patients of each cohort. • if VTX-801 is well tolerated in both patients, as per the pre-defined stopping rules, then ≥ 12-week data (W12) from the first 2 patients of each cohort will be reviewed by the Sponsor and the Data Monitoring Committee (DMC): ○ <u>if first 2 patients are VTX-801 Responders at W12,</u> the remaining 2 patients of the concerned cohort may be enrolled; the decision of dose escalation will be based on the review of all available safety data of 3 to 4 patients at 12 weeks by the DMC. If well tolerated according to DMC, dose escalation may proceed after Sponsor agreement. ○ <u>if either or both first patients are Insufficient VTX-801 Responders at W12</u>, dose escalation may proceed without dosing the remaining 2 patients of the concerned cohort, in order to limit the exposure of patients who do not benefit sufficiently from the treatment and may not be retreated with an efficacious dose because of seroconversion to the vector ○ In case at least 1 out of the 2 first patients is an <u>Insufficient VTX-801 Responder at W12</u> and <u>both are VTX-801 Responders at W36</u> for a given dose level, 2 additional patients may be enrolled subsequently, based upon DMC recommendation and upon Sponsor decision.

	Dose Expansion at the Selected Dose Only when an optimal VTX-801 dose level has been selected from the escalation phase, based on the results of pharmacodynamic with radiocopper and other biomarkers of copper metabolism, additional patients will be enrolled in parallel in an expansion cohort to reach a total of 8 patients receiving VTX-801 at the Selected Dose level. **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. **Background or Standard of Care WD Therapy Withdrawal, Adjustment or Reinstatement** Considering Responder status and based upon DMC review and recommendations, the following actions may be taken after Sponsor approval: ▪ **Week 14**: Background WD therapy may be withdrawn for Week 12 Responders but will be continued for Week 12 Insufficient Responders.

	▪ **Week 38**: Background WD therapy may be withdrawn in Week 36 Responders but will be re-initiated (if previously interrupted) in Week 36 Insufficient Responders. In case of biochemical or chemical WD deterioration, the DMC may recommend WD SoC therapy re-initiation in such patients.
Eligibility Criteria	Inclusion: 1. Male or female aged 18 - 65 years (inclusive) at the time of signing the informed consent. 2. Patient diagnosed with WD, as established (by historical and/or current data), documented by Leipzig score ≥ 4, as per the 2012 EASL Clinical Practice Guidelines (EASL, 2012) and either: i) historical or current 24h urinary Cu > 40 µg/day (or 0.6 µmol/day) off chelator therapy, if any OR ii) two pathogenic or likely pathogenic *ATP7B* variants. 3. Patient has the ability to understand, date and sign informed consent prior to initiation of any study procedures. 4. Male patients: willing to use two methods of contraception from the day of the first radiocopper injection through 6 months following VTX-801 infusion and also for the week following the W36 radiocopper injection (sperm donation during this time is also prohibited). 5. Female patients: if of childbearing potential, willing to use two methods of contraception from signing informed consent through at least one week after W36 radiocopper injection. If using oral contraception, it must have remained unchanged for ≥ 3 months prior to inclusion. 6. Treated for WD according to international recommendations with no current evidence for inadequate treatment (EASL, 2012; Schilsky et al, 2022) o for at least 1 year with either zinc salt, a copper chelator [trientine or D-penicillamine], or a combination of thereof; previous treatment with investigational bis-choline-tetrathiomolybdate is acceptable as well, provided that it has been stopped ≥6 months prior to study entry;

	o without any changes in dosing regimen for at least the last 6 months prior to study entry; o compliant with current WD treatment, as judged by the Investigator. 7. Stable WD for ≥ 1 year, defined as: a. No significant change in neurologic examination and in status of mood disorder, if present, as judged by a physician-expert(s) in assessing neurological and psychiatric manifestations of WD. b. Stable laboratory parameters used to assess copper metabolism including 24-hour urinary copper, free serum copper such as NCC or CuEXC (when available), as well as liver enzymes, hemoglobin, and white blood cell count. The last assessments should be stable (no significant change), on at least 2 occasions assessed 6 to 8 weeks apart prior to enrollment (the interval may be extended as needed for logistical reasons beyond 8 weeks, after sponsor approval). The US and EU guidelines, as well as more recent publications should be used as a reference for WD management (EASL, 2012; Schilsky, 2017, Schilsky et al, 2022). 8. Patient expected to live for the study duration in the Investigator's opinion. <u>Exclusion</u> 1. ALT level ≥ 2 x ULN that is not readily explained by extrinsic factors (e.g., strenuous exercise, medication use). 2. Total bilirubin > 1.5x ULN in the absence of proven Gilbert's syndrome; in case of Gilbert's syndrome, direct bilirubin > ULN. 3. INR > 1.2. 4. Platelet count < 120,000/μL. 5. Absolute neutrophil count (ANC) < 1,000/μL. 6. Patient with fasting triglycerides ≥ 200 mg/dL [> 2.3 mmol/L], on optimal therapy, if any.

	7. On liver biopsy at inclusion: severe liver fibrosis (Metavir stage F3) or liver cirrhosis (Metavir stage F4) or steatosis > 33 % (steatosis score ≥ 2, per NASH-CRN scoring system). The liver biopsy may be replaced Fibroscan®, in patients of the dose escalation cohorts only; the cut offs are defined as (Sini et al, 2012; Park et al, 2017): a. In sites equipped with Fibroscan® i. LS ≥ 8.4 kPa ii. CAP score (Controlled attenuation parameter) ≥ 305 dB/m b. If the patient meets any of the above criteria and still declines the liver biopsy, he/she will be excluded; a liver biopsy (if performed finally) will however prevail for eligibility over Fibroscan® as the gold standard. 8. Any signs of liver cirrhosis decompensation, including gastrointestinal bleed within 6 months (24 weeks) prior to screening/enrollment visit. 9. Patient has moderate or severe renal impairment defined as eGFR CKD-EPI < 60 mL/min/1.73 m^2, or patient has nephritis or nephrotic syndrome. 10. Active infection requiring systemic antibiotic treatment or immunocompromised patients. 11. Any history or current evidence of HIV-1, HIV-2, HTLV-1 or HTLV-2 infection. 12. Any history or current evidence of hepatitis B infection, i.e. HBs antigen or antibodies anti-HBc positive. 13. Any history of hepatitis C infection, unless previous viral RNA assays in two samples, collected at least 6 months apart, are negative 14. Positive QuantiFERON®-TB Gold tuberculosis test result, history of active or latent tuberculosis or a history of positive PPD or Tine test; however, a history of positive PPD or Tine test in a patient who has received a BCG vaccine will not be exclusionary if QuantiFERON®-TB Gold test is negative. 15. Positive for *in vitro* anti-AAV3B neutralizing antibody activity.

	16. Any concomitant disorder/condition - including hepatic disorder - or treatment possibly interfering with the conduct or evaluation of the study, according to the Investigator. 17. Any history of angioedema. 18. Any history of diabetes. 19. Known allergy or hypersensitivity to components of VTX-801. 20. Contraindication to corticosteroid or Sirolimus use, as judged by the Investigator. 21. Contraindication [redacted]. 22. Psychosis or history (less than 10 years ago) of hospitalization for depression. 23. Severe neurological impairment defined as either [UWDRS part II subscales 2, 4 or 11 ≥ 3] or [UWDRS part II subscales 3, 6, 7, 8, 9 or 10 >3], or history of seizure activity within 6 months prior to signing informed consent. 24. Patients with dementia or moderate to severe cognitive impairment defined as MoCA score < 18 (as corrected for educational level). 25. Pregnancy or breastfeeding. 26. BMI ≥ 35 kg/m^2. 27. Moderate or heavier alcohol drinker, defined as drinking > 3 drinks/week on average over the past year. 28. Recent drug (amphetamines, opiates, cocaine or phencyclidine (PCP)) use: history or positive urinary drug screen results for either amphetamines, opiates, cocaine, or phencyclidine (PCP) at any of the Screening visits (Screening 1 or Screening 2); however, positive detection of licit, medically prescribed medication is not exclusionary. 29. Received a gene therapy treatment or participated in a gene therapy clinical trial. 30. Received any investigational drug and/or participated in any interventional clinical trial within the past 6 months.

	31. Individuals with documented history of malignancy, excepted basal or squamous cell carcinoma which has been treated and fully resolved for a minimum of 5 years. 32. Prior vaccination with live vaccine within 30 days before Sirolimus administration.
Description of Investigational Product	The investigational medicinal product (VTX-801) is a replication-deficient recombinant adeno-associated viral vector (rAAV) consisting of an AAV3B capsid containing a single-stranded DNA genome carrying a shortened version of the *ATP7B* gene (*ATP7B*-minigene). VTX-801 is provided in its final formulation and in a container closure system; a subsequent reconstitution will be performed on site. VTX-801 should be handled as a biohazardous product according to local regulations for biosafety level class 1 agents (BSL1). The IMP will be administered as a single dose intravenous (IV) administration per patient, at up to 3 different dose levels. The initial VTX-801 dose, 5E12 VG/kg, has been selected primarily based upon non-clinical pharmacology and toxicology studies, as a balance between expected pharmacodynamics and safety. Since re-treatment of patients exposed to a sub-optimal VTX-801 dose may not be possible due to seroconversion to the AAV capsid, the starting dose has been selected to be potentially therapeutic. 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: o Cohort 1: 5E12 VG/kg o Cohort 2: 1.5E13 VG/kg o Cohort 3: 3E13 VG/kg The Selected Dose for the expansion cohort will be one of the previously tested doses. VTX-801 will be provided to the

	responsible pharmacist at the study site, who will handle and dispense study product in accordance with the VTX-801 Pharmacy Manual that includes the reconstitution protocol which will be developed according to ICH GCP guidelines and applicable local laws.
Clinical Study Reports and Periodic Analyses	A data lock will be done when all patients reach one year of follow-up post-VTX-801 administration and the results will be reported in a first CSR. The long-term follow-up will continue until up to 5-years post-treatment, in line with the current EMA and FDA guidelines on follow-up of patients administered with non-integrative, non-replicative gene therapy medicinal products. A second and final CSR will cover all 5 years of follow-up.

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Table 1 Summary of Schedule of Events: Screening

Period	Screening 1	Screening 2
Visit # (V#)	V1A	V1B
[redacted]		

Table 1 Summary of Schedule of Events: Screening

Period	Screening 1	Screening 2
Visit # (V#)	V1A	V1B
[redacted]		

Table 2 Summary of Schedule of Events: Baseline to Week 12

Period	Baseline	Treatment	Follow-up
[redacted]			

Table 2 Summary of Schedule of Events: Baseline to Week 12

Period	Baseline	Treatment	Follow-up
[redacted]			

Table 2 Summary of Schedule of Events: Baseline to Week 12

Period	Baseline	Treatment	Follow-up
[redacted]			

[redacted]

Table 3 Schedule of Events: Weeks 13 to 52 (End of Year 1)

Period	Follow up
[redacted]	

Table 3 Schedule of Events: Weeks 13 to 52 (End of Year 1)

Period	Follow up
[redacted]	

Table 3 Schedule of Events: Weeks 13 to 52 (End of Year 1)

Period	Follow up
[redacted]	

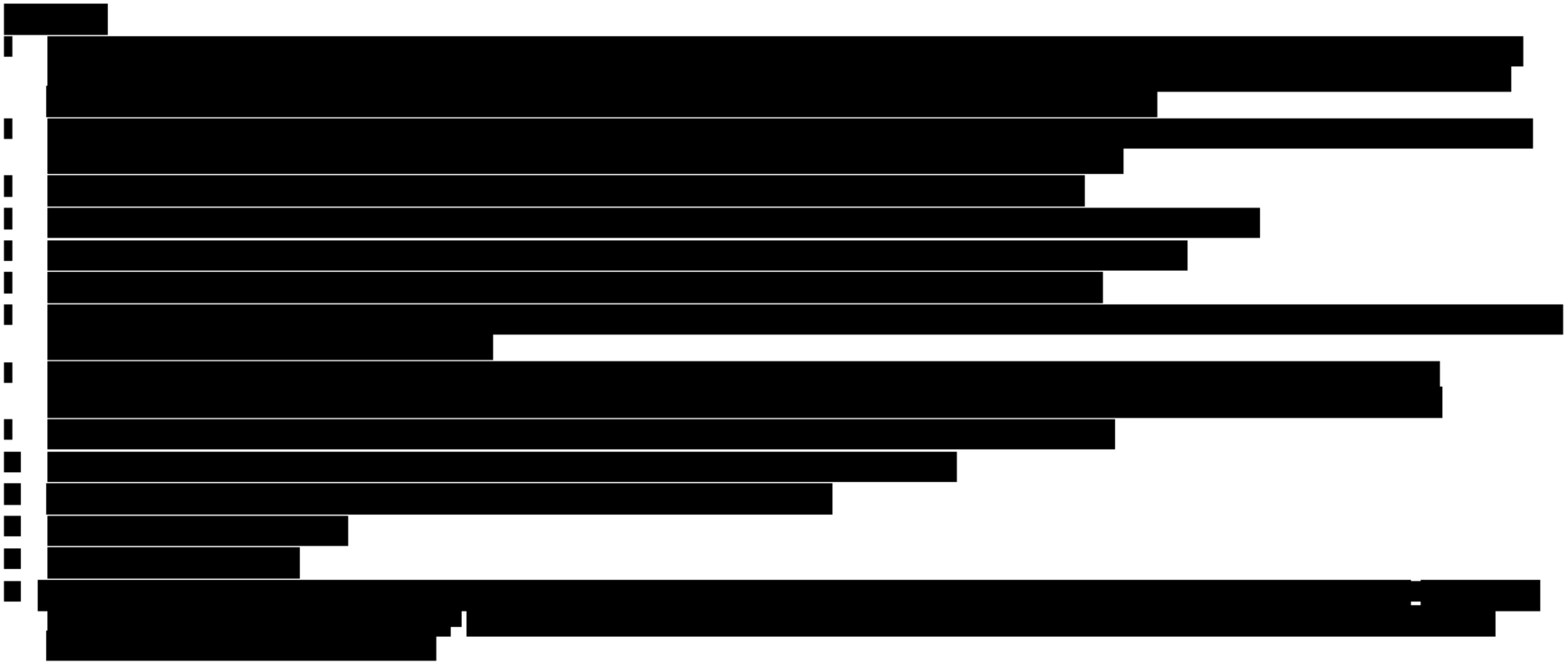

Table 4 Schedule of Events: Years 2 to 5 Follow up

Period	Year 2 Visits every 3 months	Year 3 Visits twice a year	Year 4 Visits twice a year	Year 5 Visits twice a year
[redacted]				

[redacted]

1 ROLES AND RESPONSIBILITIES

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Medical Monitor	[redacted] Aixial Group [redacted] [redacted] Aixial Group [redacted] [redacted] Aixial Group [redacted]

Serious Adverse Event Reporting	Drug Safety and Pharmacovigilance Aixial Group CRO Ashurst, Broadlands Business Campus Langhurstwood Road Horsham, RH12 4QP United Kingdom [redacted]
CRO Services	Aixial Group CRO (formerly Cmed) Ashurst, Broadlands Business Campus Langhurstwood Road Horsham, RH12 4QP United Kingdom [redacted] W: https://www.aixialgroup.com/

2 INTRODUCTION

2.1 Wilson's Disease and Copper Metabolism

Wilson´s Disease (WD), or progressive hepatolenticular degeneration, is a rare, debilitating, life-threatening disorder of copper homeostasis that is inherited in an autosomal recessive manner. It is due to variants in ATP7B, a copper transporting P-type ATPase. In the liver, which is the site of metabolism for dietary copper, *ATP7B* is responsible for the dual role of (i) regulating copper hepatocyte concentration by eliminating excess copper into the feces via the biliary route and (ii) transferring Cu to Cu-dependent enzymes, including circulating ceruloplasmin. In WD, *ATP7B* variants lead to decreased biliary copper excretion and tissue copper accumulation on the one hand, and to reduced circulating ceruloplasmin levels on the other hand. The primary site of copper accumulation is the liver, but central nervous system (CNS) as well as other organs accumulate copper, that may eventually result in organ dysfunction or failure. At time of diagnosis, patients typically present with low serum ceruloplasmin levels and increased urinary copper, associated or not with elevated transaminases, hepatic and/or neuropsychiatric symptoms and/or a Kayser-Fleischer ring. Onset of symptoms typically occurs in the teenage years or in young adulthood. Left untreated, the condition progresses to severely debilitating complications and death. The prevalence of WD is approximately one in 30,000 individuals worldwide, with wide geographical variations. For a full review see Członkowska et al, 2018b.

The goals of WD treatment depend upon the phase of disease and must consider both drug safety and efficacy in the individual patient (EASL, 2012; Schilsky et al, 2022); the approach to treatment initiation (D-penicillamine, trientine, zinc salt) depends on whether the patient is symptomatic or not and whether organ damage is present. A low-copper diet is recommended as an adjunct to medical therapy, especially during the de-coppering phase. If WD is detected early and treated properly over the course of a life-time, then the patient may have a favorable prognosis including control of symptoms and normal life expectancy with an overall better outcome for patients with the hepatic course, as compared to patients having predominantly neuropsychiatric symptoms (Merle et al, 2007).

While liver transplantation is the only curative option, it is reserved for severe liver disease and liver failure. Of note, a few case reports and a retrospective study describe liver

transplantations indicated for neurological worsening despite available medication, and neurological improvement or stabilization has been observed in several cases (Walker et al, 2018; Poujois et al, 2020). VTX-801 is a replication-deficient recombinant adeno-associated viral vector (rAAV) consisting of an AAV3B capsid containing a single-stranded DNA genome carrying a shortened version of the *ATP7B* gene (*ATP7B*-minigene) under the control of a liver-specific promoter and flanked by AAV2 ITRs. Based upon preclinical studies, liver-directed AAV-based gene therapy offers a potential alternative to current therapeutic options: by transferring a corrective *ATP7B* gene into in the liver, gene therapy may allow for a prolonged, physiological restoration of copper homeostasis, with ensuing clinical benefit to WD patients.

A comprehensive review of VTX-801 preclinical studies is contained in the Investigator brochure (IB) supplied by Vivet Therapeutics. Investigators are to review this document prior to initiating this study.

2.2 Unmet Needs

All diagnosed WD patients must be treated for life to prevent the occurrence of severely debilitating and life-threatening complications. However, despite recognized benefits, current management options have limitations (Schilsky et al (AASLD) 2022; EASL, 2012):

- Current WD medications may be associated with side effects; in particular, up to 31% patients experienced severe side effects with widely used D-penicillamine and 10-30% patients suffered paradoxical neurological worsening upon initiating chelator treatments (Merle et al, 2007; Ala et al, 2007).
- All current WD treatment regimens are constraining since they must be taken up to 3-4 times/day for life, at specific times away from meals and as mentioned above may be associated with significant side effects. As a result, adherence to treatment is sub-optimal: up to 50% non-compliance has been reported. Non-compliance or drug interruption may result in poor outcomes, including dramatic complications such as acute liver failure (ALF) or severe irreversible neuro-psychiatric deterioration (Scheinberg et al, 1987; Maselbas et al, 2010; Maselbas et al, 2019).
- Today, liver transplantation remains the only curative option for WD and it is indicated only for acute liver failure (ALF) or end stage liver disease (ESLD); in addition, it is limited by organ supply, significant morbidity, immunosuppression for life and cost.

- Long-term outcomes of WD cohorts have been studied by several authors; in a representative Austrian cohort of 229 WD patients followed for a mean of 14.8 years (3,116 patient-years) and treated with chelation therapy, 35% patients clinically stabilized, 26% improved, 15% deteriorated, 8% required a liver transplant and 7.4% died within the observation period (71% of deaths directly related to WD); overall, a lower proportion of WD patients survived for 20 years (92%) as compared to healthy Austrians (97%) and only 84% of patients with cirrhosis survived 20 years after diagnosis (Beinhardt et al, 2014).
- Recent studies showed that despite Standard of Care (SoC) treatment availability, overall survival of WD patients remains significantly reduced (Chand et al, 2021, Choe et al, 2020, Członkowska et al, 2022, Daniel-Robin et al, 2022).

Therefore, although the use of copper chelators - and later on zinc – have greatly improved WD prognosis, there is still a need for improved treatment options in order to further reduce the morbidity and the mortality of this severe condition.

2.3 Non-Clinical Studies

For details of the non-clinical studies and results, please refer to the current version of the VTX-801 IB. A summary of the main findings is provided below.

2.3.1 Pharmacology studies

The non-clinical VTX-801 Proof of Concept (PoC) studies were performed in the Atp7b$^{-/-}$ (WD) mouse model, which spontaneously recapitulates the hepatic (but not neurological) component of WD. Because the vector used for VTX-801 (AAV3B) efficiently transduces human hepatocytes but not mouse livers, surrogate vectors AAV8 and AAVAnc80 known to have high liver tropism in mice were used instead and the resulting study products have been named VTX-801(8) or VTX-801(Anc80), respectively.

The PoC pharmacology studies in 6-week-old WD mice demonstrated that the administration of VTX-801(8) or VTX-801 (Anc80) at doses ranging from 5E11 to 1.5E13 VG/kg was leading to a:

- Significant dose-dependent reduction in hepatic copper content, urinary copper excretion and increase of ^{64}Cu fecal elimination;

- Significant dose-dependent increase in ceruloplasmin levels in WD mice treated with 5E12 VG/kg and high (1.5E13 VG/kg) doses;
- Significant reduction and normalization of the liver damage biomarker alanine aminotransferase (ALT), bilirubin, and leukocytes at all tested doses (1.5E12, 5E12 and 1.5E13 VG/kg);
- Protection of the liver irrespective of the dose injected, with histological analysis of liver sections showing that livers of treated mice were indistinguishable from liver of WT mice and clearly different from untreated WD mouse livers;
- Dose-dependent proportion (%) of vector expressing cells measured by *in situ* hybridization (ISH) quantification of VTX-801 expression (mRNA);
- Correlation between the liver function correction and the percentage of hepatocytes expressing miniATP7B, showing that an average of 11% liver cells positive for VTX-801 transcript (at a vector dose of 1.5E12 VG/kg) led to a significant improvement of the disease, while approximately 32% of hepatocytes positive for miniATP7B mRNA (with a vector dose of 5E12 VG/kg) led to a phenotypic correction.

Efficacy was sustained at least 1 year after VTX-801(Anc80) administration and no deaths were observed in the WD treated group, while 4 out of 13 mice died in the untreated group due liver damage associated with the progression of the disease. Urinary copper excretion rate and liver biochemistry i.e. transaminase levels, bile acids and bilirubin remained comparable to those observed in WT animals and significantly different from untreated WD controls. Histopathology analysis of liver tissue showed no significant differences from healthy control. Administration of VTX-801(Anc80) to young 6-week old WD mice prevented liver inflammation, hepatocyte ballooning and necrosis, in contrast with the severe chronic inflammation and extensive fibrosis observed in livers of untreated WD animals.

Older WD mice were then treated with VTX-801(Anc80) doses of 5E12 or 1.5E13 VG/kg at 12- 16- and 20-weeks of age, when progressive liver inflammation develops. Although most pharmacodynamic effects of VTX-801(Anc80) observed in younger mice were retained and significant copper reduction in liver was observed, liver transduction efficiency measured 24-week post treatment showed lower levels when treated at advanced disease stage of the disease. Moreover, a vector dose-dependent transient transaminase increase was observed in some animals following VTX-801(Anc80)

administration and this effect was more pronounced in males and older animals with advanced disease stage that included liver inflammation. At necropsy (24 weeks after vector administration), the same animals had developed extensive liver fibrosis. In further experiments, when 5E12 VG/kg VTX-801(Anc80) was administered to 20-week old WD mice pretreated with zinc salts or a copper chelator (D-penicillamine), no toxicity was observed, and the pretreatments had a protective effect over transaminase elevation and development of liver fibrosis. Such beneficial effect of D-penicillamine is likely attributable to the stabilization of the liver disease in these mice prior to vector infusion. Regarding zinc salts treatment alone, at the dose and mode of administration used in this study, it had little effect on disease progression and copper accumulation.

2.3.2 Safety and toxicology studies

The non-clinical safety assessment of VTX-801 to be used in the clinical trial was performed in a 6-month follow up GLP toxicology and biodistribution study in non-human primates (NHP), following a single administration of VTX-801. At 3 months interim timepoint, single doses of VTX-801 up to [redacted] VG/kg were well tolerated with no treatment-related effect on clinical signs, food consumption, body weights, ophthalmic, cardiovascular, respiratory, hematological, coagulation and urinalysis parameters evaluated. There was no treatment-related effect on cytokine or complement levels evaluated in this study. Mild, transient test article-related increases in ALT and AST were observed at the high dose of [redacted] VG/kg on Days 3 and/or 8 post administration. These changes are non-adverse due to their low magnitude, low incidence, transient nature and lack of associated microscopic findings.

Immunogenicity: Dosing with VTX-801 did not result in antigen-specific T-cell IFN-γ responses following incubation with peptide pools covering the entire AAV3B capsid or miniATP7B protein sequences.

The assessment of AAV neutralizing antibodies from Day 8 up to Day 183 after treatment indicated that the antibodies titers in serum increased in both males and females following VTX-801 administration. NAbs increased more markedly in animals receiving the highest dose, with some showing titers over upper limit of quantification (titer >1:10935).

Biodistribution: At 1, 3 and 6 months post-administration, biodistribution assessment in NHP showed that liver was the organ predominantly targeted by VTX-801 (from 4.9E5 to 1.8E7 copies/µg of total DNA) in all animals analyzed and at both doses tested ([redacted]

and [redacted] VG/kg). Other tissues where VTX-801 genome was detected at 1 month post-administration were, in order of importance, spleen, gall bladder, lymph nodes, kidneys and adrenals.

No vector was detected in CNS and related structures for both doses at 3-month post-administration.

[redacted]

No gender differences were observed in the biodistribution profile of VTX-801 and no histological findings in all analyzed organs were reported.

Altogether, these results confirmed the strong tropism of AAV3B for the liver in NHP and are in agreement with the biodistribution profile reported for liver tropic AAVs (including AAV3B), also showing no associated toxicity in NHP (Wang et al, 2015).

Shedding: Results from shedding after a single IV administration of VTX-801 in NHP showed that in:

- **Plasma:** five (5) animals out of nine (9) injected with the lowest dose of vector were positive at D8, two (2) animals were still positive at D15 and only one (1) animal had quantifiable amount of vector genome at D29. All animals that received the highest dose of VTX-801 ([redacted] VG/kg) were positive for the presence of the vector genome in plasma until D8, and three (3) out of nine (9) animals remained positive until D15, while one (1) out of nine (9) animals remained positive until D29. All animals were negative from D57.
- **Saliva:** vector genome was detected in four (4) animals out nine (9) from the low-dosed group and in six (6) animals out of nine (9) from the high-dosed group until D29. Only one (1) animal remained positive until D57 and became negative at the next two (2) testing points (D92 and D120).
- **Nasal fluid:** vector genome was detected until D57 only in one (1) animal injected with the lowest dose of vector and at D92 all animals were negative.

- **Urine:** vector genome was detected for both doses of VTX-801 until D8 and all animals were negative for the presence of vector genome in urine at D15.
- **Feces:** vector genome was detected in animals treated with the lowest dose of VTX-801 until D15 and only four (4) animals injected with the high dose of VTX-801 were positive at D15. At D29 all animals were negative.

In conclusion, no dissemination of VTX-801 in blood, saliva, nasal fluid, urine and feces was observed from 3 months after administration and onward. It should be noted that the maximal dose tested in NHP is higher than the maximal dose to be tested in trial subjects.

2.4 Study Rationale

VTX-801_CLN_001 is a First-in-Human (FIH) clinical study designed to assess the relationship of vector dose (single IV administration) with the restoration of physiological copper metabolism in adult WD patients, and whether this restoration is maintained durably and safely after withdrawal of WD SoC therapy.

In order to prevent WD worsening, WD SoC therapy may be withdrawn only in VTX-801 Responders and after Data Monitoring Committee (DMC) consultation and Sponsor approval. All patients will be followed for a total of 5 years, in agreement with current FDA and EMA guidelines for the use of non-integrating gene therapy vectors (FDA guideline, 2020; EMA guideline, 2009).

2.5 Summary of Potential Risks and Benefits

For details of the non-clinical studies and results, please refer to the current version of the VTX-801 IB.

2.5.1 Risk of drug-induced liver toxicity:

- Systemic AAV gene therapy has been often associated with transient rises in transaminases, most often within the first 12 weeks after vector administration, which has been associated with subsequent loss of clinical efficacy (for a review see Nathwani et al, 2017). Transient oral steroid treatment initiated upon transaminase increase onset, or even better, prophylactically, has shown efficacy to reduce or prevent such effect in several cases, but it has been insufficient in others (Nathwani et al, 2017; Pipe et al, 2017). An improved immune modulation regimen may therefore

be useful to optimally mitigate such effects. Therefore, in study VTX-801_CLN_001, a combination of sirolimus and oral steroids (prednisone or prednisolone) will be administered transiently as a prophylaxis against potential AAV associated ALT increase, together [redacted].

- [redacted]
- In WD patients, hepatic presentation at time of WD diagnosis may naturally vary from persistently elevated serum aminotransferases to chronic hepatitis, cirrhosis (decompensated or compensated) or acute liver failure (with or without haemolytic anemia) (Członkowska et al, 2018b). Upon treatment for Wilson's Disease, hepatic biochemistry metrics typically show a progressive improvement, but may not normalize completely in all patients. In order to minimize the risk of drug-induced liver toxicity that might be favored by a progressive and/or severe underlying WD liver pathology, VTX-801 will be administered in this FIH study only to patients on stable SoC medical treatment according to current WD management guidelines (Schilsky et al, 2022; EASL, 2012), with stable and preserved disease-related liver biochemistry (ALT<2xULN) and hematology parameters as well as non-severe liver histology.
- Of note, a few cases of fatal hepatotoxicity have been reported after high dose (1.4-3.4 E14 vg/kg) AAV-mediated gene therapy with different vectors in patients with severe neuromuscular disorder (Morales et al, 2020; Shieh et al, 2020 and Shieh, 2021 - European Society of Gene and Cell Therapy Congress; Chand et al, 2021; Philippidis, 2022).

Risk of Infusion-Associated Reactions (IARs): To prevent potential IARs to VTX-801 that may occur during or within 24 hours post-VTX-801 infusion, methylprednisolone will be administered IV prior to VTX-801 infusion.

Risk of complement activation: In a few patient who received intravenously AAV gene therapy products for various indications at dose levels ranging from 5E13 to 3E14 vg/kg,

i.e. higher than those being evaluated in the current study, complement activation has been observed and presented as different combinations of thrombocytopenia, acute kidney injury, hematuria, proteinuria and/or anemia, and the outcome was fatal in one case (Duan, 2018; Sini et al, 2012; Smith et al, 2022; Guillou et al, 2022). When patients were treated with a complement inhibitor (eculizumab), these effects usually resolved within 2-3 weeks (Binks, 2021).

Risk of copper deficiency: The theoretical risk of copper deficiency as a result of potential overdosing with VTX-801 has been carefully considered: copper deficiency did not occur in any of the preclinical studies conducted to date with VTX-801 in WD or healthy animals. Nevertheless, in the VTX-801_CLN_001 study, total serum copper, hematology parameters and neurological status will be regularly monitored. Overall, there is a theoretical risk that hypocupremia would result from VTX-801 treatment; response to dietary copper supplementation (Kumar, 2006) is unknown, and it is possible that such condition would be permanent.

Risk of worsening of neurological and psychiatric disorders: CNS symptoms observed in WD patients may be the consequence of acute copper toxicity linked to “free” circulating copper and/or accumulated copper causing chronic damage and neuronal loss. Although no neurological toxicity has been observed in preclinical studies, there is a theoretical risk that VTX-801 would result in a worsening of pre-existing neurological conditions or in the onset of new neurological conditions, and it is possible that such condition would be permanent.

Risk of insertional mutagenesis: The risk of AAV-vector-induced insertional mutagenesis and tumorigenesis has been documented in preclinical and clinical studies and is viewed as minimal (Tenenbaum et al, 2003; Gil-Farina et al, 2016).

Risks of inadvertent germ-line transmission: [redacted] risks of germ-line transmission with AAV vectors is considered low (Tenenbaum et al, 2003; Gil-Farina et al, 2016).

Risk related to radiocopper administration: [^{64}Cu]$CuCl_2$ (thereafter also referred to as “radiocopper”) will be administered intravenously as a tracer for pharmacodynamics evaluations. Each patient is planned to receive, on 3 separate occasions, one intravenous administration of a [redacted] MBq (±10%) dose; the total effective dose received by each patient

in this study is estimated to be < 10 mSv, which is well below deterministic thresholds and corresponds to a minor to intermediate cumulative risk level based on ICRP Publication (see radiocopper IB and Section 7.4 for rationale). The radioactivity levels to be injected have precedence (Section 7.4) and are considered acceptable, based upon applicable regulations.

Risks related to study procedures and concomitant treatments: Repeated liver biopsies carry some well-described risks, but all study sites have been selected to be hepatology centers with extensive experience in performing liver biopsy, thus minimizing the risks of this procedure. The side effects of prophylactic immunosuppression or [redacted] have been well described and are considered acceptable within the context of this study.

Risk of treatment failure: The starting dose has been selected to be potentially therapeutic. Withdrawal of background WD treatment is planned only after demonstrating pre-defined VTX-801 pharmacodynamic effects, and close monitoring after withdrawal is planned thereafter to ensure patient safety and prompt background WD treatment reinstatement, as appropriate.

Benefits and risk-benefit assessment: Recent or emerging favorable data in various genetic disorders highlight the potential clinical benefits of AAV-based gene therapy (Mendell et al, 2021; Ohmori, 2020 and D'Antiga et al, 2021, European Society of Gene and Cell Therapy Congress). Participants to study VTX-801_CLN_001 have the potential to benefit from long-term disease stabilization (possibly an improvement) together with complete cessation of SoC WD therapy and low copper diet, if any. The risks of the study, especially those associated with pre-existing liver disease and systemic AAV3B vector administration, have been carefully considered, gaining insight from recent gene therapy trials, and have led to the definition of strict enrollment criteria and provision of extensive monitoring as well as prophylactic or reactive treatments. Based upon these considerations, the potential risks of participation in the VTX-801_CLN_001 study have been minimized, while patients may potentially benefit from VTX-801 treatment.

3 OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 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 WD therapy withdrawal.

3.1.2 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

3.2 Study Endpoints

3.2.1 Primary Endpoints

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

3.2.2 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 responses 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

3.2.3 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

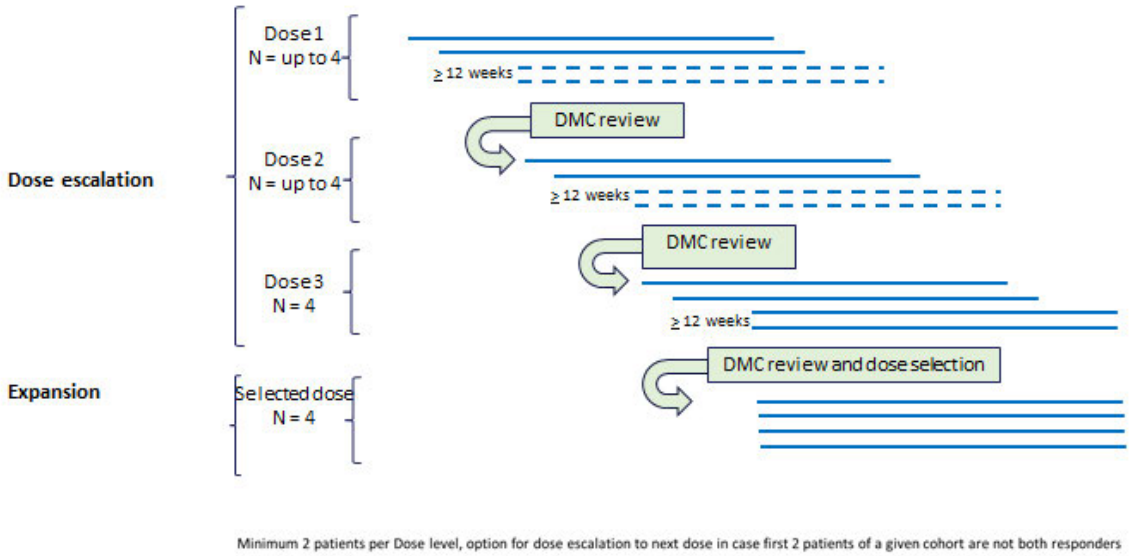
4 STUDY DESIGN

4.1 Overview

VTX-801_CLN_001 is 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 on background WD therapy (Figure 1).

The dose-escalation phase will involve up to 3 cohorts, each consisting of approximately 4 adult WD patients on chronic and stable treatment with SoC; once a safe and potentially efficacious VTX-801 dose level has been selected for further evaluation, an expansion cohort of approximately 4 adult WD patients on chronic and stable treatment with SoC will be enrolled at this 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 may not be possible due to seroconversion to the AAV capsid.



Abbreviations: DMC= Data Monitoring Committee; N= Number of patients.

Figure 1 Study Design

The above scenario assumes an efficacious dose is reached at Cohort 3.

Full line = enrolled patients

Dashed lines = patients that may be omitted due to insufficient pharmacodynamic response in a cohort (see Section 4.2, below)

4.2 VTX-801 Dose Escalation

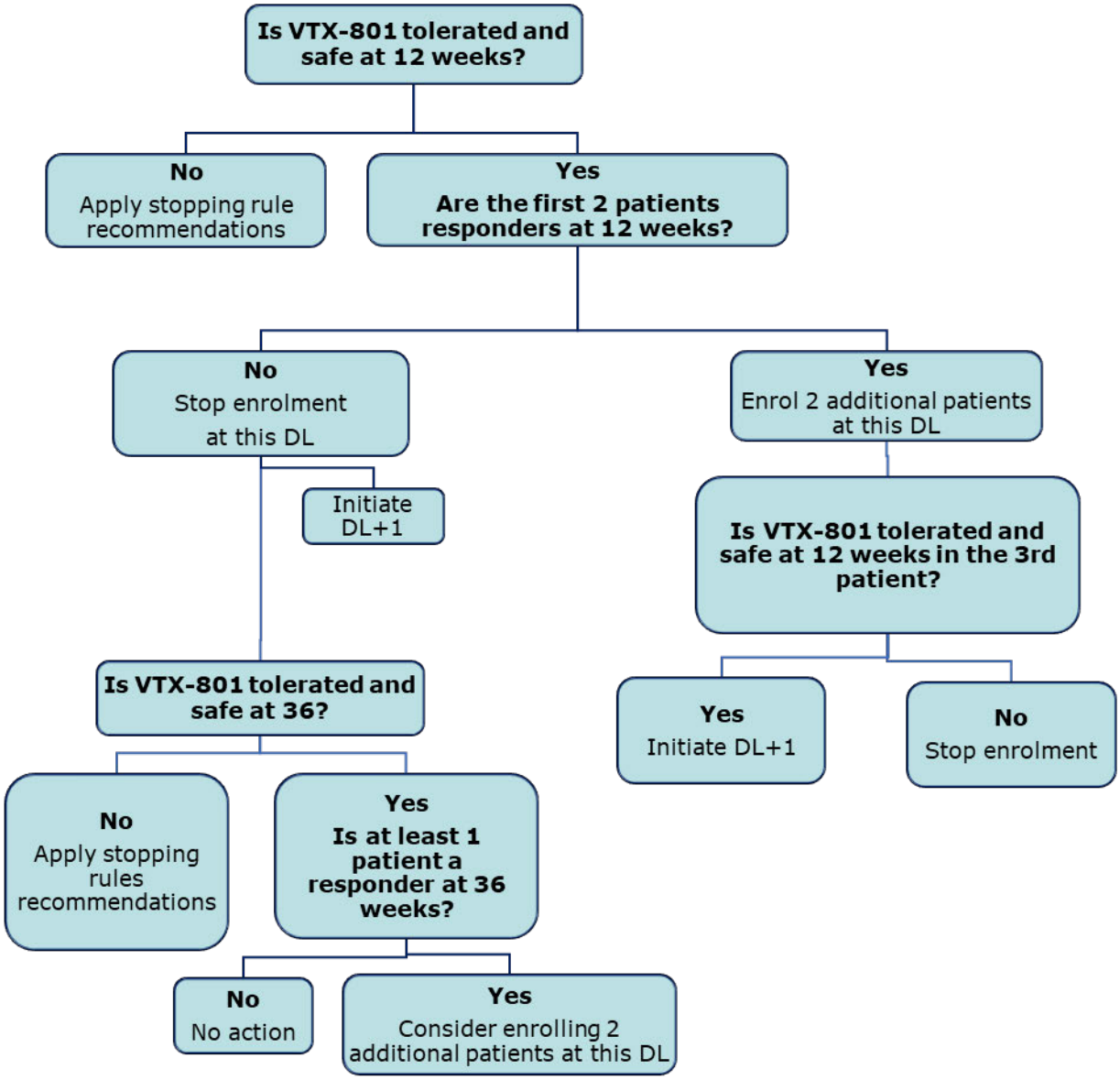
Adult male and female WD patients receiving SoC therapy with either zinc salt, a copper chelator (D-penicillamine or trientine) or the association thereof and who meet all eligibility criteria will be sequentially enrolled and treated with escalating doses of VTX-801 in up to 3 consecutive cohorts of approximately 4 patients each; each patient will receive a single VTX-801 infusion, starting with a potentially therapeutic dose (Section 7.2). The best efforts will be made to enroll at least 1 patient of each gender in each cohort of 4.

Note for patients receiving chelators or dual chelator and zinc therapy, a chelator wash-out period will be required around each radiocopper injection (starting 3 days before radiocopper injection and continuing until the end of the radiocopper investigations – refer

to Sections 8.2.6.1 and 8.2.6.2) planned during the week preceding the VTX-801 administration and at Weeks 12 and 36 from VTX-801 administration. The objective of the wash-out period is to prevent any possible interference of chelators with 24-hour urinary copper and radiocopper assessments (no wash-out is required for patients on any zinc-only treatment). Importantly, such a short wash-out period is not considered to put patients at risk, since accumulation of copper is a slow process.

Dose escalation will proceed according to the following enrollment scheme (refer to the Enrollment Decision Tree in Figure 2 and the Stopping Rules in Section 6.3):

- ≥ 6-week intervals will be maintained between the VTX-801 infusion of the first 2 patients of each cohort
- if VTX-801 is well tolerated in both patients, as per the pre-defined Stopping Rules outlined in Section 6.3, then ≥ 12-week data (W12) from the first 2 patients of each cohort will be reviewed by the Sponsor and the DMC:
    - if first 2 patients are VTX-801 Responders at W12 (see Section 4.5), the remaining 2 patients of the concerned cohort may be enrolled; the decision of dose escalation will be based on the review of all available safety data of 3 to 4 patients at 12 weeks by the DMC. If well tolerated according to DMC, dose escalation may proceed after Sponsor agreement.
    - if either or both first patients are Insufficient VTX-801 Responders at W12, dose escalation may proceed without dosing the remaining 2 patients of the concerned cohort, in order to limit the exposure of patients who do not benefit sufficiently from the treatment (and may not be retreated with an efficacious dose because of seroconversion to the vector).
        - In case at least 1 out of the 2 first patients is an Insufficient VTX-801 Responder at W12 and at least 1 out of the 2 is a VTX-801 Responder at W36 for a given dose level, 2 additional patients may be enrolled subsequently, based upon DMC recommendation and upon Sponsor decision.



Abbreviations: DL=Dose Level

Figure 2 Enrollment Decision Tree

In case of safety signal in a sentinel cohort (first 3 patients at ≥ 12 weeks), the following rules will apply:

- If 1 patient with AE Grade 3 that resolved quickly and that can be addressed by supportive care, dose escalation may proceed after DMC positive recommendation;
- If 1 patient with AE Grade 3 persistent or 1 patient with AE > Grade 3, bring cohort to total N=6; however, if less than 2 patients are Responders in the sentinel cohort, dose escalation may proceed without additional patients in the concerned cohort after review and positive recommendation of the DMC.

Adverse events that are incontrovertibly not related to IMP will not count in dose escalation rules.

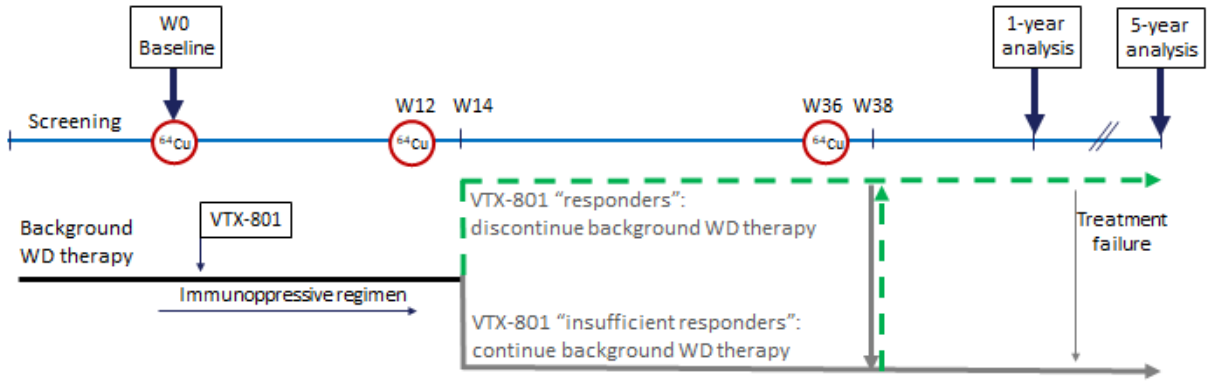
In case a Stopping Criterion is reached, the procedure described in Section 6.3 will be implemented. If dose escalation is terminated, the DMC will then provide a recommendation from a benefit/risk perspective on whether de-escalation may be acceptable and the Sponsor will decide if it is useful or futile to continue the study. If de-escalation occurs, the dose will be divided by 2 compared to the dose limiting level.

At the end of the dose escalation, a VTX-801 dose level that has been determined to be both safe and potentially efficacious following DMC review will be selected by the Sponsor for further testing (the Selected Dose) as outlined in Section 4.3.

4.3 Expansion 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**,** additional patients will be enrolled in parallel in an expansion cohort to reach a total of 8 patients receiving VTX-801 at the Selected Dose level.

4.4 Patient Treatment and Follow-up Scheme



Abbreviations: ^{64}Cu= Radiocopper; W= Week; WD= Wilson's Disease.

Figure 3 Patient Treatment and Follow-up Scheme

Each patient of each cohort will follow the scheme depicted in Figure 3; enrolled patients will start the immunosuppressive regimen before undergoing the first radiocopper related assessments. They will then receive a single VTX-801 infusion without interrupting their background WD therapy (except for planned chelator wash-out periods in chelator-treated patients, Section 10.2).

Patients will have an increased frequency of assessments for 12 weeks post-VTX-801 administration; the rationale behind this being:

(i) in two published experiences of liver-directed gene therapy in hemophilia, the pharmacodynamics endpoint (blood coagulation factor levels) tended to reach a maximum and to stabilize by around Week 12 post administration (Rangarajan et al, 2017; George et al, 2017);

(ii) most ALT increases occurred within the first 12 weeks post AAV administration (Nathwani et al, 2017). Therefore, at Week 12, each patient will undergo a second radiocopper injection and the VTX-801 Responder status will be determined.

In addition, 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 then be followed up for a total of 5 years from the time of VTX-801 administration.

Considering Responder status and based upon DMC review and recommendations the following actions may be taken after Sponsor approval:

- Week 14: Background WD therapy may be withdrawn for Week 12 Responders but will be continued for Week 12 Insufficient Responders.
- Week 38: Background WD therapy may be withdrawn in Week 36 Responders but will be re-initiated (if previously interrupted) in Week 36 Insufficient Responders.

The same schedule of investigations will be followed for Responders and Insufficient Responders until the end of Year-1 follow up (Visit 46).

4.5 Responder/Insufficient Responder Definitions

[redacted]

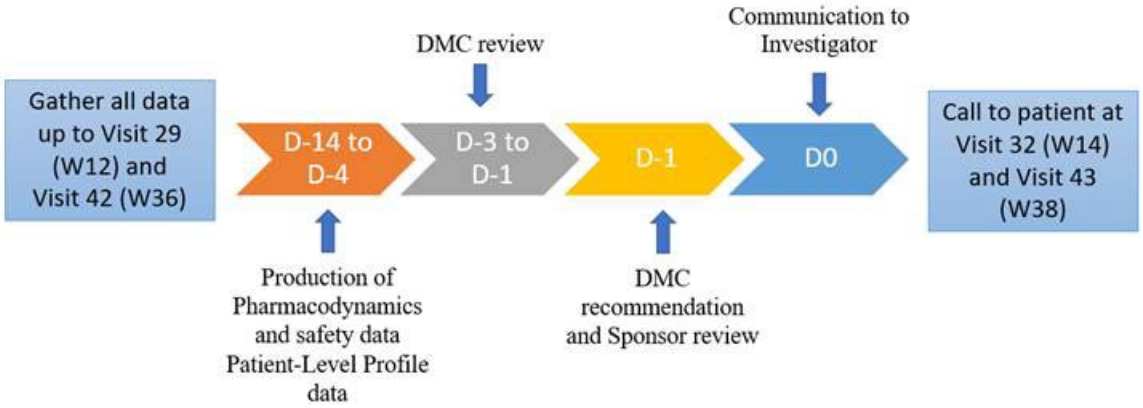
[redacted]

Figure 4 Responder Decision Tree - SoC Withdrawal Only in Responders

[redacted]

Responder status will be evaluated for each patient after review of data collected until Week 12 and Week 36.

The Responder/Insufficient Responder process associated timelines are described in Figure 5.



Abbreviations: D= Day; DMC= Data Monitoring Committee; W= Week.

Figure 5 Responder/Insufficient Responder Process Associated Timelines

4.6 Background or Standard of Care WD Therapy Withdrawal, Adjustment or Reinstatement

WD treatment withdrawal or reinstatement based upon Responder status: the DMC will review patient data collected up to and including Week 12 and Week 36, as appropriate, in order to provide a recommendation from a safety standpoint regarding background WD therapy withdrawal, adjustment or reinstatement, as appropriate.

For background WD therapy withdrawal, the DMC will:

1. Evaluate if the WD of the patient is stable, based upon clinical and biochemical data, including:

[redacted]

2. [redacted]

[redacted]

Management of copper deficiency: in case a patient would develop copper deficiency at any time during the trial, background or WD SoC therapy (if any), dose and regimen may be adjusted and/or the patient may receive dietary copper supplementation, after

DMC consultation and upon Sponsor confirmation. Please refer to Section 9.7 for further details.

Management of immediate patient safety: the Investigator should make every effort to follow the planned protocol treatments and schedule and to await DMC recommendations when needed; however, at any time during the trial, the Investigator may not be able to await Sponsor or DMC response before taking appropriate urgent therapeutic measures needed to ensure immediate patient safety (see Section 13.4).

4.7 Study Committees

4.7.1 Data Monitoring Committee

A DMC will be involved throughout the trial duration. The DMC will be independent from any investigational sites and will not include any members from Vivet Therapeutics. It will be comprised of 4 medical clinician members experienced with WD, including a Chairman.

The DMC members, roles and responsibilities, as well as the timing and support required will be fully detailed in a DMC Charter (reviewed and approved by the DMC members).

In summary, the DMC will review patients' data in order to provide recommendations, mostly relative to patient safety. The reviews will be done:

- At pre-defined time points: patient-level review for Responder status determination (see Section 4.5), cohort-level review and determination of acceptable risk/benefit prior to first VTX-801 dosing in next dose escalation, background WD therapy withdrawal, adjustment or SoC reinstatement.
- On an ad-hoc basis, especially in case of significant clinical or biological deterioration post background WD therapy withdrawal, oral steroid (prednisone or prednisolone) and/or sirolimus withdrawal, or after an SAE.

Pre-defined DMC reviews will be based on patient profiles, and/or on aggregated statistical outputs (tables, listings, figures), as required. Data/information required for ad-hoc DMC reviews will be determined on a case-by-case basis.

4.7.2 Hepatic Adjudication Committee

The Hepatic Adjudication Committee (HAC) will be comprised of 2 or 3 hepatologists (including at least 2 U.S.-based hepatologists), who can also be DMC members and have expertise in review and adjudication of suspected Drug Induced Liver Injury (DILI).

The HAC is responsible for reviewing and adjudicating all suspected DILI reports completed and submitted by the clinical sites and they are responsible for providing an overall event assessment to the clinical site, the DMC and the Sponsor.

4.7.3 Eligibility Review Committee

The Eligibility Review Committee (ERC) will include at least 4 US-licensed physicians (Principal Investigators, Co-Investigators or physicians) who have experience and expertise in the management of patients in Wilson's Disease and experience in the recruitment and monitoring of clinical trials.

- The ERC will advise on the determination of patient eligibility prior to inclusion in the VTX-801_CLN_001 study and dosing of VTX-801.

4.8 Long Term Follow-up

A long-term follow up will be performed for all patients treated with VTX-801. Patients withdrawn before VTX-801 administration will not be followed for 5 years.

A first data lock will be done when all patients reach one year of follow-up post-VTX-801 administration and the results will be reported in a first CSR. The long-term follow-up will continue until up to 5-years post-treatment, in line with the current EMA and FDA guidelines on follow-up of patients administered with non-integrative, non-replicative gene therapy medicinal products (EMA guideline, 2009; FDA guideline, 2020). A second and final CSR will cover all 5 years of follow-up.

4.9 Study Start and End of Study Definitions

The expected duration of participation for each patient is approximately 5 years. The study will start from first patient first visit and end after completion of Last Patient Last Visit.

5 STUDY POPULATION

5.1 Number of Patients

As part of this study, up to approximately 16 WD male and female adult patients will be administered VTX-801 in 3 dose-escalation cohorts consisting of approximately 4 patients and one expansion cohort consisting of approximately 4 patients treated at the Selected VTX-801 dose.

- Patients for whom radiocopper data is missing at Week 12 may be replaced, as appropriate, however, the total number of patients will not exceed 16 patients.
- The Sponsor may consider amending the protocol to include additional patients at the Selected Dose if judged necessary and/or to include a cohort of patients with more advanced liver disease (Metavir hepatic fibrosis stage ≥ F3 or higher) after (1) safety data in non-cirrhotic patients is available and reviewed by the DMC; and (2) FDA and the other concerned Regulatory Authorities have approved the amended protocol.

5.2 Inclusion Criteria

Patients may be enrolled into the study if they fulfil all of the following criteria:

1. Male or female aged 18 – 65 years (inclusive) at the time of signing the informed consent.
2. Patient diagnosed with WD, as established (by historical and/or current data), documented by Leipzig score ≥ 4, as per the 2012 EASL Clinical Practice Guidelines (EASL, 2012) and either:
    i) historical or current 24h urinary Cu > 40 µg/day (or 0.6 µmol/day) off chelator therapy, if any OR
    ii) two pathogenic or likely pathogenic *ATP7B* variants
3. Patient has the ability to understand, date and sign informed consent prior to initiation of any study procedures.
4. Male patients: willing to use two methods of contraception from the day of the first radiocopper injection through 6 months following VTX-801 infusion and also for the week following the W36 radiocopper injection (sperm donation during this time is also prohibited).

5. Female patients: if of childbearing potential, willing to use two methods of contraception from signing informed consent through at least one week after W36 radiocopper injection. If using oral contraception, it must have remained unchanged for ≥ 3 months prior to inclusion.
6. Treated for WD according to international recommendations with no current evidence for inadequate treatment (EASL, 2012; Schilsky et al, 2022);
    - for at least 1 year with either zinc, a copper chelator [trientine or D-penicillamine], or a combination of thereof; previous treatment with investigational bis-choline-tetrathiomolybdate is acceptable as well, provided that it has been stopped ≥6 months prior to study entry.;
    - without any changes in dosing regimen for at least the last 6 months prior to study entry;
    - compliant with current WD treatment, as judged by the Investigator.
7. Stable WD for ≥ 1 year, defined as:
    a. No significant change in neurologic examination and in status of mood disorder, if present, as judged by a physician-expert(s) in assessing neurological and psychiatric manifestations of WD.
    b. Stable laboratory parameters used to assess copper metabolism including 24-hour urinary copper, free serum copper such as NCC or CuEXC (when available), as well as liver enzymes, hemoglobin, and white blood cell count.

    The last assessments should be stable (no significant change), on at least 2 occasions assessed 6 to 8 weeks apart prior to enrollment (the interval may be extended as needed for logistical reasons beyond 8 weeks, after sponsor approval). The US and EU guidelines, as well as more recent publications should be used as a reference for WD management (EASL, 2012; Schilsky, 2017, Schilsky et al, 2022).
8. Patient expected to live for the study duration in the Investigator's opinion.

5.3 Exclusion Criteria

Patients will be excluded from enrollment into the study if they have any of the following:

1. ALT level ≥ 2 x ULN that is not readily explained by extrinsic factors (e.g., strenuous exercise, medication use).
2. Total bilirubin > 1.5 x ULN in the absence of proven Gilbert's syndrome; in case of Gilbert's syndrome, direct bilirubin > ULN.
3. INR > 1.2.
4. Platelet count < 120,000/µL.
5. Absolute neutrophil count (ANC) < 1,000/µL.
6. Patient with fasting triglycerides ≥ 200 mg/dL [> 2.3 mmol/L], on optimal therapy, if any.
7. On liver biopsy at inclusion: severe liver fibrosis (Metavir stage F3) or liver cirrhosis (Metavir stage F4) or steatosis > 33 % (steatosis score ≥ 2, per NASH-CRN scoring system). The liver biopsy may be replaced by Fibroscan® in the dose escalation cohorts only; the cut offs are defined as (Sini et al, 2012; Park et al, 2017)
   a. In sites equipped with Fibroscan®
      i. LS ≥ 8.4 kPa
      ii. CAP score (Controlled attenuation parameter) ≥ 305 dB/m
   b. If the patient meets any of the above criteria and still declines the liver biopsy, he/she will be excluded; a liver biopsy (if performed finally) will however prevail for eligibility over Fibroscan® as the gold standard.
8. Any signs of liver cirrhosis decompensation, including gastrointestinal bleed within 6 months (24 weeks) prior to Screening/enrollment visit.
9. Patient has moderate or severe renal impairment defined as eGFR CKD-EPI < 60 mL/min/1.73 m^2, or patient has nephritis or nephrotic syndrome.
10. Active infection requiring systemic antibiotic treatment or immunocompromised patients.
11. Any history or current evidence of HIV-1, HIV-2, HTLV-1 or HTLV-2 infection.
12. Any history or current evidence of hepatitis B infection, i.e. HBs antigen or antibodies anti-HBc positive.
13. Any history of hepatitis C infection, unless previous viral RNA assays in two samples, collected at least 6 months apart, are negative.
14. Positive QuantiFERON®-TB Gold tuberculosis test result, history of active or latent tuberculosis or a history of positive PPD or Tine test; however, a history of positive

PPD or Tine test in a patient who has received a BCG vaccine will not be exclusionary if QuantiFERON®-TB Gold test is negative.

15. Positive for *in vitro* anti-AAV3B neutralizing antibody activity.
16. Any concomitant disorder/condition - including hepatic disorders - or treatment (see Section 7.6.2) possibly interfering with the conduct or evaluation of the study, according to the Investigator.
17. Any history of angioedema.
18. Any history of diabetes.
19. Known allergy or hypersensitivity to components of VTX-801.
20. Contraindication to corticosteroid or Sirolimus use, as judged by the Investigator.
21. Contraindication [redacted]
22. Psychosis or history (less than 10 years ago) of hospitalization for depression.
23. Severe neurological impairment defined as either [UWDRS part II subscales 2, 4 or 11 ≥ 3 (greater than or equal to 3)] or [UWDRS part II subscales 3, 6, 7, 8, 9 or 10 >3 (greater than 3)] or history of seizure activity within 6 months prior to signing informed consent.
24. Patients with dementia or moderate to severe cognitive impairment defined as MoCA score < 18 (as corrected for educational level).
25. Pregnancy or breastfeeding.
26. Body Mass Index ≥ 35 kg/m^2.
27. Moderate or heavier alcohol drinker, defined as drinking > 3 drinks/week on average over the past year.
28. Recent drug (amphetamines, opiates, cocaine or phencyclidine (PCP)) use: history or positive urinary drug screen results for either amphetamines, opiates, cocaine or phencyclidine (PCP) at any of the Screening visits (Screening 1 or Screening 2); however, positive detection of licit, medically prescribed medications is not exclusionary.
29. Received a gene therapy treatment or participated in a gene therapy clinical trial.
30. Received any investigational drug and/or participated in any interventional clinical trial within the past 6 months.

31. Individuals with documented history of malignancy except basal or squamous cell carcinoma which has been treated and fully resolved for a minimum of 5 years.
32. Prior vaccination with live vaccine within 30 days before Sirolimus administration.

6 ENROLLMENT AND MANAGEMENT OF DROPOUT PATIENTS

6.1 Enrollment Procedures

The study begins for a patient with the signing and dating of the informed consent form in accordance with Section 14.3.

A master patient list will be maintained by the site. This list will include screen failures, i.e., patients who are screened but fail to meet all eligibility criteria and patients who are enrolled but do not receive VTX-801. Waivers for eligibility will not be granted.

The presence of inclusion criteria listed in Section 5.2 and absence of exclusion criteria listed in Section 5.3 will be documented in the source data and the eCRF (electronic Case Report Form).

The Screening period (Section 10.1) will include 2 mandatory parts (Screening 1 and Screening 2) in order to determine patient suitability. Patient eligibility will be assessed in full at V1B. Based upon V1A results, only those patients that are anti-AAV3B NAb-negative (see Section 8.2.1) may be allowed to proceed to V1B visit to assess patient eligibility.

According to the dose escalation design and the competitive inclusion, approval by the Sponsor is required for each patient:

- Prior to Screening 1 visit;
- Prior to Screening 2 visit;
- Prior to inclusion (after ERC review and approval);
- Prior to re-screening any patient who never received VTX-801.

The enrollment procedure will be detailed in the Medical Monitoring Plan and in the Eligibility Review Committee Charter.

6.2 Treatment Assignment/Randomization Procedures

Since this is a non-randomized study, randomization procedures are not applicable. Patients will be assigned to treatment with a unique patient number in ascending, sequential order. The Investigator will enter the patient number in the eCRF.

6.3 Stopping Rules

Any of the following occurrences will result in pause of further dosing (including escalation to a higher dose level) while the events are under investigation:

- Any death during the study period;
- Any patient develops Grade 3-4 (CTCAE) toxicity;
- Any patient develops copper deficiency (Section 9.7);
- Any occurrence of a newly diagnosed malignancy at any point after vector infusion;
- Neurological, psychiatric or behavior-related adverse event (either new or worsening from baseline) suggestive of IMP-induced deterioration (possibly, probably or definitely related), per Investigator judgment;
- Dose limiting toxicity (DLT), as per DLT definition below;
- Two cases of DILI, as defined below, irrespective of causality.

Definition of DILI criteria:

a. <u>For patients with baseline AST and ALT values ≤ULN:</u> ALT or AST ≥ 3x ULN and Total Bilirubin ≥ 2x ULN;

   <u>For Patients with baseline AST or ALT values >ULN:</u> AST or ALT >2x baseline and ≥3x ULN] and Total Bilirubin ≥ 2x ULN.

b. ALP ≥ 2x ULN and Total Bilirubin ≥ 2x ULN;

c. For patients with Gilbert's syndrome: ALP ≥ 2x ULN and Direct Bilirubin ≥ 2x ULN;

d. ALT or AST ≥ 3x ULN and INR ≥ 1.5;

e. ALP ≥ 2x ULN and Direct Bilirubin or Total Bilirubin ≥ 2x ULN and INR ≥ 1.5;

f. ALT or AST ≥ 5x ULN; or

g. Hepatic decompensation.

In the event a patient meets any of these DILI triggers, a search for causality should be conducted (as per current guidelines: Clinical Practice Guidelines: Drug-induced liver injury, EASL, 2019 and Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, FDA guideline, 2009), the corresponding suspected DILI forms should be completed and the event reported (see Section 9.6). Testing of liver biochemistry should be repeated within 48 to 72 hours to confirm the abnormalities and the patient should be placed in close monitoring and followed until they normalize or stabilize.

If two patients experience serious liver injury (as defined by above thresholds) or a hepatic decompensation event, the trial should be paused, and the DMC should conduct a review and provide supplemental causality assessment. If the DILIs are deemed to be related to VTX-801, then the study will remain on hold and further study continuation should be discussed with FDA.

Definition of DLT: Two patients receiving the IMP develop similar > Grade 3 (CTCAE) laboratory, ECG or vital signs abnormalities, or severe AEs in the same organ class, indicating dose limiting intolerance. Adverse events that are incontrovertibly not related to IMP will not count in determining DLT.

Overall, enrollment and dosing in the trial may resume after review of concerned clinical cases by and upon positive recommendation from the DMC, after Sponsor agreement and if the study is on temporary hold, after discussion with and agreement of the FDA.

6.4 Patient Withdrawal Criteria

Patients may withdraw their consent from participation in the study at any time, for any reason, during the trial.

The Sponsor can terminate prematurely the trial at any time for futility or safety reasons, based upon Health Authorities' request or DMC recommendation.

6.5 Patient Withdrawal Procedures

Patients will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and that they are not obliged to state their reasons. Any withdrawal will be documented in the eCRF and followed up by the Investigator.

If a patient withdraws or is withdrawn from the study, the reason for withdrawal will be recorded in the eCRF if available and all efforts must be made to complete and report the observations as thoroughly as possible.

For any study withdrawal, all efforts should be made to conduct an Early Termination Visit. This visit should be performed within 4 weeks following the decision to withdraw and as described in Section 10 and recorded in the Early Termination eCRF.

The extent of the termination visit will depend on whether the patient has received VTX-801 administration (even partial) or not; every effort should then be made to follow each patient who received at least a partial VTX-801 infusion for up to 5 years post-VTX-801 administration with at least one phone call every 6 months to collect potential adverse events.

If a patient fails to return for follow-up, attempts should be made to contact the patient to ensure the reason for not returning is not an AE. After 3 unsuccessful calls or emails, a certified letter will be sent; all attempts will be documented in source data and eCRF. For patients considered lost to follow-up, the eCRF must be completed up to the last visit performed.

Ongoing AEs should be followed up in accordance with the procedures described in Section 9.2.7.

Patients without evaluable Responder status evaluation may be replaced, as appropriate.

6.6 Premature Termination or Suspension of the Study

This study may be suspended or prematurely terminated for futility or for safety reasons, in the following circumstances:

- Safety, i.e. determination of unexpected, significant, or unacceptable risk to the patients;
- Futility, i.e. plans to modify, suspend or discontinue the development of VTX-801.

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/Institutions, and the Regulatory Authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the

Sponsor or by the Investigator/Institution, as specified by the applicable regulatory requirement(s).

Regardless of the reason for study termination, all patients having fully or partially received VTX-801 will have to complete the 5-year safety follow-up consisting of, at minimum, a call by the Investigator every 6 months to the patient.

7 VTX-801 TREATMENT, AUXILIARY TREATMENTS, DIET AND OTHER STUDY SPECIFICATIONS

7.1 Wilson's Disease Background Therapy

Per enrollment criteria, all patients entering the study will already be on background WD therapy according to SoC therapy for WD (Schilsky et al, 2022; EASL, 2012); such treatment is referred to as "background WD therapy" in this study protocol (Enrollment criteria, Sections 5.2 and 5.3). Patients will be instructed to continue their background WD therapy upon entering the study and the dosing regimen should remain unchanged, unless requested otherwise: such treatment will be withdrawn or continued following the rules described in Section 4.6. Similarly, WD SoC therapy may be re-initiated following the rules described in Section 4.6 and may or may not be identical to background WD therapy, upon Investigator's decision.

Background WD therapy and WD SoC therapy in case of reinstitution will not be provided as part of the study.

The Investigator will question patients for their compliance to background WD therapy at Screening (cf. Inclusion Criteria, Section 5.2) and also, during the periods when patients are requested to discontinue (Responder status, wash-out period) or reinstate WD medications.

7.1.1 Zinc Salt Treatments

Any zinc salt formulation prescribed by the treating physician is acceptable. No wash-out period will be necessary for zinc-only treated patients around the radiocopper related assessments, since zinc salts are not expected to significantly interfere with the metabolism of IV-injected radiocopper.

7.1.2 Copper Chelator Treatments

All D-penicillamine and trientine formulations approved in the patient country for the treatment of WD are acceptable as background WD therapy. Any other copper chelator is prohibited at enrollment.

Wash-out periods will need to occur for copper chelators around radiocopper related assessments, since they may chelate radiocopper and interfere with the evaluations (Section 10.2).

7.2 Investigational Product: VTX-801

Please refer to the VTX-801 IB and VTX-801 Pharmacy Manual for full details.

7.2.1 VTX-801 Description and Supply

The investigational medicinal product (VTX-801) is a replication-deficient recombinant adeno-associated viral vector (rAAV) consisting of an AAV3B capsid containing a single-stranded DNA genome carrying a shortened version of the *ATP7B* gene (*ATP7B*-minigene).

VTX-801 Solution for Infusion, 5.4 mL/vial, is supplied in its final formulation in a 10 mL closed vial. Each vial is for a single use in a single patient. A subsequent reconstitution will be performed on site.

VTX-801 should be handled as a biohazardous product according to local regulations for biosafety level class 1 agents (BSL1).

7.2.2 Selection of VTX-801 Doses Used in the Study

Starting VTX-801 dose: The initial VTX-801 dose has been selected primarily based upon non-clinical pharmacology and toxicology studies, as a balance between expected pharmacodynamics and safety. VTX-801(Anc80) 1.5E12VG/kg treatment is efficacious in 6-week-old WD mice and is associated with ~11% of liver cells positive for miniATP7B transcripts; the same dose results in similar mRNA signal in healthy mice. To reach ~11% of liver cells expressing VTX-801 in NHPs, a dose of 5E12VG/kg of vector is necessary. Assuming liver transduction is equivalent between NHP and humans (based upon *in vitro* experiments in hepatocytes), the dose of 5E12VG/kg is considered potentially therapeutic in WD in patients. In addition, re-treatment of WD patients exposed to a sub-optimal VTX-801 dose may not be possible due to seroconversion to the AAV3B capsid. Based upon these considerations, as well as the safety profile in mice and NHPs, VTX-801 5E12VG/kg is considered appropriate as a starting dose for the dose escalation.

VTX-801 dose increments during dose escalation: VTX-801 dose will be incremented by a factor of 3 between Cohorts 1 and 2; VTX-801 dose may be incremented by a factor of 2 between Cohorts 2 and 3. Therefore, the following will be used:

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

Patients with BMI >30kg/m^2: for patients with BMI >30 kg/m^2, the dose will be calculated based upon an adjusted body weight determination that assumes a maximum permitted BMI of 30 kg/m^2 for that patient respective height (actual).

7.2.3 VTX-801 Packaging and Labelling

The packaging of VTX-801 is compliant with the IATA regulation for genetically modified organism (UN3245). VTX-801 will be labelled in accordance with applicable local regulatory requirements and applicable ICH Good Manufacturing Practice (GMP) and ICH GCP guidelines.

VTX-801 is supplied in 10 mL vials in an individual package. Each vial is for a single use.

7.2.4 VTX-801 Storage and Stability

Before reconstitution:

Upon receipt, VTX-801 vials must be stored frozen at -60°C to -90°C (-76 ºF to -130 ºF) in a secured and temperature-controlled freezer as well as in a locked and restricted access storage facility under pharmacist supervision.

After reconstitution:

When reconstituted, with or without dilution in normal saline (0.9% sodium chloride), VTX-801 in the infusion bag for intravenous administration may be stored at ambient temperature prior to use but administration must be completed within 8 hours of the start of the first vial thaw.

7.2.5 VTX-801 Dosage, Preparation and Administration

Quantity of VTX-801, final volume, infusion rate and duration of administration will depend on patient's weight and cohort to which the patient has been assigned. However, for patients with BMI >30 kg/m^2, the dose will be calculated based upon an adjusted body weight determination that assumes a maximum permitted BMI of 30 kg/m^2 for that patient respective height (actual).

Administration of VTX-801 will always be upon the Investigator written prescription at V5 (D-1) and approved by the Sponsor.

VTX-801 will be provided to the responsible pharmacist at the study site, who will handle and dispense study product in accordance with the VTX-801 Pharmacy Manual that includes the reconstitution protocol which is developed according to ICH GCP guidelines and applicable local laws.

The VTX-801 will be administered as a single dose intravenous (IV) administration, at up to 3 different doses levels.

The prepared volume of VTX-801 in Normal Saline (0.9% sodium chloride) is intended to be administered with the aid of an Infusion Pump. Recommendations for decontamination and destruction of the material used for IMP preparation and administration will be available in the VTX-801 Pharmacy Manual.

7.2.5.1 Infusion Procedure

VTX-801 infusions should be administered by appropriately qualified staff used to manage infusion associated reactions; resuscitation and safety equipment and procedures must be available throughout the end of the expected patient post-infusion safety follow up period. A 24/7 emergency medical coverage is also expected at site.

- Fast patient overnight prior to VTX-801 administration and during administration;
- The VTX-801 infusion administration should be started early in the morning in order to limit as much as possible the total duration of the fasting period;
- In order to make sure that patients are well hydrated, small volumes of per os fluids only (no solid meals) are acceptable up to 2 hours before the infusion starts. Thereafter, only IV fluids should be given, as necessary;

- Administer methylprednisolone 100 mg IV one hour before the VTX-801 infusion;
- Have ready a keep-vein-open (KVO) port normal saline as a slow drip;
- Measure pre-infusion blood pressure and heart rate;
- Start VTX-801 infusion according to the VTX-801 Pharmacy Manual;
- Measure blood pressure and heart rate every 15 min during the infusion, at the end of the infusion, 1 hour after the infusion and then every 4-hour until patient goes to sleep in the evening on the day of administration;
- It is recommended that the patient also fasts for 2 hours after the administration for infusions shorter than 1 hour, but this time may be reduced for patients receiving longer infusions;

Should the patient develop during or following the VTX-801 infusion clinical symptoms such as hypotension, fever, tachycardia, chills, rash or headache, this will be treated by standard methods used for infusion associated reactions; such methods may include (but are not limited to) slowing down the infusion rate to 50% of previous rate at the Investigator's discretion. The infusion may be subsequently titrated back to the original rate, if tolerated by the patient. Additional therapeutic measures may include symptomatic treatment such as rehydration, acetaminophen (paracetamol), antihistamine and/or intravenous methylprednisolone administration. The infusion will be interrupted in the case of a CTCAE Grade 2 or 3 adverse event occurs (such as bronchospasm or anaphylaxis) (refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017), and symptomatic measures will be implemented; when the situation has improved to Grade 1 or Grade 0 AE, the infusion of the IMP may resume, as long as the time elapsed since IMP thawing does not exceed 8 hours; if not, dosing will be permanently stopped for this patient. In the case of Grade 4 AE, the infusion will be stopped permanently in this patient (and cf. the stopping rules in Section 6.3). If the patient is at risk of vomiting following the VTX-801 infusion, the next day oral steroid (prednisone or prednisolone) may be replaced by an equivalent dose of IV methylprednisolone, as appropriate.

Section 7.2.5.2 provides guidance for laboratory exams to be performed in case of severe event of IAR.

7.2.5.2 Biochemical Analysis of Infusion-Associated Reactions by Laboratory Sampling

In an effort to characterize the etiology should a **severe** event of IAR occur, an attempt should be made to collect blood samples for exploratory analysis as close as possible to the event, after acute clinical management steps have been taken. Note that these analyses will be tested locally at the site with fresh samples for optimal patient management; the choice of the tests for cytokines and complement (which will depend on local availability), sample volume and storage conditions should be checked in advanced with each site.

Specifically, blood samples should be obtained for the following tests :

- Cytokine panel, including but not limited to IL-6; measurements of other cytokines such as IL-10, IL-2, IFNγ, TNFα should be performed if available in the selected panel.
- Complement assessment including at minimum C3 and C4; measurement of CH50 (total hemolytic complement) and C5b-9 should be performed if available.
- Liver biochemistry, creatinine, CRP, fibrinogen and complete blood count.
- Any additional tests deemed necessary by the Investigator.

On the day following the IAR, the tests outlined above should be repeated to evaluate if the inflammatory response has resolved. Liver biochemistry, creatinine, fibrinogen, and complete blood count follow-up testing should also be considered until resolution of the IAR and stabilization of the patient.

7.2.6 VTX-801 Accountability Procedures

Records will be maintained of the delivery of VTX-801 vials to the study sites, the inventory at the study sites, the allocation to, and use of VTX-801 vials by each patient at the site, and the destruction or return of unused VTX-801 vials to the Sponsor.

These records will include dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the study product and to the study patients.

The Investigator will be responsible for ensuring the records adequately document that the patients are given the doses specified in the protocol and all VTX-801 received from the Sponsor is reconciled.

7.2.7 VTX-801 Compliance

The assigned study product VTX-801, dosage, timing and mode of administration may not be changed. The number and duration of any interruptions of the infusion during administration will be recorded in the eCRF.

As the single VTX-801 administration will be performed under direct medical supervision, patient non-compliance with treatment is not anticipated to be a significant issue. However, any departures from the intended regimen will be recorded in the eCRF.

VTX-801 accountability and compliance will be documented throughout the study using study-specific dispensing and return record forms.

7.3 Diluent for VTX-801

The diluent for VTX-801 will be normal saline for infusion (0.9% sodium chloride in sterile water). The diluent will be supplied by the investigational sites.

7.4 Radiocopper - $[^{64}Cu]CuCl_2$

Please refer to the Radiocopper IB and Radiocopper Administration Manual for full details.

[redacted]

7.4.1 Radiocopper Description and Supply

The radiocopper to be used ($^{64}CuCl_2$) has a half-life of 12.7 hours.

The sterile ready-to-use injectable solution of radiocopper suitable for intravenous administration into humans will be provided to clinical sites. The administration instructions will be available in the Radiocopper Administration Manual.

7.4.2 Selection of the Radiocopper Dose for this Study

For each administration of [^{64}Cu]$CuCl_2$ a delivered activity of [redacted] MBq was chosen. This administered activity represents the lowest reasonably achievable activity that will permit reliable radioanalysis of biological samples[redacted]

A recent study by Sandahl et al, 2019 aimed to evaluate the diagnostic potential of $^{64}CuCl_2$ PET in WD management. The study evaluated the difference in hepatic copper

metabolism in 8 healthy subjects, 5 healthy heterozygote subjects, and 9 WD patients after administration of radiocopper (71.2 ± 5.5 MBq). All subjects underwent ^{64}Cu imaging by means of dynamic PET/CT of the liver (time 0-90 minutes) and static whole-body PET/CT (90 minutes and 20 hours after radiocopper administration). Human $^{64}CuCl_2$ PET/CT demonstrated increasing hepatic copper accumulation over a 20-hour period in patients with WD compared to healthy and heterozygote controls. [redacted]

As summarized in Table 5, a total effective dose for patients in this study is estimated to be < 10 mSv, which is well below deterministic thresholds and corresponds to a minor to intermediate cumulative risk level based on ICRP Publication 62, 1992.

A comprehensive review of radiocopper is contained in the IB supplied by Vivet Therapeutics. Investigators are to review this document prior to initiating this study.

7.4.3 Radiocopper Packaging and Labelling

The labelling of the radiocopper ready-to-use solution for clinical use will comply with the applicable (local) laws and regulations.

7.4.4 Radiocopper Dosage, Preparation and Administration

During the study, each patient will receive on 3 separate occasions one intravenous administration of [redacted] MBq (±10%) radiocopper.

Administration of radiocopper will take place under the supervision of an Investigator or designee. Before administration of the bolus, 10 mL of sterile sodium chloride solution (0.90% w/v of NaCl) will be injected to confirm that the intravenous access is intact. After administration of the bolus, the intravenous access will be flushed with 10 mL of the same solution. The Investigator or designee will check for extravasation (i.e. using a gamma camera or handheld probe) after each radiocopper injection.

The time of administration of radiocopper will be recorded in the source data and eCRF.

7.4.5 Radiocopper Storage, Disposal and Accountability

Upon receipt of the radiocopper, the responsible person will inspect the shipment and return the enclosed acknowledgement of receipt form duly completed and signed (date/time point of receipt must be noted).

In accordance with applicable local Radiation Protection Regulations, the study site is responsible for all radiocopper received, processed, stored and disposed. Sites' trained personnel will be responsible for storage in a locked container in the 'hot room' (a restricted access room) according to instructions provided by manufacturer. Only trained personnel will handle the radiocopper.

After decay below the legal limit, all unused material radiocopper and packaging must be disposed by the site according to its standard operating procedure (SOP) on nuclear waste.

The sites' trained personnel will be responsible for the inventory and accountability of radiocopper.

7.5 Immunosuppressive Regimens [redacted]

All treatments given as part of the immunosuppressive (IS) regimen will be supplied and reconciled by the study site in accordance with their local dispensing and accountability procedures. The products should be stored, handled and prepared in accordance with

the manufacturer's instructions. The Investigator will record patient compliance with the IS regimen in the eCRF.

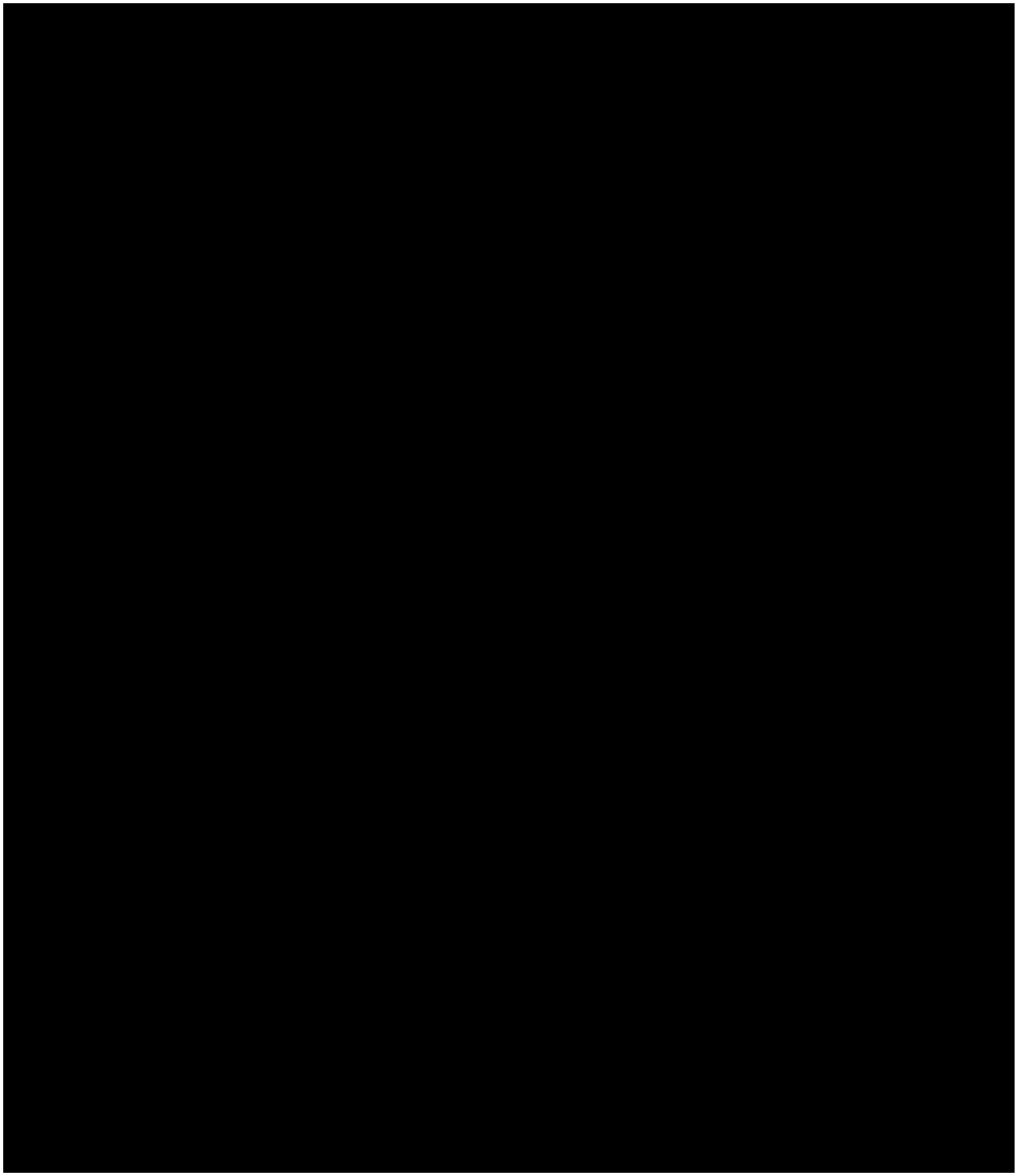
7.5.1 Prophylaxis of IARs, Immune T-cell Response Against the AAV Capsid and [redacted]

In order to prevent potential IARs that may occur during or within 24 hours post-VTX-801 infusion, a single injection of 100 mg of methylprednisolone will be administered intravenously prior to any VTX-801 infusion (see Section 7.2.5.1).

Based upon recent published experience in AAV-based gene therapy trials, mitigation of the immune T-cell response against the AAV vector capsid will include oral steroid (prednisone or prednisolone) prophylaxis. Furthermore, Sirolimus will be added in order to improve such immune modulation regimen. Such a regimen may be useful to optimally mitigate the above effects, especially in the context of a liver disorder that may be more susceptible to developing reactions to hepatic viral infections. The rationale to use Sirolimus in this setting is the known effect on regulatory T-cells, which are essential to establish and maintain immune tolerance. Of interest, tacrolimus is currently used in a hemophilia AAV-based gene therapy (IV route) trial for the same purpose (ClinicalTrials.gov Identifier: NCT03369444). Furthermore, Sirolimus in combination with methylprednisolone and rituximab has also been safely co-administered with an AAV4 vector in a phase I/II trial of intra-diaphragmatic gene transfer in children affected by Pompe disease (Corti et al, 2014). Mammalian target of rapamycin (mTOR) inhibitors have been shown to be effective and safe in adults and children following solid organ transplantation. Interestingly, prospective and retrospective data in pediatric patients (the most fragile population in this field) converted from calcineurin inhibitor therapy to mTOR inhibition suggest preservation of Immunomodulatory efficacy without adding significant risk of side effects (Ganschow et al, 2013).

The IS regimen should be administered according to the protocol below, in line with drug labels.

- **Prevention of hypersensitivity reactions**:
    - **Methylprednisolone** 100 mg will be administered IV one hour before the VTX-801 infusion.
- **Prevention of T-cell immune response against AAV capsid:**



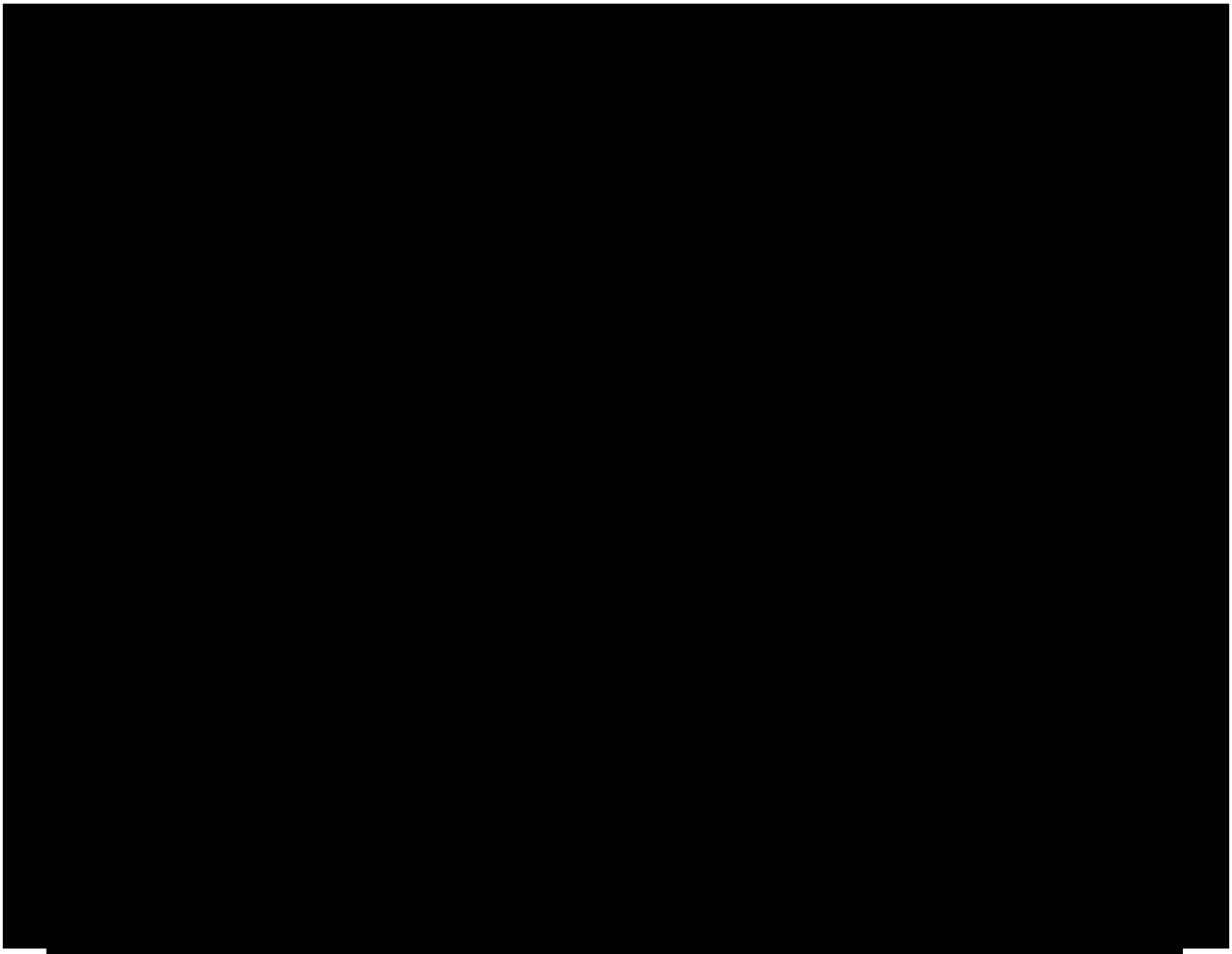
- **Oral steroid (Prednisone or Prednisolone)** 60 mg/day administered orally for one week starting the day after VTX-801 administration according to Table 6 and stopped at the end of Week 8 (8 weeks in total).

The tapering course of steroid treatment has been chosen to prevent the development of hypothalamic pituitary adrenal (HPA) suppression; the Investigator should nevertheless keep in mind the possible need for stress steroid coverage for any stress situation (e.g. infection, surgery) around or after steroid treatment.

Table 6 Dose Tapering for Oral Steroid

Week number	Oral steroid (Prednisone or Prednisolone) dose
Week 1, from Day 2 (6 days in total)	60 mg, oral
Week 2	40 mg, oral
Week 3	20 mg, oral
Week 4	10 mg, oral
Week 5	10 mg, oral
Week 6	10 mg, oral
Week 7	5 mg, oral
Week 8	5 mg, oral
Week 9	Stop

- History of depression is frequent in WD patients; particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first-degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.



. DMC data monitoring will continue and the committee will be informed should any adverse events of interest, especially ALT increases, occur after the end of the IS regimen; therefore, the most up-to-date safety information will be taken into account in the DMC evaluation and recommendation for dose escalation at the next dose level (cf. DMC Charter).

7.5.2 Mitigation of Overt Transaminase Increase

7.5.2.1 Surveillance of transaminase increase

During the post-administration follow-up period, each patient will follow a comprehensive surveillance plan monitoring liver biochemistry, including ALT. Instances of ALT ≥ 1.5 x baseline (in any laboratory in charge of analysis) up to 9 months post-VTX-801 infusion should be reported to the Sponsor within 24 hours of the laboratory value being available; reporting is via data entry into the clinical trial database. Laboratory alerts will also be put in place where possible. Due to the unknown timing of the potential rise in hepatic transaminases, unscheduled visits and blood/urine samples may be necessary to evaluate safety and/or potential or suspected loss of efficacy.

7.5.2.2 Reporting, management and search for etiology of transaminase increase

In case an ALT increase ≥ 1.5 x baseline is observed between Week 2 and Month 9 post-VTX-801 administration, and **within 24 hours of awareness,** the Investigator will enter the AE into the eCRF and discuss with the Sponsor medical monitor (or delegate) the appropriateness of initiating reactive steroid treatment.

If the above-mentioned transaminase increase is ALT or AST ≥ 5x ULN (consistent with suspected DILI criteria listed in Section 6.3), a DILI form will be completed and reported as outlined in Section 9.6. A liver biopsy will be performed as soon as possible (if possible, within 24-48 hours), in order to assess the results of the liver biopsy and the respective transaminase elevation for causality through HAC adjudication; furthermore, testing of liver biochemistry should be repeated within 48 to 72 hours to confirm the abnormalities and the patient should be placed in close monitoring and followed until normalization or stabilization. *Note that DILIs will be evaluated as per current guidelines: Clinical Practice Guidelines: Drug-induced liver injury, EASL, 2019 and Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, FDA guideline, 2009.*

If the decision is taken to initiate reactive steroid treatment:

- An unscheduled sampling for IFN-gamma ELISpot to AAV3B capsid and miniATP7B transgene assays will be taken, ideally before steroid reactive treatment initiation.

- The investigator will perform the evaluation for an alternative etiology for liver disease (other than T-cell immune response to VTX-801), including:
  - acute viral hepatitis (immediate testing):
    - PCR for HSV, CMV, EBV, HCV
    - serology for HAV: HAV IgM
    - HBV testing: HBsAg and if positive HBV DNA
    - serology for HEV (IgG and IgM) and HEV RNA
  - alcoholic and autoimmune hepatitis: ANA, SMA, and anti-LKM1 auto-antibodies, as well as total IgG testing,
  - hepatobiliary disorders other than WD,
  - cardiovascular causes,
  - concomitant treatments.
- Reactive steroid treatment: without awaiting all results of the above-mentioned evaluations and within 24 hours of receiving the ALT results ≥ 1.5x baseline, if no contra-indication has been identified, the patient will be administered oral steroid (prednisolone or prednisone) 1 mg/kg per day for 1 week (maximum dose 60 mg/day), tapered down by 10 mg every week until complete withdrawal (whatever the ALT response to reactive prednisolone treatment), replacing the prednisolone dose scheduled for T-cell immune response prophylaxis (cf. Section 7.5.1). Should the schedule of the reactive steroid treatment result in a shorter course of treatment than the planned prophylactic steroid treatment, then the course of reactive steroids will be prolonged so that it is not shorter (the taper will be adjusted by the investigator according to medical judgement). *This approach is based upon the Clinical Practice Guidelines published by the European Association for the study of the Liver on treatment of autoimmune hepatitis, a T-cell mediated disease of the liver commonly controlled by a steroid course both at diagnosis and during relapses (EASL, 2015).*
- The DMC will be informed and based on the whole information received, it will provide its recommendation to maintain the (altered) regimen or not.

- In case testing is positive for viral hepatitis, any steroid treatment will be stopped or tapered immediately and sirolimus treatment (if still ongoing) will be stopped immediately.

7.5.2.3 HAC assessments and recommendation for patient management

Data regarding suspected DILI events will be provided to the HAC for adjudication via sending of a completed suspected DILI form along with all additional information received from site. These events will be followed up as AEs of special interest (AESI; see Section 9.6).

In instances where a liver biopsy was taken, the HAC will assess the liver biopsy report for causality and provide its assessment and recommendation to the DMC on whether to maintain the reactive steroid regimen or not, and the DMC will then provide their own (prevailing) recommendation.

7.5.2.4 Long-term follow-up

Patients will then be followed long-term (at least 12-24 months) by monitoring liver enzymes to ensure their normalization or stabilization, as well as to ensure the clinical status of the patient is stable or normal; in this case, unscheduled biological sampling may be added to the planned assessments, as necessary.

7.6 Other Concomitant Medications/Treatments

7.6.1 Contraception

“Highly-effective” methods of contraception are recommended. A highly-effective method of birth control is defined in ICH M3(R2) as one that results in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence, or a vasectomized partner (the vasectomized partner must have received medical assessment of the surgical success). Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- **Male patients** must be willing to use two methods of contraception from the day of the first radiocopper injection through 6 months following VTX-801 infusion and also

for the week following the W36 radiocopper injection. Male patients must also not donate sperm. All sexually active male patients must use a condom and those with female partners of childbearing potential must require their partner to use an additional form of adequate contraception as approved by the Investigator, such as an established form of hormonal contraceptive, a diaphragm or cervical/vault cap, IUD, or sponge with spermicide.

- **Female patients** of childbearing potential must be willing to use two methods of contraception from signing the informed consent through one week after W36 radiocopper injection. If using oral contraception, it must have remained unchanged for ≥ 3 months prior to inclusion. Female patients using oral contraception should refrain from changing their contraception regimen during the study (in accordance with inclusion criterion #5, Section 5.2); any change must be recorded in the eCRF.
- Note: contraception is warranted for both genders after the administration of VTX-801 as a gene therapy product for 6 months; thereafter, males can stop contraception and restart only during Week 36 radiocopper explorations, while females will continue contraception up to Week 36 included, in order to prevent any fetal exposure to ionizing radiations during Week 36 explorations.

7.6.2 Drug Interactions and Prohibited Medications

Use of known hepatotoxic agents should be avoided as much as possible during the course of the clinical trial.

Sirolimus is known to be a substrate for both cytochrome P-450 3A4 (CYP3A4) and P-glycoprotein (P-gp). Inducers of CYP3A4 and P-gp may decrease Sirolimus concentrations whereas inhibitors of CYP3A4 and P-gp may increase Sirolimus concentrations (Rapamune US label and SPC).

Strong inducers (e.g., rifampin, rifabutin) and strong inhibitors (e.g., ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, clarithromycin) of CYP3A4 and P-gp are **contraindicated** during the Sirolimus treatment period. Alternative agents with lesser interaction potential with Sirolimus should be considered.

The dosage of Sirolimus and/or the following co-administered drug may need to be **adjusted**:

- Drugs that could increase Sirolimus blood concentrations: bromocriptine, cimetidine, cisapride, clotrimazole, danazol, diltiazem, fluconazole, HIV-protease inhibitors (e.g., ritonavir, indinavir), metoclopramide, nicardipine, troleandomycin, verapamil.
- Drugs and other agents that could decrease Sirolimus concentrations: carbamazepine, phenobarbital, phenytoin, rifapentine, St. John's Wort (*Hypericum perforatum*).
- Drugs with concentrations that could increase when given with Sirolimus: verapamil.
- Since Sirolimus has been shown to increase blood lipids (Rapamune US label and SPC), the Sirolimus dose may need to be adjusted during the transient Sirolimus treatment in patients with abnormal values or treated for hyperlipidemia at baseline; such adjustment will be made by the Investigator, in consultation with the Sponsor, and will be based upon the routine monitoring of hyperlipidemia in the patient, trying to maintain Sirolimus level within the target range as far as possible.
- Immunosuppressants may affect response to vaccination. Vaccination with live vaccine within 30 days before Sirolimus administration is prohibited (cf. Exclusion Criteria) up to and including Week 14. The use of non-live vaccines, including for COVID-19 or seasonal flu, should be avoided within 2 weeks before Sirolimus initiation and up to the end of the Sirolimus treatment. For this reason, if a patient is to be vaccinated, according to local recommendations, he/she is encouraged to do it before enrolling into the trial.
- Sirolimus with other drugs known to cause angioedema, such as ACE-inhibitors, may increase the risk of developing angioedema; therefore, in case a patient would develop new angioedema during the coadministration period, the ACE inhibitor will be temporarily replaced by a different medication until the end of the Sirolimus administration period, if possible; if not possible, the Sirolimus regimen will be interrupted.
- Since cases of abnormal wound healing have been reported in patients treated with Sirolimus, the Investigator will evaluate the risk/benefit of the continuation of Sirolimus treatment in case of significant wound (surgical intervention that cannot be postponed or accident).

7.6.3 [redacted]

[redacted]

7.7 Dietary or Other Protocol Restriction or Specification

Low-copper diet: low copper diet followed at the time of study entry will be maintained throughout the study (cf. Appendix 17.3). However, once an effective dose has been selected, withdrawal of the diet may occur in VTX-801 Responders.

Alcohol: Patients should refrain from drinking any alcohol during the 9 months following VTX-801 infusion; in any case, patients should not consume more than 3 alcohol drinks per week for the whole study period (per "light alcohol drinker" definition by US Centers for Disease Control and Prevention, https://www.cdc.gov/nchs/nhis/alcohol/alcohol_glossary.htm).

Grapefruit juice inhibits the CYP3A4-mediated metabolism of Sirolimus, as a consequence, it must not be taken with or be used for dilution of Sirolimus. Overall, grapefruit juice should be avoided during the whole period of Sirolimus administration.

[redacted]

Exercise: Patients should avoid strenuous exercise (such as intensive weightlifting) during the Screening period and the first 9 months of the study, as this may confound transaminase assessments (Pettersson et al, 2007; Park et al, 2017).

8 STUDY PROCEDURES AND EVALUATIONS

8.1 Clinical Evaluations

8.1.1 Demographics and Medical History

Demographic and baseline characteristic data will be collected on all patients. Relevant medical history/baseline medical conditions including substances usages will be recorded in the eCRF.

Medical history includes Leipzig score (EASL, 2012) from historical records and *ATP7B* genotype. *ATP7B* genotype is to be assessed from Screening 1, V1A sample, for patients without historical genotyping available from a CLIA-certified laboratory. Note: Due to the extended time needed to obtain genotyping results, ERC review and patient inclusion and treatment may occur before receiving genotyping results, provided that Leipzig score ≥ 4 based upon the other parameters.

8.1.2 Prior and Concomitant Medications

Prior and concomitant medications (including background WD therapy) will be recorded (prescription medications, over-the-counter and herbal remedies).

Reasonable effort will be made to determine and record all relevant prior treatments (e.g. prescription medications, over-the-counter and herbal remedies) or procedures (e.g. operative procedures, radiologic tests, biopsies, etc.) received by the patients within 1 month before Screening until administration of VTX-801. All available WD treatment history will be recorded.

Assessment of eligibility during Screening visits will include a review of permitted and prohibited medications.

Concomitant treatments (e.g. prescription medications, over-the-counter and herbal remedies) or procedures (e.g. operative procedures, radiologic test, biopsies, etc.) received by the patient will be recorded from VTX-801 administration to last patient study visit included.

8.1.3 Physical Examination

The physical examination will include: general appearance, skin, head and neck, eyes-ears-nose-throat, lymph node palpation, lungs, chest, abdomen, extremities, and neurological function.

In the absence of any abnormal findings, the physical examination will be reported "normal" for all items in the eCRF.

Height and BMI will be recorded at screening only.

Weight will be recorded at each visit that includes physical examination. On Visit 5 occurring the day before VTX-801 administration only weight will be recorded.

8.1.4 Vital Signs

Vital signs include systolic and diastolic blood pressures (BP), pulse (P), respiratory rate (RR), temperature (°C), and should be taken after the patient has been resting supine or upright for 5 minutes.

Additionally, blood pressure and heart rate will be regularly measured during the safety follow up period related to VTX-801 administration:

- prior to VTX-801 administration
- at 15-minute intervals during the VTX-801 administration duration (+/- 3 min)
- at the end of the administration
- 1 hour after the end of the administration (+/- 10 min)
- and then at 4-hour intervals until night sleep (+/- 15 min)

All abnormalities should be clearly documented.

8.1.5 Electrocardiogram

12-lead ECG will be recorded; each ECG recording will be retained in the patient's file and uploaded to the vendor's portal for central reading (refer to Image Acquisition Guidelines). ECG recordings will be reviewed locally by the Investigator or delegate for immediate action if needed. In addition, ECG will be analyzed systematically by a central reading vendor based on following parameters: heart rate, QRS axis, PR interval, QRS

duration and QT and QTc (Fridericia (primary) and Bazett formulas). In case of discrepancy between local and central interpretation, central reading and interpretation will prevail.

Patients will be in a lying position for 5 minutes prior to the measurements. ECGs will be evaluated and classified as normal/abnormal. In case of “abnormal”, the abnormality has to be described.

8.1.6 Ophthalmology

A slit lamp eye examination will be performed, and abnormalities will be documented, in particular the presence or absence of a Kayser-Fleischer ring. Additional gross ophthalmic abnormalities, if any detected at examination, will be reported as well.

Examination can be performed any time from Baseline V2 to before the day of radiocopper administration as long as results are available before the day of radiocopper administration.

8.1.7 Questionnaires

The Unified Wilson's Disease Rating Scale (UWDRS) and Mini-International Neuropsychiatric Interview (M.I.N.I.) will be used to assess neurological and psychiatric symptoms at Screening 1 and 2 (UWDRS part II and III only), baseline (excepted M.I.N.I), Weeks 12, 36 and 52 in Year 1 and, at 6 months and 12 months visits in Years 2 to 5.

The Montreal Cognitive Assessment (MoCA) will be performed at Screening 2 to exclude patients having dementia or moderate to severe cognitive impairment.

The Symbol Digit Modality Test (SDMT) and Stroop Test will be used to assess executive functions at baseline, W12, W52 and every 12 months visits in Years 2 to 5.

The M.I.N.I Screening 2 results will be used as baseline data. Baseline UWDRS, Stroop and SDMT can be performed any time from Baseline V2 to the day before radiocopper administration as long as results are available before the day of radiocopper administration.

UWDRS will be conducted by a trained neurology specialist and M.I.N.I., MoCA, SDMT and Stroop Test by a trained medical doctor or designee, ideally the same Healthcare Provider (HCP) will conduct the same assessment(s) throughout the study. At least two

appropriate staff representatives for each site will be trained to administer the questionnaires to allow for a replacement, as needed.

In a situation where a patient cannot reliably report a change in symptoms, a capable caregiver will be involved in providing assessments regarding changes in mood or function. The same caregiver should provide the assessments at each visit, if possible.

8.1.8 Abdominal MRI, Liver MR Elastography

Abdominal MRI (to detect any gross abnormalities) and MR liver elastography will be performed either at Screening 1 (V1A) or Screening 2 (V1B) (to also include MRI for liver volume) and Week 52 (end of Year 1) and at each 12-month visit of Years 2 to 5. In case of initial screening failure, the abdominal MRI and MR liver elastography, if any, may be re-used for re-screening if no longer than two months have elapsed between screening assessments.

The abdominal MRI and MR liver elastography results at Screening 1 or 2 will be used as baseline data.

- The elastography must be performed in at least a 4-hour fasted state.

All the abdominal MRI and MR liver elastographies will be analyzed by a central reading vendor.

In case of contraindication to abdominal MRI and MR elastography, these will be replaced by non-centralized hepatic ultrasound and Vibration-controlled transient elastography (Fibroscan®), respectively. If performing Fibroscan®, both liver stiffness and CAP score should be collected at the site. Any AEs will be collected.

In case where the site is equipped with MRI but not MR elastography, vibration-controlled transient elastography should be used instead of the MR elastography. In any case, the Sponsor should be notified of the change.

8.1.9 Brain MRI

Brain MRI will be performed at Screening 1 or 2 and at the 12-month visit of Year 3 (V52), and at the end of the 5-Year follow up. In case of initial screening failure, the brain MRI, if any, may be re-used for re-screening if no longer than two months have elapsed between screening assessments.

The results at Screening 1 or 2 will be used as baseline data.

Brain MRI will be analyzed by a central reading vendor.

In case of contraindication to brain MRI, it will be neither performed nor replaced.

8.1.10 Central and Local Laboratories for Standard Clinical Evaluations

Several blood and urine samples will be taken throughout the study for analysis at either the site ("Local") or Central Laboratories.

Local Laboratory data will be entered into the eCRF by the site. In case of discrepancy between Local and Central Laboratory data for a same visit, Central Laboratory data will prevail.

The instructions for sample collection, specimen preparation, handling, storage and shipping are described in the Central Laboratory Manual.

The main Central Laboratory will provide the site with the corresponding kits to support the management of all samples, from preparation of sampling to sending samples to respective Central Laboratories.

8.1.11 Central Laboratory Standard Evaluations

Table 7 lists the standard parameters to be analyzed by the Central Laboratory. Please refer to Table 8 for the Liver Biochemistry Panel sampling frequency and the Schedule of Events for the related time points.

Table 8 Standard Parameters to be Analyzed by the Central Laboratory

Hematology	Blood Biochemistry	Urinalysis	Others
CBC: • Hematocrit • Hemoglobin • Relative reticulocyte counts • Red blood cell (RBC) Count • Differential and absolute WBC count • Platelet count • Mean cell volume **Coagulation:** • INR • Activated Partial Thromboplastin time (aPTT) • Fibrinogen assay	• Glucose • Total protein • Albumin • Creatinine • Creatine kinase • Total cholesterol • Triglycerides • Sodium • Potassium • Chloride • BUN • CRP **Liver biochemistry panel:** • ALT • AST • GGT • LDH • Total bilirubin • Direct bilirubin • ALP **Lipid Panel (fasting):** • Low-density lipoprotein (LDL) • High-density lipoprotein (HDL) • Total cholesterol • Triglycerides	• Urobilinogen • Nitrites • Glucose • Protein • Ketones • Leukocyte esterase • Bilirubin • Specific gravity • Color • Appearance • Occult blood • pH	• Antibodies anti-HIV-1, anti-HIV-2, anti-HTLV-1 and anti-HTLV-2 • HBS antigen and antibodies anti-HBC • Antibodies anti-HCV (Note: not to be performed if previous viral RNA assays in two samples, collected at least 6 months apart, are negative (cf. exclusion criterion)). • *ATP7B* genotyping • Alpha-fetoprotein • Serum pregnancy test

Abbreviations: ATP7B= *Copper-transporting P-type ATPase*; ALP= ALkaline Phosphatase; ALT= ALanine aminoTransferase; aPTT= activated Partial Thromboplastin Time; AST= ASpartate aminoTransferase; BUN= Blood Urea Nitrogen; CBC= Complete Blood Count, GGT= Gamma-Glutamyl Transpeptidase; HBC= Hepatitis B Core antibody; HBS antigen= Hepatitis B Surface antigen; HCV= Hepatitis C Virus; HIV= Human Immunodeficiency Virus; HTLV= Human T-cell Lymphotropic Virus; INR= International Normalized Ratio; LDH= Lactate DeHydrogenase; LDL= Low-Density Lipoprotein; RBC= Red Blood Cell; RNA= RiboNucleic Acid; WBC White Blood Cell

In relation to the Sirolimus treatment, patients will be monitored for hyperlipidemia. A lipid panel consisting of low-density lipoprotein (LDL), high-density lipoprotein (HDL),

triglycerides and total cholesterol is included at Screening 1, Screening 2, Week 4 and Week 8.

Each patient will have a comprehensive surveillance plan which monitors liver enzymes and liver function tests post administration of VTX-801. It will include a test at each visit occurring either on site or at home (home nurse) and twice a week sampling between Week 4 and Week 12. Additionally, availability of laboratory results will be optimized in order to ensure quick Investigator accessibility to the results (less than 3 days) to make a decision on further action.

Furthermore, reports of abnormal ALT (defined as ≥ 1.5 x baseline) will also be made available to Sponsor within 24 hours of the laboratory value being available (cf. Section 7.5.2).

Remnant blood and urine samples may be used for future biomarker explorations (excluding any genotyping) as data emerges; this will be the subject of an optional approval by patients in the informed consent (tick box).

Table 8 outlines the frequency of sampling of liver biochemistry parameters after VTX-801 administration, including both locally and centrally analyzed samples.

Table 9 Sampling Frequency of Liver Biochemistry Panel Following VTX-801 Administration

Period	Frequency
Weeks 1 to 3	Once a week
Weeks 4 to 12	Twice a week
Weeks 13 to 16	About Weekly, except for week 14
From Week 20 till End of Year 1	About monthly
Year 2	Every 3 months
Years 3-5	Every 6 months

8.1.12 Local Laboratory Standard and Special Evaluations

The parameters listed in Table 9 will be analyzed by the Local Laboratories. Please refer to Table 8 for full sampling frequency and to the Schedule of Events (Table 2, Table 3) for the related time points.

Table 10 Standard and Special Parameters to be Analyzed by the Local Laboratory

Liver Biochemistry Panel[a]	Others
• ALT • AST • GGT • LDH • Total bilirubin • Direct bilirubin (DB) • ALP	• Urine pregnancy test • Tuberculosis tests (QuantiFERON®-TB Gold) • Urine drug test screen (amphetamines, cocaine, opiates, phencyclidine (PCP)) ***Special investigations*** *(refer to Section 7.2.5)* • Cytokines (including at least IL-6) • Complement ***Special investigations*** *(refer to Section 9.7)* • Blood smear with corrected reticulocyte count ***Special investigations*** *(refer to Section 7.5.2)* • PCR for HSV, CMV, EBV, HCV • Serology for HAV IgM • HBsAg and if positive HBV DNA • Serology for HEV (IgG and IgM) and HEV RNA • Autoimmune hepatitis: ANA, SMA, anti-LKM1 auto-antibodies, total IgG

a. Liver biochemistry panel will be performed by both Local and Central Laboratories. The local results will primarily be used by the site to guide decisions by the treating physician to ensure patient safety; the central results will be used for the statistical analysis. Both sets of data will be captured in the EDC (Electronic Data Capture) system.

Abbreviations: ALP= ALkaline Phosphatase; ALT= ALanine aminoTransferase; ANA= AntiNuclear Antibodies; AST= ASpartate aminoTransferase; CMV= CytoMegaloVirus; DB= Direct Bilirubin; DNA= DeoxyriboNucleic Acid; EBV= Epstein-Barr Virus; EDC= Electronic Data Capture; GGT= Gamma-Glutamyl Transpeptidase; HAV= Hepatitis A Virus; HBV= Hepatitis B Virus; HCV= Hepatitis C virus; HEV= Hepatitis E Virus; HSV= Herpes Simplex Virus; IgG= Immunoglobulin G; IgM= Immunoglobulin M; IL-6= Interleukin-6; LDH= Lactate DeHydrogenase; LKM1= Liver-Kidney Microsome Type 1; PCP= Phencyclidine; PCR= Polymerase Chain Reaction; RNA=RiboNucleic acid; SMA= Smooth Muscle Antibodies.

8.1.13 Ceruloplasmin and Copper-Related Assays

The biomarkers listed below will aid the evaluation of the pharmacodynamics of VTX-801.

Table 11 Blood Ceruloplasmin and Copper-Related Assays to be Performed by Specialized Central Laboratories

Serum based parameters (assay values)	• Ceruloplasmin by enzymatic assay • Ceruloplasmin level determination by nephelometry • Total copper • Exchangeable copper (CuEXC) • Ceruloplasmin-bound copper (Cp-copper) *(intermediate parameter)*
Serum based parameters (calculations)	• Accurate non-ceruloplasmin bound copper (ANCC) = total serum copper - Cp-Copper (Solovyev et al, 2020) • Relative exchangeable copper (REC) = CuEXC/total serum copper (%) • Relative ANCC (RAC) = ANCC/total serum copper
Urine based parameters (assay values)	• 24-hour urinary copper (after 2-day wash-out if patient is on chelators or dual copper and zinc therapy)

Abbreviations: ANCC= Accurate non-ceruloplasmin-bound Cu; Cp-copper= Ceruloplasmin-bound copper; CuEXC= Exchangeable Copper; RAC= Relative Absolute Neutrophil Count; REC= Relative Exchangeable Copper.

8.1.14 Clinical Calculations Based on Laboratory Tests

The clinical scores listed in Table 11 are based on laboratory results and will be calculated by the Sponsor's designee using data provided by the concerned Central Laboratory.

Table 12 Clinical Calculations Based on Laboratory Tests

Parameter	Calculation	Reference
MELD Score	3.78 x ln[bilirubin (mg/dl)] + 11.2 x ln(INR) + 9.57 x ln[creatinine (mg/dL)] + 6.43.	Kamath et al, 2001
APRI Score	[(AST (IU/L)/ upper normal limit AST) x 100]/Platelet count (10^9/L).	Zhong-Hua Lin et al, 2011
FIB4 Score	[Age (years) x AST (IU/L)]/[platelet count (10^9/L) x √(ALT (IU/L)].	Sterling et al, 2006

Abbreviations: APRI= Aspartate aminotransferase to Platelet Ratio Index; AST= ASpartate aminoTransferase; FIB4= Fibrosis-4 Index for Liver Fibrosis; INR= International Normalized Ratio; IU= International Unit; L= liter; MELD= Model for End-stage Liver Disease.

8.2 Central Laboratories for Specialized Evaluations

The instructions for sample collection, specimen preparation, handling, storage and shipping are described in the Central Laboratory Manual.

The main Central Laboratory will provide the site with the corresponding kits to support the management of all samples, from preparation of sampling to sending samples to respective central laboratories.

Some specialized central laboratories will be in charge of the tests related to anti-AAV3B neutralizing antibodies assay, viral vector shedding, immunogenicity and biopsies.

Some other specialized central laboratories will be in charge of the tests related to ceruloplasmin, and copper related assays.

8.2.1 Anti-AAV3B Neutralizing Antibodies

Patients will be enrolled based upon results from an *in vitro* anti-AAV3B neutralizing antibody (NAb) assay (Section 5.3, Exclusion criterion #15)

- A test will be performed at or before Screening 1 to exclude NAb-positive patients, and if negative repeated at Screening 2 as part of eligibility criteria confirmation.

- An additional NAb test will be performed shortly before VTX-801 administration (Day 1, Visit 6), then 1 month after VTX-801 administration (Week 4, Visit 10) and at the end of the 1-year follow up (Visit 46).

8.2.2 Genotyping

Patients will have a sample taken for genotyping at or before Screening 1, in case biallelic pathogenic or likely pathogenic *ATP7B* variants have not been already identified in a CLIA-certified laboratory as part of their medical history (see Section 8.1.1).

Note: Due to the extended time needed to obtain genotyping results, ERC review and patient inclusion and treatment may occur before receiving genotyping results, provided that Leipzig score ≥ 4 based upon the other parameters.

8.2.3 Viral Vector Shedding

In order to detect and follow up the presence of the AAV in different substrates (blood, urine, saliva, feces), samples will be collected at specific patient visits until 3 consecutive samples are negative for the concerned substrate after VTX-801 administration:

- Mandatory:
  - Baseline (starting after last radiocopper sampling and stopping within 24 hours before VTX-801 administration; note that permitted window for VTX-801 is +7D during which period viral vector shedding samples can be taken)
  - Day 2 post-VTX-801 administration, Week 2 and Week 4 site visits
- Based on results: Discontinuation of sampling (for a given substrate) once 3 consecutive samples are negative (≤quantification limit). Site will be informed of the shedding results as soon as possible in order to avoid performing unnecessary sampling for a given substrate.
- During each of the Week 12 and Week 36 period of 4 consecutive visits (V26 to V29 and V39 to V42 respectively), only 1 sample per substrate will be taken per period and if applicable.

For the shedding samples related to feces, all efforts will be done to get the required number of feces samples as per protocol, considering the uncertainty related to patient's bowel movements.

8.2.4 Immunogenicity

In order to detect and follow-up potential humoral and cellular immune responses, the tests listed in Table 12 will be conducted on the samples collected at specific patient visits: Baseline, W4, W8 and W12 (refer to the Schedule of Events).

Nevertheless, in case reactive steroid treatment is indicated, an unscheduled sampling for IFN-gamma ELISpot to AAV3B capsid and miniATP7B transgene assays will be taken ideally before reactive steroid treatment initiation, if not, shortly thereafter, if possible.

Table 13 Humoral and Cellular Immune Response Tests to be Performed by Specialized Central Laboratories

Humoral Response Tests	Cellular Response Tests
ELISA: antibodies against AAV3B capsid and miniATP7B transgene	IFN-gamma ELISpot to AAV3B capsid and miniATP7B transgene

Abbreviations: AAV3B= Adeno-Associated Virus serotype 3B; ATP7B= *Copper-transporting P-type ATPase*; ELISA= Enzyme-Linked ImmunoSorbent Assay; IFN-gamma= interferon gamma.

8.2.5 Liver Biopsy

A maximum of 3 liver biopsies will be performed including one at Screening.

To minimize the burden on patients, all efforts should be made to perform the first liver biopsy (at Screening 2) after confirmation of the other eligibility criteria. In case of initial screening failure, the liver biopsy, if any, may be re-used for re-screening if not older than 3 months.

The second biopsy will occur at the end of the first year post-VTX-801 administration and the third one will occur at the end of the third year post-VTX-801 administration.

Liver biopsy will be conducted according to institutional standards. The instructions for sample collection, specimen preparation, handling, storage and shipping are described in the Laboratory Manual.

For each biopsy, 2 passes for each timepoint are required as long it is technically feasible.

Table 14 Liver Biopsy Related Tests to be Performed by Specialized Central Laboratories

Analysis/Tests
• Standard liver histology analysis • In situ hybridization for detection of VTX-801 positive cells • Tissue copper content

After planned analyses have been performed, unused biopsy material located at the Central Laboratories may be used for unplanned biomarker explorations (except genotyping) as data emerges; this will be the subject of an optional approval by patients in the informed consent (tick box).

An additional biopsy should be performed in case of suspected DILI with ALT or AST ≥ 5x ULN (cf. Sections 6.3 and 7.5.2).

Note: All efforts should be made to collect liver biopsies for each patient as described in the schedule of events. However, for the dose escalation cohorts only, if a patient declines to have liver biopsies taken, these can be replaced with Fibroscan®. Should Fibroscan® be used instead of liver biopsy at Screening, this should be implemented for the rest of the study, to ensure consistency for the longitudinal analysis.

8.2.6 Local Nuclear Laboratories for Radiocopper-Related Evaluations

The instructions and information on equipment for sample collection, specimen preparation, handling, storage, local assessments as well as data transfer of the results to the Central Laboratories in charge of Central Reading/Analysis are described in the Radiocopper Assessments manual.

The gamma counter related activities and expectations, including calibration, will also be included in the Radiocopper Assessments manual.

[redacted]

[redacted]

[redacted]

8.3 Total Blood Volume

The maximal total volume of blood to be taken per patient during the entire course of the study will be as follows: 1,488 mL Refer to Appendix 17.1.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

The safety of the study intervention will be assessed through the recording, reporting and analyzing of baseline medical conditions, AEs, general physical examination, laboratory tests, and vital signs data. The timing and frequency of safety assessments are described in Section 9.2.6.

9.2 Adverse Events

9.2.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or disease that emerges or worsens during an interventional clinical study with an IMP or NIMP, regardless of causal relationship and even if no IMP or NIMP has been administered.

Worsening of a pre-existing medical condition, (e.g., migraine headaches, gout) is to be considered an AE if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

9.2.2 Severity of Adverse Events

AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017 grading system. The CTCAE v5 grading criteria must be used when available for an AE. Only when CTCAE v5 grading criteria are not available for a specific AE, will the Investigator assess the severity of the AE based on the following definitions:

- **Grade 1 (mild):** the patient is aware of the event or symptom, but the event or symptom is easily tolerated.
- **Grade 2 (moderate):** the patient experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- **Grade 3 (severe):** the patient is unable to carry out usual activities due to significant impairment of functioning.

- **Grade 4 (life-threatening):** the patient's life is at risk from the event.
- **Grade 5 (fatal):** the event results in the patient's death.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

9.2.3 Causality Assessment

The Investigator will determine whether or not, in his/her opinion, the AEs are related to VTX-801 according to the following definitions:

Relationship to VTX-801

- **Unrelated**: The AE is temporally independent of study product and/or the event appears to be explained by another etiology
- **Unlikely related**: The AE has a time to drug intake that makes a relationship improbable (but not impossible) and/or disease or other drugs provide plausible explanations
- **Possibly related**: The AE has a reasonable time sequence to administration of the drug, but could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
- **Probably related**: The AE has a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information (if applicable) is not required to fulfil this definition
- **Definitely related:** The AE occurred in a plausible time relationship to drug administration, and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically. A satisfactory rechallenge procedure (if applicable) may be utilized if necessary

- In addition, the Investigator will also determine whether the AEs are definitely, probably, possibly, unlikely related or unrelated with the study procedures and radiocopper.
- Relationship assessments will be captured in the eCRF in all cases.

The DMC will also review all liver and neuropsychiatric TEAEs (on an ad-hoc basis if they meet the SAE/AESI or Stopping Rules criteria and at patient level/cohort level review for all other events) and provide supplemental causality assessment in addition to Investigator assessment. These assessments must be submitted to the FDA for review, either as individual case safety reports (for SUSARs) or as aggregate reports (for all other events).

The liver and neuropsychiatric serious TEAEs will be reported to the DMC (within 24 hours) and expeditiously adjudicated by the HAC in case of suspected DILI or by the DMC in case of neuropsychiatric TEAE (if possible, within 48 hours). All SUSAR will be reported to the FDA and the other concerned Regulatory Authorities as per regulatory timeline (7 to 15 days).

9.2.4 Abnormal Laboratory Test Values and Other Objective Measurements

Abnormal laboratory findings and other objective measurements such as vital signs and ECGs, should NOT routinely be captured and reported as AEs as they will be collected and analyzed separately in the eCRF. However, abnormal laboratory findings and other objective measurements which (i) meet the criteria for a SAE or (ii) result in early discontinuation or in treatment being interrupted, (iii) require medical intervention or (iv) are considered clinically significant should be captured and reported in the AE pages of the eCRF.

If reporting an abnormal laboratory finding in the AE pages of the eCRF, a clinical diagnosis should be recorded rather than the abnormal value itself, if available (for example “anemia” rather than “decreased RBC count” or “hemoglobin = 10.5 g/dL”).

9.2.5 Eliciting Adverse Events

AEs will be obtained by the Investigator at scheduled or unscheduled study visits, following physical examination, based on information spontaneously provided by the patient and/or through questioning.

To elicit AEs, simple questions with minimal connotations should be used as the initial questions at all evaluation points during the study. For example:

- How have you felt since your last visit?
- Have you had any health problems since you were here last?

In the case that a patient was seen by a health care professional other than the Investigator (e.g., at a different institution) concerning an AE, every effort should be made by the Investigator to contact the treating physician in a timely manner in order to obtain all necessary information and report the event appropriately.

9.2.6 Recording Adverse Events

As quality and precision of acquired AE data is of key importance, the Investigator should use the AE definitions provided in above sections and observe the following guidelines when completing the AE pages of the eCRF:

- Whenever possible, recognized medical terms should be used to describe AEs rather than colloquialisms (for example, ‘influenza’ rather than ‘flu’), and abbreviations should be avoided.
- AEs should be described using a specific clinical diagnosis rather than component signs or symptoms, if this is available (for example, ‘congestive heart failure’ rather than ‘dyspnea, rales and cyanosis’). However, signs and symptoms considered unrelated to an identified disease or syndrome should be reported as individual AEs in the eCRF.
- AEs occurring secondary to other events (e.g., sequelae or complications) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term to record in the AE pages of the eCRF.

Additional guidance can be found in the eCRF completion conventions provided by the Sponsor.

An Adverse Event (AE) is any untoward medical occurrence in a study subject which is temporally associated with the use of a medicinal product or study conduct, regardless of its potential relationship to the medicinal product or study conduct. An AE, therefore, can be any unfavorable or unintended sign, including any abnormal laboratory finding, symptom, or disease (new or exacerbated), whether or not related to the IMP or study

conduct. AEs should be followed-up in accordance with the procedures described in Section 9.2.7.

AEs will be captured differently in the eCRF depending on the date of onset and causality assessment (per Investigator's judgment) as described below:

Table 16 Capture of Adverse Events in the eCRF

AE onset date	Types of AEs to be captured in the eCRF
From signing the ICF, including Screening 1 and until start of Screening 2	• Only AEs considered to be possibly, probably or definitely related to the study procedures
From Screening 2 included until 1-year post VTX-801 infusion visit included	• All AEs
After the 1-year post infusion visit until completion of the 5-year follow-up visit included	• All AEs except those AEs incontrovertibly unrelated to VTX-801, radiocopper and study procedures
After the 5-year follow up period	• Only SAEs considered to be possibly, probably or definitely related to VTX-801

Abbreviations: AE= Adverse Event; eCRF= electronic Case Report Form; ICF= Informed Consent form; SAE= Serious Adverse Event.

Note: The above table refers to newly onset AEs. *Follow-up* details regarding the AEs *previously* entered into the eCRF will be captured regardless of the type of AE. (Refer to Section 9.2.7).

9.2.7 Follow-up of Adverse Events

Follow-up of AEs is defined as follows:

- The AEs which occur after signing the ICF and up to completion of the 5-Year follow-up period after VTX-801 administration will be recorded in the AE pages of the eCRF per the criteria defined above.

- All AEs that were previously captured in the eCRF, and all SAEs, will be followed until resolution or until the Investigator assesses them as ‘chronic’ or ‘stable’.
- If the Investigator becomes aware of a SAE, including death, after the 5-Year follow-up period and the SAE is considered by the Investigator to be possibly, probably or definitely related to the study product, it will be reported to the designated CRO safety group in accordance with Section 9.3.2.

Taking the above post-treatment safety surveillance reporting requirements into account, AE follow-up information data will be recorded in the AE pages of the eCRF up until Last Patient Last Visit.

After Last Patient Last Visit and 2 weeks prior to any data lock, the status of all outstanding ongoing AEs will be checked and any up-to-date change made in the eCRF. At that stage, as considered appropriate by the Sponsor, follow-up information will continue to be requested from the Investigator on specific AEs (and in any case all SAEs considered possibly, probably or definitely related to the study product by the Investigator) although related details will not be recorded in the eCRF beyond database lock.

9.3 Serious Adverse Events

9.3.1 Definition of Serious Adverse Event

A SAE is defined as an AE which meets one of the following criteria:

- Results in death.
- Is life-threatening (defined as a patient at immediate risk of death at the time of the event).
- An event requiring inpatient hospitalization or prolongation of existing hospitalization.

Note: In general, hospitalization signifies that a person has been detained (usually overnight) at a hospital or emergency ward for observation and/or treatment. Emergency room visits which do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious, medically important event).

- Results in a persistent or significant disability/incapacity.

Note: The term significant disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions, i.e., the AE resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

- Is a congenital anomaly or birth defect in the case of pregnancy.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the above criteria. An AE of severe intensity might not necessarily be considered serious. For example, persistent nausea for several hours may be considered severe, but not a SAE. Conversely, a stroke resulting in only a limited degree of disability may be considered mild, but would be a SAE.

SAEs will be:

- Recorded in the eCRF if the criteria described in Section 9.2.6 (Table 15) are met.
- Reported in accordance with the procedures described in Section 9.3.2.
- Followed until resolution, stabilization or until determined to be chronic by the Investigator.
- Reviewed and evaluated by the Investigator.

9.3.2 Reporting of Serious Adverse Events and Adverse Events of Special Interest

Any SAE meeting the criteria described in Section 9.2.6 (Table 15), any AESI meeting the definitions in Section 9.6, or any event applicable to the study Stopping Rules must be **entered into the eCRF within 24 hours of first awareness** of the event by study personnel. A causality assessment must be provided at the time of reporting and a

narrative should also be provided. Any SAEs experienced after the 5-Year follow up period should be reported to the designated CRO designee safety group if the Investigator has assessed that the SAE is possibly, probably or definitely related to IMP administration.

Entry of an SAE/AESI (or updated SAE/AESI information) into the eCRF will trigger an automatic alert to the designated CRO Safety group (Aixial).

If the EDC system is **not available**, SAEs/AESIs should be reported by emailing or faxing a completed paper SAE/AESI Report Form to the designated CRO safety group within 24 hours of site awareness. The SAE/AESI may be reported by telephone; however, this must be followed up within 24 hours with either a completed paper SAE/AESI Report Form (if EDC system is still not available) or by recording it into the eCRF (if EDC becomes available in the meantime). Additionally, it may be necessary for the designated CRO safety group to communicate with the Investigator if additional information is required. Note: when EDC becomes available, the SAE/AESI Report must still be entered in the eCRF despite the paper SAE Form being submitted.

During both business and non-business hours, the email address, telephone and fax numbers listed below can be used to notify the designated CRO safety group. If a paper SAE/AESI Report Form is submitted via email or fax and no acknowledgement is received within one working day, the report should be re-submitted.

Reportable Events Hotline:

Aixial Group CRO (formerly Cmed)

Email: [redacted]

All additional follow-up evaluations must be reported within 24 hours of site awareness, following the same processes. The Sponsor is responsible for complying with applicable regulatory reporting requirements for SAEs and, where necessary, for ensuring the relevant authorities are notified (see Section 9.4). The Investigator will ensure the

appropriate IRBs/IECs are notified of the SAE in accordance with ICH GCP and local regulatory requirements.

9.4 Regulatory Reporting of Safety Events

Following notification from the Investigator, the Sponsor and/or its designee (CRO) will report adverse events which are both serious and unexpected (not previously described in the reference safety information in the approved IB) and that are possibly, probably or definitely related with the IMP (otherwise known as SUSARs) to the FDA, EMA, other concerned Regulatory Authorities, IRB/IECs and Investigators within the required timelines as specified in 21 CFR Part 312.32, EU Directive 2001/20/EC, the European Commission's "Detailed guidance on the collection, verification, and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use" (CT-3, June 2011), ICH GCP Guidelines and other applicable national regulatory requirements. Typically, fatal and life-threatening SUSARs must be reported within 7 calendar days and all other SUSARs must be reported within 15 calendar days. All SAEs designated as not related to the IMP, will be reported to the concerned Regulatory Authorities, and IRB/IECs at least annually in a summary format.

Additionally, adverse events may occur during a clinical trial which do not fall within the definition of a SUSAR and thus are not subject to the reporting requirements for SUSARs, even though they may be relevant in terms of patient safety. Examples are new adverse events related to the conduct of a trial or the development of an IMP likely to affect the safety of patients such as:

- A SAE which could be related with the trial procedures and which could modify the conduct of the trial.
- A significant hazard to the patient population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease.
- A major safety finding from a newly completed animal study (such as carcinogenicity).
- A temporary halt of a trial for safety reasons, e.g. in accordance with Stopping Rules (see Section 6.3); or if the trial is conducted with the same IMP in another country by the same Sponsor, recommendations of the DMC, if any, where relevant for the safety of patients.

These adverse events/observations are not to be reported as SUSARs, but they might require other action, such as urgent safety measures and their notification, substantial amendments, or early termination of the trial, and shall be reported in accordance with applicable local regulations and guidelines.

In addition, the liver and neuropsychiatric serious TEAEs will be reported to the DMC (within 24 hours of awareness) and expeditiously adjudicated by the HAC in case of suspected DILI or by DMC in case of neuropsychiatric TEAE (if possible, within 48 hours). If the SAE is also unexpected, i.e., a SUSAR, this SAE must be timely reported to FDA and the other concerned Regulatory Authorities as per regulatory requirements (within 7 to 15 calendar days). The DMC will review all liver and neuropsychiatric TEAEs and provide supplemental causality assessment in addition to PI assessment and these assessments must be submitted to FDA for review. In addition, all TEAEs, irrespective of causality and grade, will be submitted in the Clinical Study Report.

9.5 Reporting of Pregnancy

In case of unexpected ongoing pregnancy in a female study participant at the time of radiocopper related assessments, despite the contraceptive measures, the radiocopper administration and assessments should not be performed and the Sponsor will be notified.

If any **female partner of a male patient** who has been exposed to VTX-801 becomes pregnant and the presumed date of conception falls after the date VTX-801 or radiocopper was administered then the pregnancy will be documented, based on information provided by the patient, subject to specific written consent provided by the pregnant partner. Taking into consideration the presumed date of conception, all pregnancies that occur after VTX-801 or radiocopper exposure and during the entire study following VTX-801 infusion will be recorded in the eCRF.

For **female patients,** all pregnancies that occur after ICF signature will be recorded in the eCRF. Any pregnancy occurring after VTX-801 or radiocopper exposure will be followed up for outcome.

Any pregnancy (either female study participants or female partners of male study participants) must be followed up to determine course and outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence

of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Consent to report information regarding pregnancy outcome will be obtained from the female partners of male study participants.

Although pregnancy itself is not considered an AE, it must be reported in the same timelines as a SAE, but by using the paper Pregnancy Notification Form. The form must be completed and forwarded via email or fax to the designated CRO safety group using the email address or fax number listed in Section 9.3.2 within 24 hours of the Investigator becoming aware of the pregnancy.

If the outcome or course of the pregnancy involves a SAE (e.g., a congenital anomaly) then the SAE Form should be completed in addition to the updated Pregnancy Notification Form. Spontaneous abortions and congenital birth defects should always be reported as SAEs (see Section 9.3.1).

9.6 Adverse Event of Special Interest

A serious or non-serious event of scientific and medical concern specific to a Vivet Therapeutics' product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor and CRO can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

AESIs are reportable to the designated Aixial DSPV group from the time of VTX-801 administration regardless of seriousness or causality. Upon receipt, these AEs will be captured in the safety database, targeted follow-up queries will be sent to sites, and source documentation will be sent to the DMC and / or HAC (as outlined in the respective study committee charters).

The AESIs for this study (defined at any timepoint in the study after VTX-801 administration) are:

- DILI as defined in Section 6.3.
- ALT ≥ 1.5 x Baseline.
- Neurological, psychiatric or behavioral AEs (either new or worsening from baseline).
- Copper deficiency as defined in Section 9.7.
- CTCAE Grade 3 or 4 AEs triggering stopping criteria (defined in Section 6.3).

- Newly diagnosed malignancy after VTX-801 administration if not reported as SAE (see Section 6.3).
- Biochemical deterioration after WD background treatment withdrawal (see Section 4.6).
- Other events identified in medical review of special interest as agreed by the Sponsor medical monitor.

Any confirmed or suspected AESIs will be closely monitored by the Investigator and reported to the designated CRO and Vivet following the same procedure as for SAEs, as described in Section 9.3.2.

9.7 Copper Deficiency Detection and Management

In case a patient would develop copper deficiency at any time during the trial, the following rules will apply:

Criteria suggesting overtreatment:

- 24h urinary Cu < 20 µg/day (after 2 days chelator wash-out if on chelators or dual chelator and zinc therapy)
- Absolute Neutrophil Count < 1,000/µL
- CuEXC < 0.40 µ/mol/L

If the patient meets any of the criteria listed above, 24h urinary Cu should be done or repeated (after 2 days chelator wash-out if on chelators or dual chelator and zinc therapy) *and* a blood cell count will be performed. If the CBC shows anemia, a peripheral blood smear analysis including corrected reticulocyte count will also be performed.

- If new value of 24h urinary Cu < 20 µg/day, overtreatment is confirmed
  - For patients on SoC treatment, SoC treatment should cease
  - For patients off SoC treatment:
    - if 24h urinary Cu < 20 µg/day and patient is neutropenic or has sideroblastic anemia, or develops symptoms consistent with copper deficiency myelopathy (see below), then Cu replacement is warranted. Initial treatment will be with Copper Gluconate 2 mg

per os, three times a day for 7 days (Huff et al, 2007). Length of treatment and dose adjustment will depend on response and will be guided by the site Investigators and the DMC;

- if 24h urinary Cu < 20 µg/day but without neutropenia or sideroblastic anemia, then the patient is expected to rebalance Cu stores through dietary intake and Cu replacement is not required.

- If new value of 24h urinary Cu ≥ 20 µg/day, no treatment change is required.

Other signs including confirmed sideroblastic anemia, pancytopenia and posterior cord syndrome are late complications. Suspicion of copper deficiency should prompt a formal neurological exam looking for findings of copper deficiency myelopathy (posterior cord syndrome), and if abnormal, imaging of the spine by MRI to assess for demyelination, or other evaluation(s) deemed appropriate by a neurology consultant.

Any patient who develops copper deficiency will be monitored closely and carefully until normalization or stabilization of biochemical abnormalities and clinical symptoms, if present.

10 STUDY SCHEDULES

The study is divided into 4 periods, each associated with a specific Schedule of Events Table, as follows:

Table 1	The Screening period.
Table 2	Baseline, VTX-801 administration and follow-up to and including Week 12.
Table 3	Follow-up until completion of Year 1 period post-VTX-801 administration (Week 13 to Week 52).
Table 4	Years 2-5 follow-up period post-VTX-801 administration.

The Study Schedules of Events include several visit categories, as follows:

Site visit	The visit occurs at site. It is either an “outpatient” or “inpatient” visit.
Outpatient visit	The patient comes to and leaves the hospital the same day without being hospitalized.
Inpatient visit	The patient comes to the hospital and is hospitalized for as long as it is required.
Home nurse visit	The visit will take place either at the patient’s home, performed by a “home nurse” to collect samples or at site at the Investigator’s discretion and with the patient’s agreement. This type of visit can be planned for all types of assessments/retests (for which the home nurse is qualified and trained accordingly) as needed. When samples are taken by the home nurse, they will be sent to the central lab, unless otherwise agreed in writing between the site and Sponsor.
Phone calls	Four phone calls are planned instead of site visits. At the discretion of the Investigator, these visits can occur on site.

	- Two phone call during which patient will be informed by the Investigator about their Responder status and associated actions. - Two phone call or a video consultation during which Investigator will check patient health and occurrence of any AE since the last visit.

Visits, Weeks and Months numbering:

- The Study Day 1/ Week 1 starts from administration of VTX-801.
- Flexibility of up to 7 additional days for VTX-801 administration is allowed if needed in order to comply with radiocopper production constraints or to accommodate the sites and/or patients. Initiation of the Sirolimus treatment [redacted] will then need to be shifted accordingly (start 7 days prior to VTX-801 administration).
- As such, any visit with a Day, Week or Month with no negative number refers to timing after VTX-801 administration (for example: Day 8; Week 2).

10.1 Visits 1A and 1B: Screening Period

10.1.1 Visit 1A - Screening 1

Refer to Table 1 Summary of Schedule of Events: Screening				
Visit 1A	**Minimum 6 to 8 weeks before Screening 2**	**Screening 1**	**Outpatient visit**	**Cross-reference**
Signed and dated informed consent				Section 14.3
Demographics, medical history and Leipzig score (taken from historical records)				Section 8.1.1

ATP7B genotype (mandatory for those patients without an historical genotyping available from a CLIA-certified laboratory) Note: Due to the extended time needed to obtain genotyping results, ERC review and patient inclusion and treatment may occur before receiving genotyping results, provided that Leipzig score ≥ 4 based upon the other parameters	Section 8.2.2
UWDRS part II and III, M.I.N.I	Section 8.1.7
Vital signs	Section 8.1.4
Weight and height recording, Body Mass index	Section 8.1.3
Alcohol consumption	Section 7.7
Brain MRI (to be performed at V1A (Screening 1) or V1B (Screening 2)	Section 8.1.9
Abdominal MRI including liver volume; Liver MR elastography. Elastography (to be performed in a > 4 hours fasted state) Note: These assessments are to be performed either at V1A (Screening 1) or V1B (Screening 2)	Section 8.1.8
Central Laboratory: blood/urine biochemistry with lipid panel, hematology; Coagulation. Fasting conditions are required for the lipid panel.	Section 8.1.11
Central laboratory: Hematology	Section 8.1.11 / Table 7
Central Laboratory: Liver panel biochemistry	Section 8.1.11 / Table 7
Ceruloplasmin (enzymatic assay and nephelometry), CuEXC, REC and total Cu.	Section 8.1.13

24-hour urinary copper	Section 8.1.13
Anti-AAV3B capsid neutralizing antibodies	Section 8.2.1
Local laboratory urine drug test screen: amphetamines, cocaine, opiates, phencyclidine.	Section 8.1.12
Adverse events	Section 9.2
Prior medications, including background WD therapy history	Section 8.1.2

10.1.2 Visit 1B - Screening 2

The duration of Screening 2 sampling is about up to 5 weeks. The screening will occur from Day -49 to Day -14 (+/- 5 days) to assess eligibility.

Laboratory values and alcohol consumption details during the past year for patient eligibility will be those from Screening 2 assessments (V1B); if laboratory results fall outside study entry criteria on initial assessment, they may be repeated, only after Sponsor approval is granted. If needed, retest samples for standard exams (hematology, blood/liver biochemistry, urinalysis) can be assayed locally at the site or using a home nurse visit.

In case of initial screening failure, the liver biopsy, if already collected, may be re-used for re-screening if not older than 3 months.

In order to fulfil inclusion criterion #7 (Section 5.3), stable laboratory parameters used to assess copper metabolism, i.e, 24-hour urinary copper, free serum copper, such as non-ceruloplasmin copper (NCC) or CuEXC, as well as liver enzymes, hemoglobin, and white blood cell count should be stable (no significant change), on at least 2 occasions assessed 6 to 8 weeks apart prior to enrollment (ERC assessment). The interval may be extended beyond 8 weeks for logistical reasons. As a consequence, the first corresponding sampling will occur at Screening 1 and the second sampling will occur at Screening 2 at the latest.

Refer to Table 1 Summary of Schedule of Events: Screening				
Visit 1B	**Day -49 to Day -14**	**Screening 2**	**Outpatient visit**	**Cross-reference**
Eligibility (inclusion/exclusion criteria)				Section 5
Medical history				Section 8.1.1
UWDRS part II and III, M.I.N.I, MoCA				Section 8.1.7
Vital signs				Section 8.1.4
Physical examination, weight and BMI calculation				Section 8.1.3
Alcohol consumption				Section 7.7
Brain MRI Note: Only to be performed at V1B (Screening 2) if not already performed at V1A (Screening 1)				Section 8.1.9
Abdominal MRI including liver volume; Liver MR elastography. Elastography to be performed in a > 4 hours fasted state Note: Only to be performed at V1B (Screening 2) if not already performed at V1A (Screening 1)				Section 8.1.8
ECG				Section 8.1.5
Urine pregnancy test (for Women of Childbearing Potential [WOCBP] only)				Section 8.1.11
Viral serology				Section 8.1.11
Tuberculosis test (QuantiFERON®-TB Gold)				Section 8.1.12
Alpha-fetoprotein				Section 8.1.12

Central Laboratory: blood/urine biochemistry with lipid panel, hematology; Coagulation Fasting conditions are required for the lipid panel.	Section 8.1.11
Central Laboratory: Liver panel biochemistry	Section 8.1.11
Ceruloplasmin (enzymatic assay and nephelometry), CuEXC, REC and total Cu	Section 8.1.13
24-hour urinary copper	Section 8.1.13
Anti-AAV3B capsid neutralizing antibodies	Section 8.2.1
Local laboratory urine drug test screen: amphetamines, cocaine, opiates, phencyclidine,	Section 8.1.12
Liver biopsy (All efforts should be made to collect liver biopsies for each patient as described in the schedule of events. However, for the dose escalation cohorts only, if a patient declines to have liver biopsies taken, these can be replaced with Fibroscan®. Should Fibroscan® be used instead of liver biopsy at Screening, this should be implemented for the rest of the study, to ensure consistency for the longitudinal analysis).	Section 8.2.5
Adverse events	Section 9.2
Prior medications, including background WD therapy history	Section 8.1.2

10.2 Visits 2-5: Baseline and Pre-VTX-801 Period

Duration: 4 study visits within a period of 7 days:

- **Visit 2**; Baseline: 1-day outpatient visit, which will also include the initiation of Sirolimus treatment [redacted].
- Flexibility of up to 7 additional days for VTX-801 administration is allowed if needed in order to comply with radiocopper production constraints or to accommodate the sites and/or patients. As a consequence, initiation of the

Sirolimus treatment [redacted] will then need to be shifted accordingly (start 7 days prior to VTX-801 administration).

- No visits for 3 days.
- **Visits 3-4-5**: a 3-day in- or outpatient visit period during [redacted].

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12

(Note permitted visit windows are allowed for some assessments; refer to Table 2 and its footnotes)

Visit 2	Day -7	Baseline	Outpatient visit	Cross-reference
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7
Serum pregnancy test (for WOCBP only)				Section 8.1.12
Central Laboratory: blood/urine biochemistry; hematology; coagulation				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11
Local Laboratory: Liver biochemistry panel				Section 8.1.12
Calculation of MELD, APRI, FIB4 by CRO				Table 11
Ceruloplasmin (enzymatic assay and nephelometry), CuEXC, total Cu, REC, RAC, ANCC, CRP				Section 8.1.13
ELISA and IFN-gamma ELISpot				Section 8.2.4
Ophthalmology: slit lamp examination. It can be performed from Baseline V2 to the day before radiocopper administration as long as results are available before the day of radiocopper administration.				Section 8.1.6

UWDRS, SDMT and Stroop Test They can be performed from Baseline V2 to the day before radiocopper administration as long as results are available before the day of radiocopper administration.	Section 8.1.7
Adverse events	Section 9.2
Prior medications	Section 8.1.2
[redacted] Sirolimus treatment	Section 7.5
[redacted]	[redacted]
For patients on copper chelator: • Patients are to be informed to start the wash-out period without copper-chelator treatment 3 days before radiocopper injection until the end of the radiocopper investigations. • The 24-hour urine copper sample will start 48 hours after initiation of the chelator wash-out period and will end prior to radiocopper administration.	

For Visits 3-4-5, patients **from expansion cohort (only)** will be hospitalized, stay at a unit with clinical support or other location approved by the [redacted]

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 3	**Day -3**	**Pre VTX-801**	**In or Out-patient visit**	**Cross-reference**
Vital signs				Section 8.1.4

Physical examination	Section 8.1.3
Sirolimus	Section 7.5
Sirolimus level test: sampling for blood trough concentration 4-5 days after starting treatment with Sirolimus	Section 7.5
[redacted]	[redacted]
24-hour urinary copper (to end prior to radiocopper administration)	Section 8.1.13
[redacted]	[redacted]
Radiocopper administration (around 9 am)	Section 7.4
[redacted]	[redacted]
[redacted]	[redacted]
Adverse events	Section 9.2
Prior medications	Section 8.1.2

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 4	**Day -2**	**Pre VTX-801**	**In or Out-patient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Sirolimus				Section 7.5
[redacted]				[redacted]

[redacted]	[redacted]
[redacted] [redacted] [redacted]	[redacted]
[redacted]	[redacted]
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 5	**Day -1**	**Pre VTX-801**	**In or Out-patient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Weight				Section 8.1.3
Sirolimus				Section 7.5
[redacted]				[redacted]
[redacted]				[redacted]
[redacted] [redacted] [redacted]				[redacted]
[redacted]				[redacted]
Vector shedding: blood, urine, saliva, feces - mandatory Vector shedding: At Day -1 baseline starting after last radiocopper sampling				Section 8.2.3

and within 24 hours before VTX-801, taking into account +7D window for administration. These assessments are to be performed either at V5 or V6.	
Adverse events	Section 9.2
Prior medications	Section 8.1.2

10.3 Visit 6: Day 1, Week 1

This is the first day of the inpatient period related to VTX-801 administration. The patient will then be hospitalized overnight and will be discharged on the following day.

If the patient's medical status post-VTX-801 administration necessitates a prolonged hospitalization, please refer to Section 9.3 Serious Adverse Events.

Flexibility of up to 7 additional days for VTX-801 administration is allowed if needed in order to comply with radiocopper production constraints or to accommodate the sites and/or patients.

Home nurse collected samples for liver biochemistry panel may be sent to the Central Laboratory instead of to the Local laboratory.

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 6	**Day 1 + 7 days**	**VTX-801**	**Inpatient visit**	**Cross-reference**
Special instructions: Patient will be fasted overnight prior to VTX-801 administration and during administration. It is recommended that the patient also fasts for 2 hours after the administration for infusions shorter than 1 hour but this time may be reduced for patients receiving longer infusions. The VTX-801 infusion administration should be started early in the morning in order to limit as much as possible the total duration of the fasting period.				Section 7.2

Vital signs before, during and after VTX-801 administration: - before VTX-801 administration - at 15-minute intervals during the VTX-801 administration (+/- 3 min) - at the end of the infusion - 1 hour after the end of infusion (+/- 10 min) - and then at 4-hour intervals until night sleep (+/- 15 min)	Section 8.1.4
ECG performed prior to VTX-801 administration	Section 8.1.5
Anti-AAV3B capsid neutralizing antibodies sampling prior to VTX-801 administration	Section 8.2.1
Sirolimus	Section 7.5
[redacted]	[redacted]
Methylprednisolone administered IV one hour before VTX-801	Section 7.5.1
[redacted]	[redacted]
[redacted]	[redacted]
For patients on chelator therapy: patient restarts WD treatment	
Vector shedding: blood, urine, saliva, feces - mandatory Vector shedding: At Day -1 baseline starting after last radiocopper sampling and within 24 hours before VTX-801, taking into account +7D window for administration. These assessments are to be performed either at V5 or V6.	Section 8.2.3

Adverse events	Section 9.2
Concomitant medications	Section 8.1.2
VTX-801 administered	Section 7.2

10.4 Visit 7: Day 2, Week 1: Post-VTX-801 Administration

This is the second day of a 2-day inpatient period related to VTX-801 administration.

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 7	**Day 2**	**VTX-801**	**Inpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Local laboratory: Liver biochemistry panel				Section 8.1.12
Vector shedding: blood, urine, saliva, feces - mandatory Note: vector shedding sampling is to occur at every site scheduled visit until 3 consecutive concerned samples are negative (at or below quantification limit)				Section 8.2.3
Sirolimus				Section 7.5
[redacted]				[redacted]
Oral steroid (Prednisone or Prednisolone)				Section 7.5.1
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

10.5 Visits 8-46: Follow-up Until End of Year 1 Post-VTX-801 Administration

10.5.1 Visit 8 (Day 8 ± 2 days)

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 8	**D8 ± 2 days**	**Follow-up**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7
Central Laboratory: Hematology				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11
Local laboratory: Liver biochemistry panel				Section 8.1.12
Vector shedding: blood, urine, saliva, feces - mandatory Note: at all visits until end of year 1, as applicable, vector shedding sampling is to occur at every site scheduled visit until 3 consecutive concerned samples are negative (at or below quantification limit)				Section 8.2.3
Sirolimus				Section 7.5
Sirolimus level test: sampling for blood trough concentration after 7 to 14 days according to local practice				Section 7.5
[redacted]				[redacted]
Oral steroid (Prednisone or Prednisolone)				Section 7.5.1
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

10.5.2 Visit 9 (Day 15 ± 2 days)

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 9	**D15 ± 2 days**	**Follow-up**	**Home nurse visit**	**Cross-reference**
Vital signs				Section 8.1.4
Local Laboratory: Liver biochemistry panel				Section 8.1.12
Sirolimus				Section 7.5
[redacted]				[redacted]
Oral steroid (Prednisone or Prednisolone)				Section 7.5.1
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

10.5.3 Visit 10 (Week 4 ± 2 days)

Importantly, from Week 4 to Week 12 inclusive post VTX-801 administration, liver function tests will be performed twice a week.

Additionally, in the case that an ALT increase ≥ 1.5 x baseline between Week 4 and Month 6 post-VTX-801 administration occurs despite the immunosuppressive regimen (Section 7.5), site has to specifically refer to Section 7.5.2 for guidance.

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 10	**Week 4 ± 2 days**	**Follow-up**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7
Central Laboratory: Blood/urine biochemistry with lipid panel; hematology; coagulation Fasting conditions are required for the lipid panel.				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11
Local laboratory: Liver biochemistry panel				Section 8.1.12
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC, CRP				Section 8.1.13
Anti-AAV3B capsid neutralizing antibodies				Section 8.2.1
Vector shedding: blood, urine, saliva, feces - mandatory Note: at all visits until end of year 1, as applicable, vector shedding sampling is to occur at every site scheduled visit until 3 consecutive concerned samples are negative (at or below quantification limit)				Section 8.2.3
ELISA and IFN-gamma ELISpot				Section 8.2.4
Sirolimus				Section 7.5
Sirolimus level test: sampling for blood trough concentration 28 days after starting treatment with Sirolimus				Section 7.5
[redacted]				[redacted]
Oral steroid (Prednisone or Prednisolone)				Section 7.5.1

Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.5.4 Visits 11-17 (Weeks 4, 5, 6 and 7 ± 2 days)

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visits 11-17	**Weeks 4, 5, 6, 7 ± 2 days**	**Follow-up**	**Home nurse visits**	**Cross-reference**
Vital signs				Section 8.1.4
Local Laboratory: Liver biochemistry panel (twice per week)				Section 8.1.12
Sirolimus				Section 7.5
[redacted]				[redacted]
Oral steroid (Prednisone or Prednisolone)				Section 7.5.1
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2
Visit 16, Week 6: A call or a video consultation between Investigator and patient (check for patient health and for the occurrence of any adverse event since the last visit)				

10.5.5 Visit 18 (Week 8 ± 2 days)

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 18	**Week 8 ± 2 days**	**Follow-up**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4

Physical examination	Section 8.1.3
Alcohol consumption	Section 7.7
Central Laboratory: Liver and lipid biochemistry panels Fasting conditions are required for the lipid panel.	Section 8.1.11
Local Laboratory: Liver biochemistry panel	Section 8.1.12
Vector shedding: blood, urine, saliva, feces - mandatory Note: at all visits until end of year 1, as applicable, vector shedding sampling is to occur at every site scheduled visit until 3 consecutive concerned samples are negative (at or below quantification limit).	Section 8.2.3
ELISA and IFN-gamma ELISpot	Section 8.2.4
Sirolimus	Section 7.5
Sirolimus level test: sampling for blood trough concentration 8 weeks days after starting treatment with Sirolimus	Section 7.5
[redacted]	[redacted]
Oral steroid (Prednisone or Prednisolone)	Section 7.5.1
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.5.6 Visits 19-25 (Weeks 8, 9, 10 and 11 ± 2 days)

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visits 19-25	**Weeks 8, 9, 10, 11 ± 2 days**	**Follow-up**	**Home nurse visits**	**Cross-reference**
Vital signs				Section 8.1.4
Local Laboratory: Liver biochemistry panel (twice per week)				Section 8.1.12

Sirolimus	Section 7.5
[redacted]	[redacted]
Oral steroid (Prednisone or Prednisolone): last dose at the end of Week 8 unless continued in the case of overt transaminase increase	Section 7.5.1
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.5.7 Visits 26-29 (Week 12)

Only for the expansion cohort: the patient is to be hospitalized, stay at a unit with clinical support or other location approved by the Sponsor [redacted]

Refer to Section 10.2, Visit 2 for the wash-out instructions for patients on copper chelators or dual chelator and zinc therapy:

Refer to Section 7.6.3, for expansion cohort only, [redacted]

The 2 samples of Week 12 for "Liver biochemistry panel" will occur at site as much as possible. For example, at Visit 26 collecting the first sample is mandatory, with the second sample collected at Visit 28 or Visit 29.

If the second sample cannot occur at site, it should be collected at the home nurse visit planned after end of hospitalization within Week 12 (Visit 30).

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 26	**Week 12 ± 5 days**	**Follow-up**	**In or Out-patient visit**	**Cross-reference**
Vital signs				Section 8.1.4

Physical examination	Section 8.1.3
Alcohol consumption	Section 7.7
Urine pregnancy test (for WOCBP only)	Section 8.1.12
Central Laboratory: Blood/urine biochemistry; hematology; coagulation	Section 8.1.11
Central Laboratory: Liver biochemistry panel	Section 8.1.11
Local Laboratory: Liver biochemistry panel (twice per week)	Section 8.1.12
Calculation of MELD, APRI, FIB4 by CRO	Section 8.1.14 Table 11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC	Section 8.1.13
24-hour urinary copper (to end prior to radiocopper administration) ***For patients on copper chelator:*** • Patients are to be informed to start the wash-out period without copper-chelator treatment 3 days before radiocopper injection and until the end of the radiocopper investigations. • The 24-hour urine copper sample will start 48 hours after initiation of the chelator wash-out period and will end prior to radiocopper administration	Section 8.1.13
Vector shedding: blood, urine, saliva, feces Note: at all visits until end of year 1, as applicable but only at this visit during this period of 4 consecutive visits (V26 to V29).	Section 8.2.3
ELISA and IFN-gamma ELISpot	Section 8.2.4
ECG	Section 8.1.5

UWDRS, M.I.N.I., SDMT and Stroop Test	Section 8.1.7
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Sirolimus [redacted]	Section 7.5
[redacted]	[redacted]
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 27	**Week 12**	**Follow-up**	**In or Out-patient visit**	**Cross-reference**
Vital signs				Section 8.1.4
[redacted]				[redacted]
[redacted]				[redacted]

[redacted]	[redacted]
Sirolimus [redacted]	Section 7.5
[redacted]	[redacted]
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12				
Visit 28	**Week 12**	**Follow-up**	**In or Out-patient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Local Laboratory: Liver biochemistry panel (this could alternatively be taken at Visits 29 or 30)				Section 8.1.12
[redacted]				[redacted]
[redacted]				[redacted]
[redacted]				[redacted]
Sirolimus administration [redacted]				Section 7.5
[redacted]				[redacted]
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

The patient will leave the hospital after following assessments:

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12 This visit is for the expansion cohort only.				
Visit 29	**Week 12**	**Follow-up**	**In or Out-patient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Local Laboratory: Liver biochemistry panel (only if not done at Visit 28)				Section 8.1.12
[redacted]				[redacted]
[redacted]				[redacted]
[redacted]				[redacted]
Sirolimus administration [redacted]				Section 7.5
[redacted]				[redacted]
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

10.5.8 Visits 30 and 31 (Weeks 12 and 13 ± 3 days)

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)

Note: Visit 30 will not occur (including recording vital signs) if the liver biochemistry sample is collected at either Visit 28 or Visit 29 at site

Visits 30-31	Weeks 12,13 ± 3 days	Follow-up	Home nurse visits	Cross-reference
Vital signs				Section 8.1.4
Local Laboratory: Liver biochemistry panel (only if not done at either Visit 28 or 29)				Section 8.1.12
Sirolimus administration [redacted]				Section 7.5
[redacted]				[redacted]
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

10.5.9 Visit 32 (Week 14 + 2 days)

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)

Note: Time window at W14 may be increased beyond 2 days to accommodate the DMC review process.

Visit 32	Week 14 + 2 days	Follow-up	Phone call	Cross-reference
Vital signs (only if visit occurs on site)				Section 8.1.4
Investigator informs the patient about his/her "Responder/Insufficient Responder" status and associated consequences: • withdrawal or continuation of the WD SoC therapy				Section 4.5 / Section 4.6

Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.5.10 Visits 33-35 (Weeks 15, 16 and 20 ± 3 days)

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)				
Visits 33-35	**Weeks 15, 16, 20 ±3 days**	**Follow-up**	**Home nurse visits**	**Cross-reference**
Vital signs				Section 8.1.4
Local Laboratory: Liver biochemistry panel				Section 8.1.12
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2
Additional for Visit 35, Week 20 only:				
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC and CRP				Section 8.1.13
24-hour urinary copper				Section 8.1.13
Visit 35, Week 20: A call or a video consultation between Investigator and patient (check for patient health and for the occurrence of any adverse event since the last visit)				

10.5.11 Visit 36 (Week 24 ± 3 days)

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)				
Visit 36	**Week 24 ± 3 days**	**Follow-up**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4

Physical examination	Section 8.1.3
Alcohol consumption	Section 7.7
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation	Section 8.1.11
Central Laboratory: Liver biochemistry panel	Section 8.1.11
Local Laboratory: Liver biochemistry panel	Section 8.1.12
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, Exchangeable Cu, ANCC	Section 8.1.13
24-hour urinary copper ***For patients on copper chelator:*** • Patients have to be reminded to have a 72-hour period without copper-chelator treatment: - 48 hours prior starting sampling of urine, - And during the 24 hours of urine collection. • They will restart their copper-chelator treatment only after the last sampling of the 24-hour urine collection.	Section 8.1.13
Vector shedding: blood, urine, saliva, feces - mandatory Note: at all visits until end of year 1, as applicable, vector shedding sampling is to occur at every site scheduled visit until 3 consecutive concerned samples are negative (at or below quantification limit)	Section 8.2.3
Calculation of MELD, APRI, FIB4 by CRO	Section 8.1.14 Table 11
Ophthalmology: slit lamp examination	Section 8.1.6
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.5.12 Visits 37-38 (Weeks 28 and 32 ± 3 days)

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)				
Visits 37-38	**Weeks 28 and 32 ±3 days**	**Follow-up**	**Home nurse visits**	**Cross-reference**
Vital signs				Section 8.1.4
Local Laboratory: Liver biochemistry panel				Section 8.1.12
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

10.5.13 Visits 39-42 (Week 36)

Only for the expansion cohort: the patient is to be hospitalized, stay at a unit with clinical support or other location approved by the Sponsor [redacted].

If it does not occur, the patient will only attend one visit (Visit 39) as [redacted]

Refer to Section 10.2, Visit 2 for the wash-out instructions for patients on copper chelator.

Refer to Section 7.6.3, for expansion cohort only, on patient to be given [redacted]

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)				
Visit 39	**Week 36 ± 5 days**	**Follow-up**	**In or Out-patient visit**	**Cross-reference**
Vital signs				Section 8.1.4

Physical examination	Section 8.1.3
Alcohol consumption	Section 7.7
Urine pregnancy test (WOCBP)	Section 8.1.11
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation	Section 8.1.11
Central Laboratory: Liver biochemistry panel	Section 8.1.11
Local Laboratory: Liver biochemistry panel	Section 8.1.12
Calculation of MELD, APRI, FIB4 by CRO	Section 8.1.14 Table 11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC	Section 8.1.13
24-hour urinary copper (to end prior to radiocopper administration) ***For patients on copper chelator:*** • Patients are to be informed to start the wash-out period without copper-chelator treatment 3 days before radiocopper injection and until the end of the radiocopper investigations. • The 24-hour urine copper sample will start 48 hours after initiation of the chelator wash-out period and will end prior to radiocopper administration.	Section 8.1.13
Vector shedding: blood, urine, saliva, feces Note: at all visits until end of year 1, as applicable but only at this visit during this period of 4 consecutive visits (V39 to V42).	Section 8.2.3
UWDRS, M.I.N.I.	Section 8.1.7
[redacted]	[redacted]

Radiocopper administration (around 9 am) if applicable	Section 7.4
[redacted]	[redacted]
[redacted]	[redacted]
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)				
Visit 40	**Week 36**	**Follow-up**	**In or Out-patient visit**	**Cross-reference**
Vital signs				Section 8.1.4
[redacted]				[redacted]
[redacted]				[redacted]
[redacted]				[redacted]
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)				
Visit 41	**Week 36**	**Follow-up**	**In or Out-patient visit**	**Cross-reference**
Vital signs				Section 8.1.4
[redacted]				[redacted]
[redacted]				[redacted]
[redacted]				[redacted]
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

The patient will leave the hospital after following assessments:

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1) This visit is for the expansion cohort only.				
Visit 42	**Week 36**	**Follow-up**	**In or Out-patient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Local Laboratory: Liver biochemistry panel				Section 8.1.12

[redacted]	[redacted]
[redacted]	[redacted]
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.5.14 Visit 43 (Week 38)

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)

Note: The time window at W38 may be increased beyond 2 days to accommodate the DMC review process.

Visit 43	Week 38 +2 days	Follow-up	Phone call	Cross-reference
Vital signs (only if visit occurs at site)				Section 8.1.4
If the patient underwent the Week 36 radiocopper related assessments, Investigator informs the patient about his/her "Responder/Insufficient Responder" status and associated consequences: • withdrawal, continuation or restart of the WD SoC therapy				Section 4.5 / Section 4.6
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

10.5.15 Visits 44-45 (Weeks 40 and 44 ± 3 days)

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)				
Visits 44-45	**Weeks 40 and 44 ±3 days**	**Follow-up**	**Home nurse visits**	**Cross-reference**
Vital signs				Section 8.1.4
Local Laboratory: Liver biochemistry panel				Section 8.1.12
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2
Additional for Visit 45, Week 44 only:				
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC and CRP				Section 8.1.13
24-hour urinary copper: only for “Responders” at that time and as such, not on SoC treatment.				Section 8.1.13

10.5.16 Visit 46 (Week 52 ± 7 days)

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)				
Visit 46	**Week 52 ± 7 days**	**Follow-up**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11

Local Laboratory: Liver biochemistry panel	Section 8.1.12
Calculation of MELD, APRI, FIB4 by CRO	Section 8.1.14 Table 11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC, CRP	Section 8.1.13
Vector shedding: blood, urine, saliva, feces - mandatory Note: at all visits until end of year 1, as applicable, vector shedding sampling is to occur at every site scheduled visit until 3 consecutive concerned samples are negative (at or below quantification limit)	Section 8.2.3
24-hour urinary copper ***For patients on copper chelator:*** • Patients have to be reminded to have a 72-hour period without copper-chelator treatment: - 48 hours prior starting sampling of urine, - And during the 24 hours of urine collection. • They will restart their copper-chelator treatment only after the last sampling of the 24-hour urine collection.	Section 8.1.13
Anti-AAV3B capsid neutralizing antibodies	Section 8.2.1
ECG	Section 8.1.5
Ophthalmology: slit lamp examination	Section 8.1.6
UWDRS, M.I.N.I., SDMT and Stroop Test	Section 8.1.7
Abdominal MRI and liver MR elastography. Elastography to be performed in a > 4-hour fasted state	Section 8.1.8

Liver biopsy (All efforts should be made to collect liver biopsies for each patient as described in the schedule of events. However, for the dose escalation cohorts only, if a patient declines to have the liver biopsies taken, these can be replaced with Fibroscan®. Should Fibroscan® be used instead of liver biopsy at Screening, this should be implemented for the rest of the study, to ensure consistency for the longitudinal analysis).	Section 8.2.5
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.6 Visits 47-50: Follow-up (Year 2)

Note concerning 24-hour urinary copper for patients on copper chelator:

- Patients have to be reminded to have a 72-hour period without copper-chelator treatment:
  - 48 hours prior starting sampling of urine,
  - And during the 24 hours of urine collection.
- They will restart their copper-chelator treatment only after the last sampling of the 24-hour urine collection

10.6.1 Visit 47 (Year 2, Month 3 ± 14 Days)

Refer to Table 4 Summary of Schedule of Events: Years 2 to 5 Follow Up				
Visit 47	**Study Month 15 ± 14 Days**	**Follow-up Year 2**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation				Section 8.1.11

Central Laboratory: Liver biochemistry panel	Section 8.1.11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC	Section 8.1.13
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.6.2 Visit 48 (Year 2, Month 6 ± 14 Days)

Refer to Table 4 Summary of Schedule of Events: Years 2 to 5 Follow Up				
Visit 48	**Study Month 18 ± 14 Days**	**Follow-up Year 2**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC				Section 8.1.13
24-hour urinary copper				Section 8.1.13
UWDRS, M.I.N.I				Section 8.1.7
Calculation of MELD, APRI, FIB4 by CRO				Section 8.1.14 Table 11
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

10.6.3 Visit 49 (Year 2, Month 9 ± 14 Days)

Refer to Table 4 Summary of Schedule of Events: Years 2 to 5 Follow Up				
Visit 49	**Study Month 21 ± 14 Days**	**Follow-up Year 2**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC				Section 8.1.13
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

10.6.4 Visit 50 (Year 2, Month 12 ± 14 Days)

Refer to Table 4 Summary of Schedule of Events: Years 2 to 5 Follow Up				
Visit 50	**Study Month 24 ± 14 Days**	**Follow-up Year 2**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11

Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC	Section 8.1.13
24-hour urinary copper	Section 8.1.13
UWDRS, M.I.N.I, SDMT and Stroop Test	Section 8.1.7
Calculation of MELD, APRI, FIB4 by CRO	Section 8.1.14 Table 11
Abdominal MRI and liver MR elastography. Elastography to be performed in a > 4-hour fasted state.	Section 8.1.8
ECG	Section 8.1.5
Ophthalmology: slit lamp examination	Section 8.1.6
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.7 Visits 51-52: Follow-up (Year 3)

Note concerning 24-hour urinary copper for patients on copper chelator:

- Patients have to be reminded to have a 72-hour period without copper-chelator treatment:
  - 48 hours prior starting sampling of urine,
  - And during the 24 hours of urine collection.
- They will restart their copper-chelator treatment only after the last sampling of the 24-hour urine collection.

10.7.1 Visit 51 (Year 3, Month 6 ± 14 Days)

Refer to Table 4 Summary of Schedule of Events: Years 2 to 5 Follow Up				
Visit 51	**Study Month 30 ± 14 Days**	**Follow-up Year 3**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC				Section 8.1.13
24-hour urinary copper				Section 8.1.13
UWDRS, M.I.N.I				Section 8.1.7
Calculation of MELD, APRI, FIB4 by CRO				Section 8.1.14 Table 11
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

10.7.2 Visit 52 (Year 3, Month 12 ± 14 Days)

Refer to Table 4 Summary of Schedule of Events: Years 2 to 5 Follow Up				
Visit 52	**Study Month 36 ± 14 Days**	**Follow-up Year 3**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC				Section 8.1.13
24-hour urinary copper				Section 8.1.13
UWDRS, M.I.N.I, SDMT and Stroop Test				Section 8.1.7
Calculation of MELD, APRI, FIB4 by CRO				Section 8.1.14 Table 11
Brain MRI				Section 8.1.9
Abdominal MRI and liver MR elastography. Elastography to be performed in a > 4-hour fasted state.				Section 8.1.8
ECG				Section 8.1.5
Ophthalmology: slit lamp examination				Section 8.1.6

Liver biopsy (All efforts should be made to collect liver biopsies for each patient as described in the schedule of events. However, for the dose escalation cohorts only, if a patient declines to have the liver biopsies taken, these can be replaced with Fibroscan®. Should Fibroscan® be used instead of liver biopsy at Screening, this should be implemented for the rest of the study, to ensure consistency for the longitudinal analysis).	Section 8.2.5
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.8 Visits 53-54: Follow-up (Year 4)

Note concerning 24-hour urinary copper for patients on copper chelator:

- Patients have to be reminded to have a 72-hour period without copper-chelator treatment:
  - 48 hours prior starting sampling of urine,
  - And during the 24-hour urine collection.
- They will restart their copper-chelator treatment only after the last sampling of the 24-hour urine collection.

10.8.1 Visit 53 (Year 4, Month 6 ± 14 Days)

Refer to Table 4 Summary of Schedule of Events: Years 2 to 5 Follow Up				
Visit 53	**Study Month 42 ± 14 Days**	**Follow-up Year 4**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7

Central Laboratory: Blood/urine biochemistry; hematology; Coagulation	Section 8.1.11
Central Laboratory: Liver biochemistry panel	Section 8.1.11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC	Section 8.1.13
24-hour urinary copper	Section 8.1.13
UWDRS, M.I.N.I	Section 8.1.7
Calculation of MELD, APRI, FIB4 by CRO	Section 8.1.14 Table 11
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.8.2 Visit 54 (Year 4, Month 12 ± 14 Days)

Refer to Table 4 Summary of Schedule of Events: Years 2 to 5 Follow Up				
Visit 54	**Study Month 48 ± 14 Days**	**Follow-up Year 4**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11

Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC	Section 8.1.13
24-hour urinary copper	Section 8.1.13
UWDRS, M.I.N.I, SDMT and Stroop Test	Section 8.1.7
Calculation of MELD, APRI, FIB4 by CRO	Section 8.1.14 Table 11
Abdominal MRI and liver MR elastography. Elastography to be performed in a > 4-hour fasted state.	Section 8.1.8
ECG	Section 8.1.5
Ophthalmology: slit lamp examination	Section 8.1.6
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2

10.9 Visits 55-56: Follow-up (Year 5)

Note concerning 24-hour urinary copper for patients on copper chelator:

- Patients have to be reminded to have a 72-hour period without copper-chelator treatment:
  - 48 hours prior starting sampling of urine,
  - And during the 24-hour urine collection.
- They will restart their copper-chelator treatment only after the last sampling of the 24-hour urine collection.

10.9.1 Visit 55 (Year 5, Month 6 ± 14 Days)

Refer to Table 4 Summary of Schedule of Events: Years 2 to 5 Follow Up				
Visit 55	**Study Month 54 ± 14 Days**	**Follow-up Year 5**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC				Section 8.1.13
24-hour urinary copper				Section 8.1.13
UWDRS, M.I.N.I				Section 8.1.7
Calculation of MELD, APRI, FIB4 by CRO				Section 8.1.14 Table 11
Adverse events				Section 9.2
Concomitant medications				Section 8.1.2

10.9.2 Visit 56 (Year 5, Month 12, ± 14 Days) – End of Study Visit

Refer to Table 4 Summary of Schedule of Events: Years 2 to 5 Follow Up				
Visit 56	**Study Month 60 ± 14 Days**	**Follow-up Year 5**	**Outpatient visit**	**Cross-reference**
Vital signs				Section 8.1.4
Physical examination				Section 8.1.3
Alcohol consumption				Section 7.7
Central Laboratory: Blood/urine biochemistry; hematology; Coagulation				Section 8.1.11
Central Laboratory: Liver biochemistry panel				Section 8.1.11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC				Section 8.1.13
24-hour urinary copper				Section 8.1.13
UWDRS, M.I.N.I, SDMT and Stroop Test				Section 8.1.7
Calculation of MELD, APRI, FIB4 by CRO				Section 8.1.14 Table 11
Abdominal MRI and liver MR elastography. Elastography to be performed in a > 4-hour fasted state.				Section 8.1.8
ECG				Section 8.1.5
Ophthalmology: slit lamp examination				Section 8.1.6
Brain MRI				Section 8.1.9
Adverse events				Section 9.2

Concomitant medications	Section 8.1.2

10.10 Early Termination Visit

If a patient withdraws or is withdrawn prematurely, the following assessments and procedures should be performed according to patient and visit status and recorded in the Early Termination eCRF.

This is an outpatient visit and it should be performed within 4 weeks following the decision to withdraw. Priority of assessments will be those related to safety (vital signs; physical examination; blood/urine biochemistry/hematology/ coagulation; liver biochemistry panel; adverse events), the other listed assessments will occur if possible or applicable.

Importantly, ongoing AEs should be followed up in accordance with the procedures described in Section 9.2.7.

If a patient discontinues between enrollment (Visit 2) and before administration of VTX-801, the Early Termination visit will contain:

Refer to Table 2 Summary of Schedule of Events: Baseline to Week 12		
Early Termination visit: If occurring prior to VTX-801 administration	**Outpatient visit**	**Cross-reference**
Vital signs		Section 8.1.4
Physical examination		Section 8.1.3
Central Laboratory: blood/urine biochemistry; hematology; Coagulation		Section 8.1.11
Central Laboratory: Liver biochemistry panel		Section 8.1.11
ECG		Section 8.1.5
Adverse events		Section 9.2
Concomitant medications		Section 8.1.2

Reason for early termination	

If a patient discontinues after administration of VTX-801 (even partial) and before completing the Year 1 follow up, the visit will be the one planned at the end of Year 1.

Refer to Table 3 Summary of Schedule of Events: Weeks 13 to 52 (End of Year 1)		
Early Termination visit: If occurring after VTX-801 administration; before end of Year 1	**Outpatient visit**	**Cross-reference**
Vital signs		Section 8.1.4
Physical examination		Section 8.1.3
Alcohol consumption		Section 7.7
Central Laboratory: blood/urine biochemistry; hematology; Coagulation		Section 8.1.11
Central Laboratory: Liver biochemistry panel		Section 8.1.11
Local Laboratory: Liver biochemistry panel		Section 8.1.12
ECG		Section 8.1.5
Adverse events		Section 9.2
Concomitant medications		Section 8.1.2
Reason for early termination		
Calculation of MELD, APRI, FIB4 by CRO		Section 8.1.14 Table 11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC		Section 8.1.13

24-hour urinary copper	Section 8.1.13
Anti-AAV3B capsid neutralizing antibodies	Section 8.2.1
ELISA and INF-gamma ELISpot	Section 8.2.4
Vector shedding: blood, urine, saliva, feces - mandatory Note: at all visits until end of year 1, as applicable, vector shedding sampling is to occur at every site scheduled visit until 3 consecutive concerned samples are negative (at or below quantification limit)	Section 8.2.3
Abdominal MRI and liver MR elastography. Elastography to be performed in a > 4-hour fasted state	Section 8.1.8
Ophthalmology: slit lamp examination	Section 8.1.6
UWDRS, M.I.N.I., SDMT and Stroop Test	Section 8.1.7

Additionally, every effort should then be made to follow each patient for up to 5 years post-VTX-801 administration with at least one phone call every 6 months to collect potential adverse events.

If a patient discontinues after completing the Year 1 follow up visits, the Early Termination visit will be the one planned at the end of Year 5.

Refer to Table 4 Summary of Schedule of Events: Years 2 to 5 Follow Up		
Early Termination visit: If occurring after completion of Year 1 follow-up	**Outpatient visit**	**Cross-reference**
Vital signs		Section 8.1.4
Physical examination		Section 8.1.3
Alcohol consumption		Section 7.7

Central Laboratory: blood/urine biochemistry; hematology; Coagulation	Section 8.1.11
Central Laboratory: Liver biochemistry panel	Section 8.1.11
ECG	Section 8.1.5
Adverse events	Section 9.2
Concomitant medications	Section 8.1.2
Reason for early termination	
Calculation of MELD, APRI, FIB4 by CRO	Section 8.1.14 Table 11
Ceruloplasmin (enzymatic assay and nephelometry), total Cu, REC, RAC, CuEXC, ANCC	Section 8.1.13
24-hour urinary copper	Section 8.1.13
Abdominal MRI and liver MR elastography. Elastography to be performed in a > 4-hour fasted state	Section 8.1.8
Ophthalmology: slit lamp examination	Section 8.1.6
Brain MRI	Section 8.1.9
UWDRS, M.I.N.I., SDMT and Stroop Test	Section 8.1.7

Additionally, every effort should then be made to follow each patient for up to 5 years post-VTX-801 administration with at least one phone call every 6 months to capture potential adverse events.

10.11 Unscheduled Visit

Unscheduled visits may be necessary during the study, especially for safety monitoring purposes and/or repeat safety assessments or in case of potential or suspected loss of efficacy.

All unscheduled study visits, procedures, examinations, clinical laboratory evaluations etc., will be noted in the patient's medical record and the eCRF including:

- Reason for visit/procedure
- Procedures, examinations, clinical laboratory evaluations, as applicable
- Follow-up
- Adverse events
- Concomitant treatments

11 STATISTICAL CONSIDERATIONS

The study statistical analysis plan (SAP) will be developed and finalized before the first interim data lock. Full details of the analysis to be performed will be included in the SAP. This Section is a summary of the planned statistical analyses at the time of protocol development.

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

11.1 Sample Size Considerations

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 enroll at least 1 patient of each gender in each cohort of 4.

11.2 Planned Interim Analyses

An interim analysis is planned before the final analysis and will cover the first patient first visit to 1 year after last patient has been treated with VTX-801.

The final analysis will cover all study data.

In addition, safety reviews will be conducted by the DMC. These will include patient-level, cohort-level and ad-hoc data reviews. The objective of these reviews will be to provide recommendations relating to patient safety and Responder status.

An additional interim analysis may occur during the study if considered necessary by the Sponsor.

11.3 Analysis Sets

The Safety Analysis Set will include all patients who received at least part of the VTX-801 dose.

The Pharmacodynamics Analysis 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).

The Efficacy Analysis 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.

Other Analysis Sets may be defined in the SAP, as necessary.

11.4 Statistical Methodology

All statistical analyses will be descriptive, there will be no hypothesis testing. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage (n, %) of patients within each classification.

11.4.1 Demographics and Medical History

Demographic and baseline measurements will be summarized using standard descriptive methods.

11.4.2 Extent of Exposure

A by-patient listing of the date and time of IMP administration and the dose administered will be presented.

11.4.3 Concomitant Medications

All concomitant medications administered, including steroids and Sirolimus treatment, will be presented in a data listing. Concomitant medications may be summarized descriptively, by therapeutic class and preferred term, as warranted by the data.

11.4.4 Safety Analyses

Safety evaluations will be based on the incidence, severity and type of AEs, and on changes in the patient's physical examination findings, vital signs, clinical laboratory results (hematology, biochemistry and coagulation), urine tests results, ECG, brain MRI,

abdominal MRI, liver MR elastography, and viral vector shedding findings. Safety results will be presented for all patients in the Safety Analysis Set.

11.4.4.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

AEs will be summarized based on the date of onset for the event. Summaries (number and percentage of patients) of treatment-emergent AEs will be provided by SOC and PT, by dose cohort and overall.

Treatment-emergent adverse event is defined as any AE that emerges during or after IMP administration having been absent pre-treatment or worsens relative to the pre-treatment state.

Events that are considered possibly, probably or definitely related to the IMP, deaths, SAEs, and AEs resulting in IMP discontinuation will also be tabulated by SOC and PT.

A tabulation will also be provided that summarizes at least treatment-emergent and treatment-related AEs (possibly, probably or definitely related) by maximum severity (i.e., CTCAE grade).

Duration of AEs will also be investigated as appropriate.

All AEs, including treatment-emergent and non-treatment-emergent AEs, will be listed in patient data listings.

11.4.4.2 Laboratory Evaluations

Summaries of clinical laboratory data from central laboratories, including transaminase results, will be provided using descriptive statistics. No inferential statistics will be provided. Quantitative values and change from baseline in quantitative values will be summarized by dose cohort and overall. Listings of all laboratory results and reference ranges will be provided.

Graded laboratory abnormalities, including for transaminases, will be defined using the grading scheme based on NCI CTCAE v5 and summarized by dose cohort and overall.

Shift tables will also be produced for gradable parameters based on the baseline CTCAE grade and the maximum CTCAE grade.

Duration of abnormalities will also be investigated as appropriate.

11.4.4.3 Other Safety Evaluations

Changes in the patient's physical examination findings, vital sign parameters, ECG and viral vector shedding findings will be summarized by dose cohort and overall, and any abnormal values will be tabulated.

All data related to the patient's physical examination findings, vital signs, ECG, brain MRI, abdominal MRI, liver MR elastography, and viral vector shedding findings will be presented in data listing format.

11.4.5 Pharmacodynamics and Efficacy Analyses

All pharmacodynamic endpoints will be analyzed for all patients of the pharmacodynamic analysis set.

Pharmacodynamic data, including free serum copper (CuEXC and ANCC), REC, RAC, total serum copper, 24-hour urinary copper and serum ceruloplasmin, will be summarized descriptively for all patients by dose cohort and planned visit, for absolute values, changes from baseline and percent change from baseline.

All efficacy [redacted] will be analyzed for all patients of the efficacy analysis set.

The number of Responders and Insufficient-Responders will be summarized by dose cohort and planned visit, with response to treatment defined as described in Section 4.5 of this protocol. The 95% confidence interval for percentage of Responders will be provided. The change in response status from W12 to W36 will also be described using a shift table.

[redacted]

[redacted] (e.g., sample size, arithmetic mean, % coefficient of variation, standard deviation, median, minimum, and maximum).

[redacted] e.g., sample size, arithmetic and geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum).

[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 and time to copper deficiency and whether correction occurs will be listed and summarized, by dose cohort using appropriate descriptive statistics.

11.4.6 Other Analyses

All other study endpoints will be analyzed for all patients of the Safety Analysis Set using appropriate descriptive statistics, by dose cohort and planned visit:

- Humoral and cellular immune responses to VTX-801: *in vitro* neutralizing antibody (NAb) anti-AAV3B capsid assay, ELISA against AAV3B capsid and miniATP7B, IFN-gamma ELISpot to AAV3B capsid and miniATP7B
- MELD, APRI, FIB4 scores
- Scores/diagnosis from the M.I.N.I.
- Scores from SDMT and Stroop Test
- Total score from the UWDRS part I, II and III

Descriptive statistics will include absolute values, changes from baseline and percent change from baseline, as appropriate.

11.5 Changes to the Planned Statistical Methods

Changes to the planned statistical methods will be documented in the clinical study report(s).

12 STUDY OPERATIONS

12.1 Study Sites

12.1.1 Investigational Sites

Sites will be selected to participate in this research after completion of feasibility and qualification assessments. Investigational sites will use their patient records/databases to identify potential patients for the study. Investigational sites will implement detailed patient identification, management and retention plans.

A selection of the investigational sites (termed “Infusion sites”) will be allowed to perform all study procedures including radiocopper related administration, radiocopper assessments and VTX-801 infusion.

The other investigational sites (termed “non-infusion sites”) will be allowed to perform all study procedures except for the inpatient stays where radiocopper-related administration and assessments and VTX-801 infusion will be performed.

Radiocopper administration and related assessments and VTX-801 infusion for patients enrolled at non-infusion sites will be performed at the infusion sites.

12.1.2 Referral Sites

The Sponsor may select patient identification centers (“Referral sites”) to identify potential patients from their records/databases and to refer them to one of the participating Investigational sites, including cross-border referrals. Study activity at Referral sites will be limited to refer potential patients to the corresponding Investigational site. In case there is a need for Referral country regulatory/ethics committee submission, the Referral sites may be involved accordingly.

12.1.3 Home Nurses

As described in Section 10 and the schedule of assessments, at the discretion of the Investigator and if agreed to by the patient, some visits may be conducted at the patient’s home by a home nurse. This type of visit can be planned for all types of assessments/retests (for which the home nurse is qualified and trained accordingly) as needed.

If home nurse visits are to be conducted instead of site visits as described in Section 10 and the schedule of assessments, this will be agreed in advance by the Investigator, patient and Sponsor. Home nurses will operate under a written agreement with the Investigational site and will fully uphold patient confidentiality. Samples collected by the home nurse may be processed by the Central Laboratory. All study data will be transferred to the Investigational site.

12.2 Study Monitoring

During the course of the study, a CRA will conduct routine site visits (both on site and remotely) to review protocol compliance, compare eCRF entries with individual patient's original source documents (accessed by the Investigator), assess product accountability and ensure the study is conducted according to applicable regulatory requirements. The review of the patient's original medical records shall be performed in a manner which ensures patient confidentiality is maintained.

The Investigator shall permit the CRA to review study data as frequently as deemed necessary to ensure that data are recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator may not enroll patients into the study until authorization is given by the Sponsor, or their designee, Aixial, which would typically be after completion of a successful Site Initiation Visit (SIV) by the CRA to conduct a detailed training of the protocol and eCRF, and confirmation that the site's essential regulatory documents have been verified.

12.3 Source Documents

Each participating site shall maintain appropriate medical and research records for this trial, in compliance with ICH GCP and regulatory and institutional requirements for the protection of patient confidentiality.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' memory aids or evaluation checklists, pharmacy dispensing records, recorded data from

automated instruments, recorded audio tapes of counseling sessions, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

The eCRF is not a source document.

12.3.1 Access to Source Data and Documents

The Investigator/institution shall provide direct access to all relevant data and records to the CRA, auditors, the Sponsor's authorized representatives, designated agents of the Sponsor, IRB, and Health Authorities, as required, for study-related monitoring, audits, inspections, IRB/EC review and regulatory inspection. An infusion site may need to provide access to patient records to a non-infusion site.

12.4 Data Handling and Record Keeping

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the source data. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Investigator.

The Sponsor and/or its designated CRO, will provide training and guidance to Investigators on recording trial data in the eCRF.

12.4.1 Data Capture Methods

Clinical data (including AEs, concomitant medications, safety assessments and outcome measures) will be entered by the site staff into a 21 CFR Part 11-compliant data capture system provided by the designated CRO. The data capture system includes password protection and internal quality checks, such as automatic range checks, to identify data appearing inconsistent, incomplete or inaccurate.

Any diagnostic and/or laboratory data collected by a central vendor will be stored electronically in the central vendor's database system. Data will subsequently be transferred to the Sponsor and/or its designated CRO, for inclusion into data collected in the EDC system.

CRO personnel will be responsible authorizing access to the EDC system for Investigator-designated site staff.

12.4.2 Study Site Responsibilities

All data requested on the eCRF must be recorded. Data will be transcribed by authorized personnel at the study site from the source documents into the eCRF for enrolled patients (i.e., all patients who have signed the ICF). All information on the eCRF must be traceable to these source documents. All electronic entries (including any changes or updates) will be traceable through the system. Only the Investigator or authorized staff may enter or modify data in the database using their unique password and User Identification. The Investigator must certify that the data entered in the eCRFs are complete and accurate by electronically signing the eCRF.

Data must be transcribed in the eCRF within 5 working days of the source data recording. In certain cases, i.e. ahead of cohort and patient level DMC meetings data used for decision making must be transcribed within 2 working days.

Any SAE meeting the criteria described in Section 9.2.6, Table 15 must be entered into the eCRF within 24 hours of first awareness of the event by study personnel.

Although pregnancy itself is not considered an AE, it must be entered in the eCRF in the same timelines as a SAE (within 24 hours of the Investigator becoming aware of the pregnancy).

12.4.3 Data Management Responsibilities

The Aixial Data and Analytics department will serve as the Statistical and Data Management Center for this study and will be responsible for data management, quality review, analysis and reporting of the study data.

Data management staff at Aixial will review the data in the eCRFs according to their internal SOPs and systematically validate the data using appropriate electronic checks in addition to relevant manual checks. For any errors identified in the data, Aixial will generate a formal query to be addressed by the investigational site staff within the EDC system.

For classification purposes, concomitant medications, AEs and medical history entered into the eCRF will be coded using relevant medication and medical term dictionaries. These will be specified in the study-specific Data Management Quality Plan.

12.4.4 Study Records Retention and Archiving

After the trial is completed, the Investigator will receive or download an electronic file with the eCRFs of the patient data for the site for archiving at the investigational study site. No records will be destroyed without the written consent of the Sponsor, if applicable.

Essential documents should be retained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable local requirements.

ICH requires that patient identification codes be retained for at least 15 years after the completion or discontinuation of the study.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Quality Management Systems

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof, and in accordance with USA FDA regulations (CFR, Sections 312.50 and 312.56) and with ICH GCP.

The Sponsor and Aixial shall implement and maintain quality control (QC) and quality assurance (QA) procedures with written SOPs to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP, US CFR Title 21 and other applicable regulatory requirements.

All participating sites are required to have written procedures in place for assuring the quality of the research being conducted, including, but not limited to:

- How data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.
- The documents to be reviewed (e.g., eCRFs, clinic notes, product accountability), who is responsible, and the frequency for reviews.
- Methods of training for staff, and methods of tracking such training.

13.2 Audit

The Sponsor may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP and ICH related guidelines.

Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by Health Authorities, the Investigator must inform the Sponsor immediately that such request has been made.

The Investigator will permit such audits by Sponsor or Health Authorities and facilitate them by providing access to the relevant source documents.

13.3 Protocol Amendment

Any substantial change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, Health Authorities and the IRB/IEC prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented without prior approval, provided the Health Authorities and the concerned IRB/IEC are subsequently notified by written protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor's designated CRO, Aixial, should be informed and AE/SAE reporting requirements followed as appropriate.

13.4 Protocol Deviation

The Investigator may not deviate from the protocol without a written protocol amendment having been established and approved by the IRB/IEC and the concerned Health Authorities, when applicable, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the patient having to be withdrawn from the study or render that patient non-evaluable.

A protocol deviation is any non-compliance with the clinical trial protocol, ICH-GCP requirements, or all Study Plans and Manuals. The non-compliance may be either on the part of the patient, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to Aixial and the Sponsor.

All deviations from the protocol must be documented in study patient source documents. Protocol deviations must be sent to the local IRB/EC per their guidelines. The Investigator and his/her staff are responsible for knowing and adhering to their local guidelines.

14 ETHICS/PROTECTION OF HUMAN PATIENTS

14.1 Ethical Standard

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

Records that may reveal the identities of patients must be well protected, with consideration given to confidentiality and the right to privacy.

Each Principal Investigator will sign this protocol and complete, sign and date the FDA 1572 form (or an equivalent document) prior to conducting any study-related activities. Each Principal Investigator and Sub-Investigator will complete, sign and date the Financial Disclosure Form (or an equivalent document) to declare any financial or other competing interests. Participating Investigators will receive protocol training either at the SIV or via attendance at an Investigator Meeting.

14.2 Institutional Review Board / Independent Ethics Committee

Before initiating the study, the Investigator/institution should obtain approval/favorable opinion from the IRB/EC for the trial protocol, written ICF, ICF updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. The IRB/IEC shall be appropriately constituted and perform its functions in accordance with FDA, EU, ICH GCP, and local requirements as applicable.

Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the CRA, auditors, the Sponsor's QA representatives, designated agents of the Sponsor, IRBs/IECs, and Regulatory Authorities as required. If an inspection of the clinical site is requested by a Regulatory Authority, the Investigator must inform the Sponsor immediately that this request has been made.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the patient's agreeing to participate in the study and continues throughout the patient's study participation. Written documentation of informed consent is required prior to any performance of study procedures.

A site-specific, IRB/EC-approved ICF, describing in detail the study treatments and procedures, visit schedule, restrictions and risks and possible benefits, will be given to the patient during a clinic visit. The patient will be asked to read and review the document. The Investigator will explain the research study to the patient and answer any questions that may arise. The patient should have the opportunity to discuss the study with others if they wish and should be given adequate time to consider their decision before to agreeing to participate. If the patient agrees to participate, he/she will sign and date the ICF with the Investigator. A copy of the signed informed consent document will be given to the patient to keep.

The patient may withdraw consent at any time throughout the course of the trial without affecting their legal rights or incurring loss of benefits to which they are otherwise entitled. The rights and welfare of the patient will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study, or by withdrawal of consent.

14.3.1 Exclusion of Women, Minorities, and Children

Women and minorities may be eligible to participate. Participants must meet all of the inclusion criteria listed in Section 5.2 and none of the exclusion criteria listed in Section 5.3 to be eligible to participate. Only adults (aged 18-65 years at the time of signing the informed consent form) will be enrolled at this early stage of VTX-801 development; children, a relevant population in WD, are to be evaluated at a later stage, after gaining experience in adults and evaluating safety.

14.4 Patient Confidentiality

Patient confidentiality is strictly held in trust by the participating Investigators, their staff, home nurses and the Sponsor(s) and their agents. This confidentiality is extended to

cover testing of biological samples and genetic tests in addition to the clinical information relating to participating patients.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

14.5 Treatment Plan in The Event of Study Discontinuation

In the event the study is prematurely discontinued, arrangements will be made for the patients' care to continue according to local standard clinical practice. Any patient will have an Early Termination visit scheduled and the assessments listed in Section 10.10 performed.

For any patient administered the IMP, even partially, every effort will be made to follow up the patient for up to 5 years post-IMP administration with at least one phone call every 6 months.

14.6 Future Use of Stored Specimens

Samples will not be labelled with information that directly identifies the patient but will be coded with the identification number for the patient.

Collected samples may be transferred for analysis to the Sponsor, or to other laboratories working for the Sponsor.

Biological samples will be stored for the time established by regulatory requirements or destroyed after the final clinical study report has been finalized if storage is not required.

Some samples require long term storage after the study ends.

There might be a new request for these samples to be used for purposes related to the QA of the laboratory tests described in this protocol, in which case they will be used for this purpose. This may include the assessment of the quality of current tests, the maintenance or improvement of these tests, the development of new test methods for the

markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.

If study results suggest that further investigations using stored biological samples are warranted, these tests might be carried out on an exploratory basis. In addition, biological samples may be used by the Sponsor or their research partners for further research that is not related to the disease or the product under study. This testing will be done on anonymized samples (meaning that any identification linking the patient to the sample is destroyed). Patients will be asked to check a box on the informed consent form for this optional testing and refusal of consent will not affect their possibility of participating in the study.

14.7 Insurance

The Sponsor has established an insurance policy for the total anticipated duration of the study, covering the participants with respect to the risks involved in taking part in this study in accordance with this protocol. In the case of injury or disability deriving from participation in the study, patients are requested to inform the Investigator or his/her staff responsible for the study at the institution without delay.

15 PUBLICATION POLICY

The Sponsor shall retain the ownership of all data. When the study is complete the Sponsor shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to Regulatory Authorities. All proposed publications based on this study must be subject to the Sponsor's approval requirements.

As per local requirements, the study will be registered with publicly searchable databases including ClinicalTrials.gov. A summary of the study results will be published on the ClinicalTrials.gov and EUDRACT websites.

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17 APPENDICES

17.1 Blood Sample Volume Tables

17.1.1 Screening

Table 17 Blood Sample Volumes at Screening 1 (V1A) and Screening 2 (V1B)

Assessment	Blood Volume (mL)		Total Volume (mL)
Visit	Screening 1 (Visit 1A)	Screening 2 (Visit 1B)	
Tuberculosis tests (QuantiFERON®-TB Gold)	-	4	**4**
ATP7B genotype	4		**4**
Viral serology	-	11	**11**
Alpha fetoprotein	-	3	**3**
Blood biochemistry (including lipid panel) and coagulation	**11**	11	**22**
Hematology	5	5	**10**
Central Laboratory: Liver biochemistry panel	5	5	**10**
Ceruloplasmin and total Cu	7	7	**14**
Anti-AAV3B capsid neutralizing antibodies	4	4	**8**
Total volume per visit	36	50	**86**

Abbreviations: AAV3B= Adeno-Associated Virus serotype 3B; ATP7B= *Copper-transporting P-type ATPase*; Cu= Copper; V= Visit.

17.1.2 Baseline (V2) to Week 12 (V29)

Table 18 Blood Sample Volumes from Baseline (V2) to Week 12 (V29)

Assessment	Blood Volume (mL)																Total Volume (mL)
Visit	V2 D-7	V3 D-3	V4 D-2	V5 D-1	V6 D1	V7 D2	V8 W2	V9 W3	V10 W4	V11-17 W4-7	V18 W8	V19-25 W8-11	V 26 W12	V27 W12	V28 W12	V29 W12	
Pregnancy test	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**2**
Blood biochemistry (with lipid panel at Week 4) and hematology, coagulation	16	-	-	-	-	-	16	-	16	-	-	-	16	-	-	-	**64**
Lipid panel											5						**5**
Central Laboratory: Liver biochemistry panel	5	-	-	-	-	-	5	-	5	-	5	-	5	-	-	-	**25**
Local Laboratory: Liver biochemistry panel	5	-	-	-	-	5	5	5	5	5 per visit	5	5 per visit	5	-	-	5	**110**
[redacted]																	
Sirolimus level test	-	3	-	-	-	-	3	-	3	-	3	-	-	-	-	-	**12**
Ceruloplasmin CuEXC Total Cu	7	-	-	-	-	-	-	-	7	-	-	-	7	-	-	-	**21**
Total Cu Ceruloplasmin bound Cu *(Cp-Cu ANCC)*	12	-	-	-	-	-	-	-	12	-	-	-	12	-	-	-	**36**
Anti-AAV3B capsid neutralizing antibodies	-	-	-	-	4	-	-	-	4	-	-	-	-	-	-	-	**8**
Vector shedding: blood	-	-	-	1	-	1	1	-	1	-	1	-	1	-	-	1	**7**
ELISA: anti-AAV3B capsid and miniATP7B antibodies	4	-	-	-	-	-	-	-	4	-	4	-	4	-	-	-	**16**

Table 18 Blood Sample Volumes from Baseline (V2) to Week 12 (V29)

Assessment	Blood Volume (mL)																Total Volume (mL)
Visit	V2 D-7	V3 D-3	V4 D-2	V5 D-1	V6 D1	V7 D2	V8 W2	V9 W3	V10 W4	V11-17 W4-7	V18 W8	V19-25 W8-11	V 26 W12	V27 W12	V28 W12	V29 W12	
ELISpot: AAV3B capsid and miniATP7B	50	-	-	-	-	-	-	-	50	-	50	-	50	-	-	-	**200**
Total volume per column	101	33	20	21	24	6	30	5	107	35	73	35	130	20	20	26	**686**

Abbreviations: AAV3B= Adeno-Associated Virus serotype 3B; ANCC= Accurate Non-Ceruloplasmin-bound Cu; ATP7B= *Copper-transporting P-type ATPase*; Cp-Cu= Ceruloplasmin-bound copper; Cu= Copper CuEXC= Exhangeable Copper; D= Day; ELISA= Enzyme-Linked immunosorbent Assay; ELISpot= Enzyme-linked ImmunoSpot; [redacted]; V=Visit D=Day W=Week

17.1.3 Week 13 (V31) to Week 52 (V46)

Table 19 Blood Sample Volumes from Week 13 (V31) to Week 52 (V46)

Assessment	Blood Volume (mL)														Total Volume (mL)
Visit	V31 W13	V33 W15	V34 W16	V35 W20	V36 W24	V37 W28	V38 W32	V39 W36	V40 W36	V41 W36	V42 W36	V44 W40	V45 W44	V46 W52	
Blood biochemistry and hematology, coagulation	--	-	-	-	16	-	-	16	-	-	-	-	-	16	**48**
Central Laboratory: Liver biochemistry panel	-	-	-	-	5	-	-	5	-	-	-	-	-	5	**15**
Local Laboratory: Liver biochemistry panel	5	5	5	5	5	5	5	5	-	-	5	5	5	5	**60**
[redacted]															
Ceruloplasmin CuEXC Total Cu	-	-	-	7	7	-	-	7	-	-	-	-	7	7	**35**
Total Cu Ceruloplasmin bound Cu *(Cp-Cu ANCC)*	-	-	-	12	12	-	-	12	-	-	-	-	12	12	**60**
Anti-AAV3B capsid neutralizing antibodies	-	-	-	-	-	-	-	-	-	-	-	-	-	4	**4**
Vector shedding: blood	-	-	-	-	1	-	-	1	-	-	1	-	-	1	**4**
Total volume per visit	5	5	5	24	46	5	5	76	20	20	26	5	24	50	**316**

Abbreviations: AAV3B= Adeno-Associated Virus serotype 3B; ANCC= Accurate Non-Ceruloplasmin-bound Cu; Cp-Cu= Ceruloplasmin-bound copper; Cu= Copper; CuEXC= EXChangeable Copper; [redacted]; V=Visit W=Week

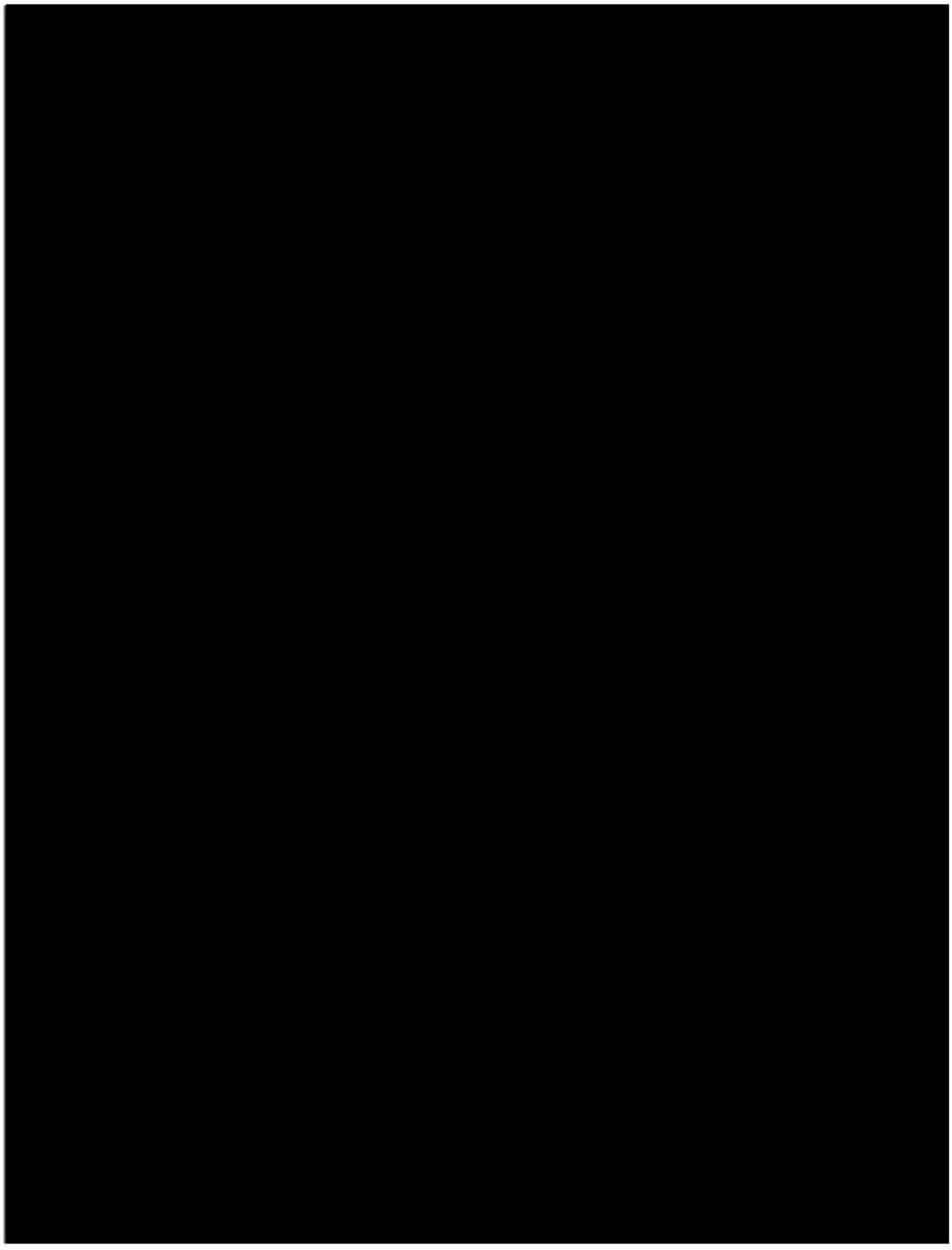
17.1.4 Year 2 to Year 5 Follow-up

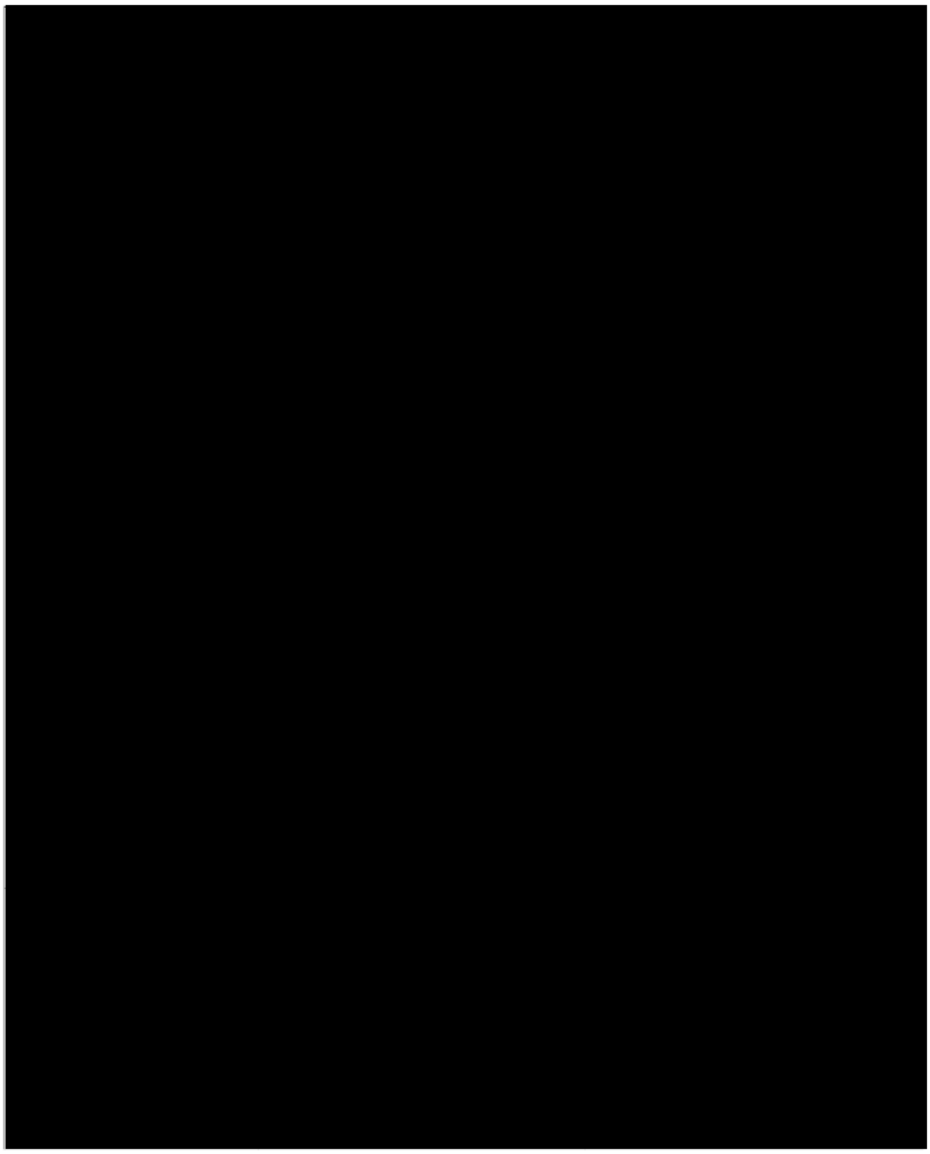
Table 20 Blood Sample Volumes from Year 2 to Year 5 Follow-up

Assessment	Blood Volume (mL)										Total Volume (mL)
Visit	V47 M15	V48 M18	V49 M21	V50 M24	V51 M30	V52 M36	V53 M42	V54 M48	V55 M54	V56 M60	
Blood biochemistry and hematology, coagulation	16	16	16	16	16	16	16	16	16	16	**160**
Central Laboratory: Liver biochemistry panel	5	5	5	5	5	5	5	5	5	5	**50**
Ceruloplasmin CuEXC Total Cu	7	7	7	7	7	7	7	7	7	7	**70**
Total Cu Ceruloplasmin bound Cu *(Cp-Cu ANCC)*	12	12	12	12	12	12	12	12	12	12	**120**
Total volume per visit	40	40	40	40	40	40	40	40	40	40	**400**

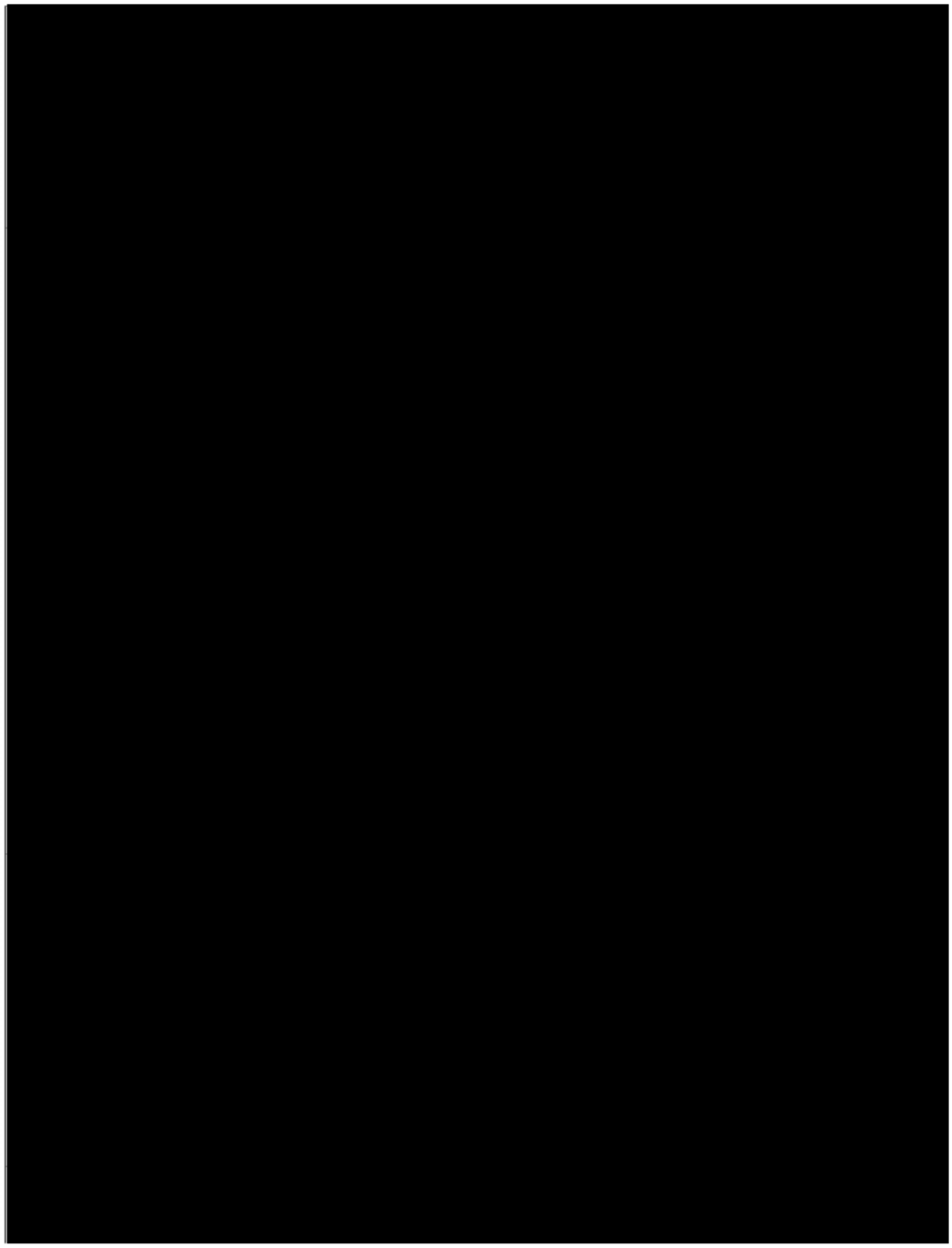
Abbreviations: ANCC= accurate non-ceruloplasmin-bound Cu; Cp-Cu= Ceruloplasmin-bound copper; Cu= Copper; CuEXC= exchangeable copper; V=Visit M=Month

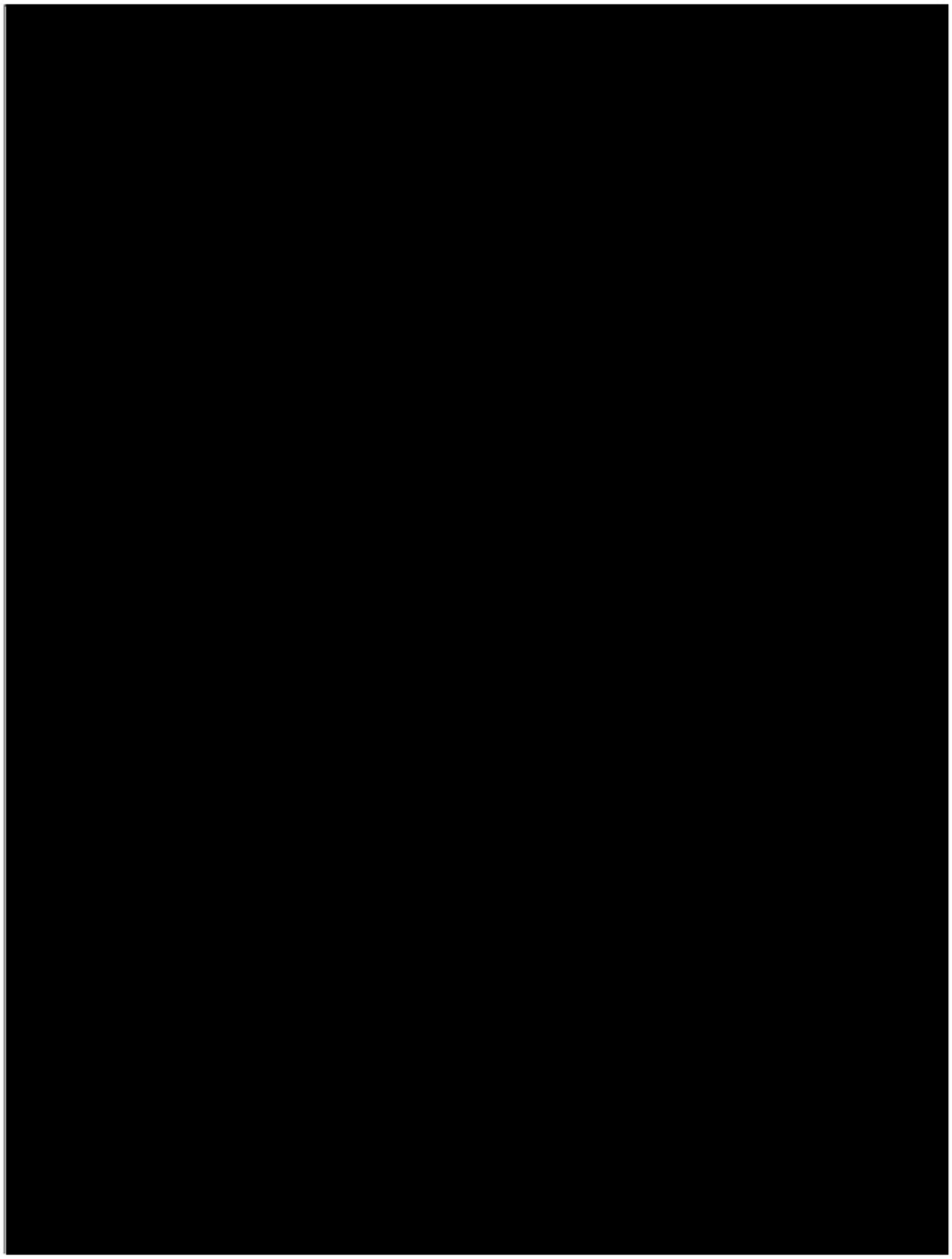
17.2 Modelling and Simulation

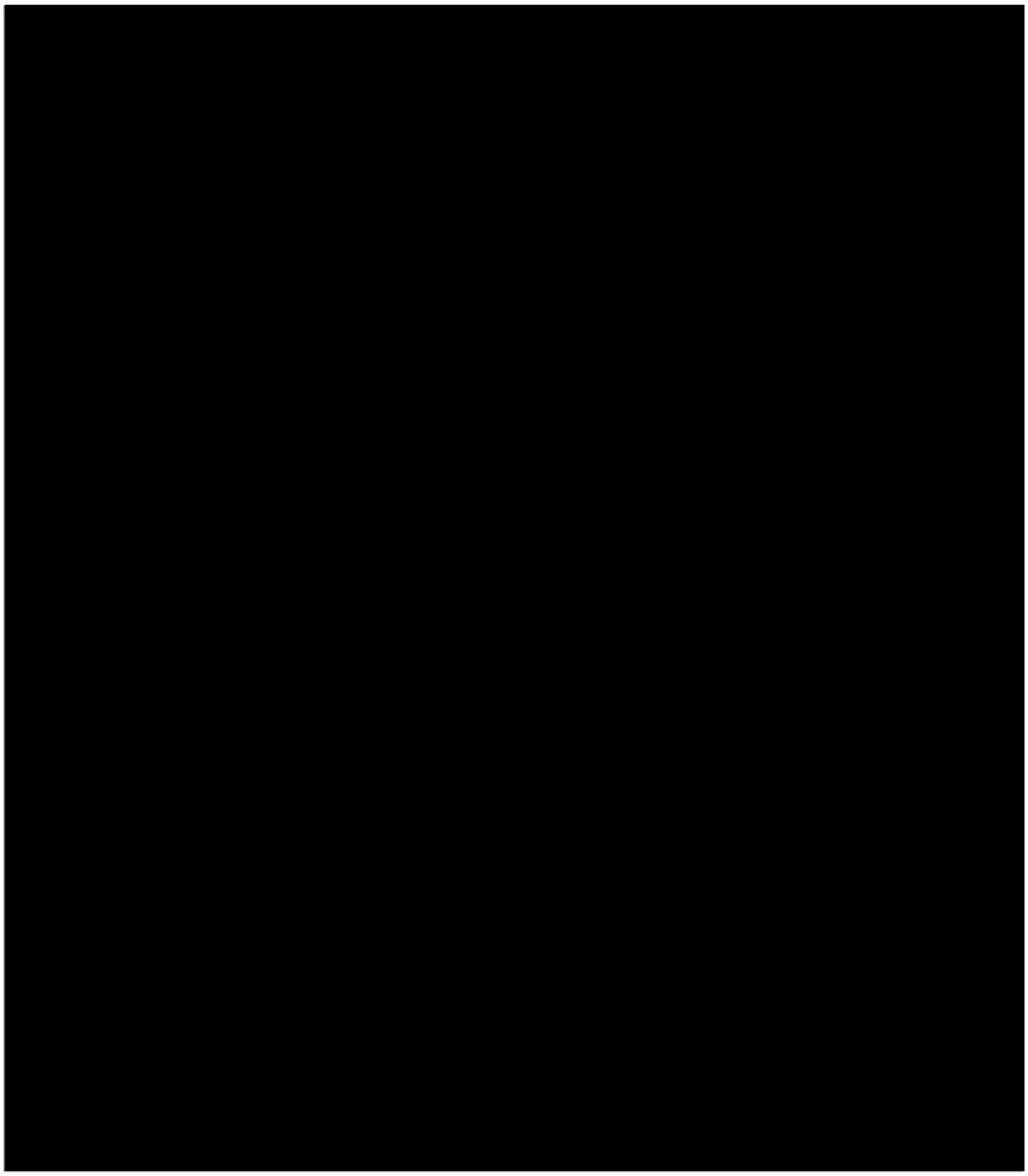


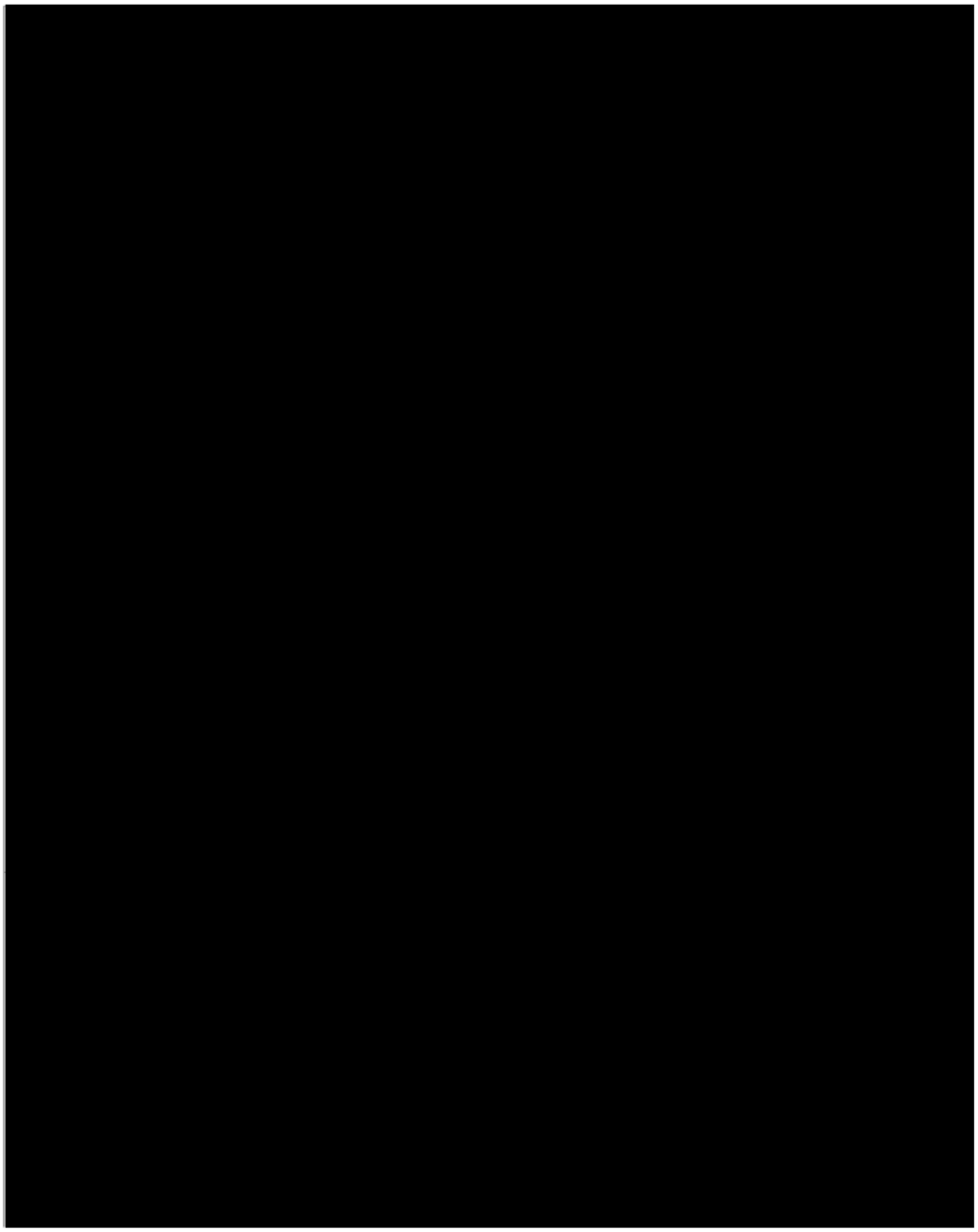


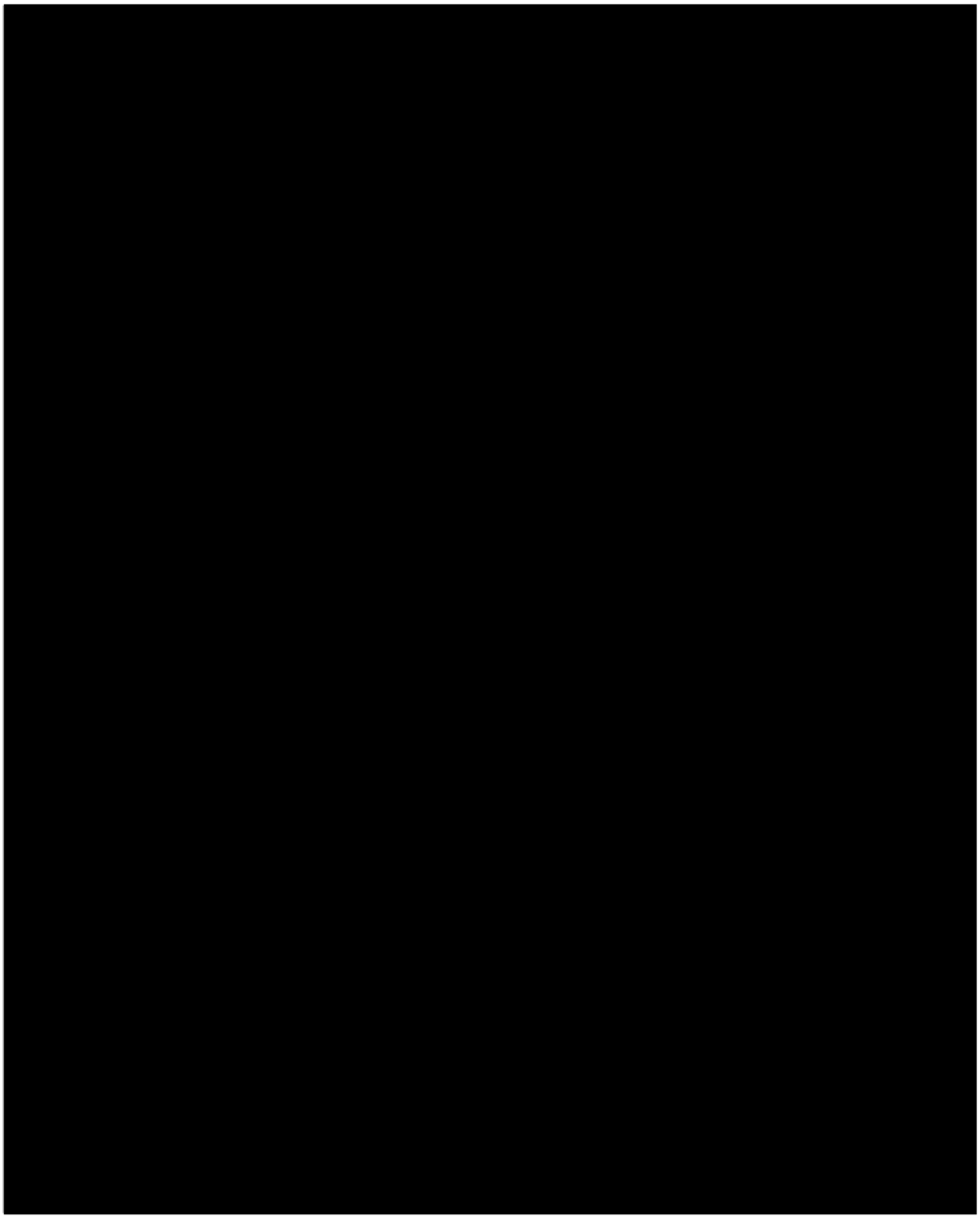
GTW_SummarySimulations_Responder_Updtmodel_210203 01-Feb-2021

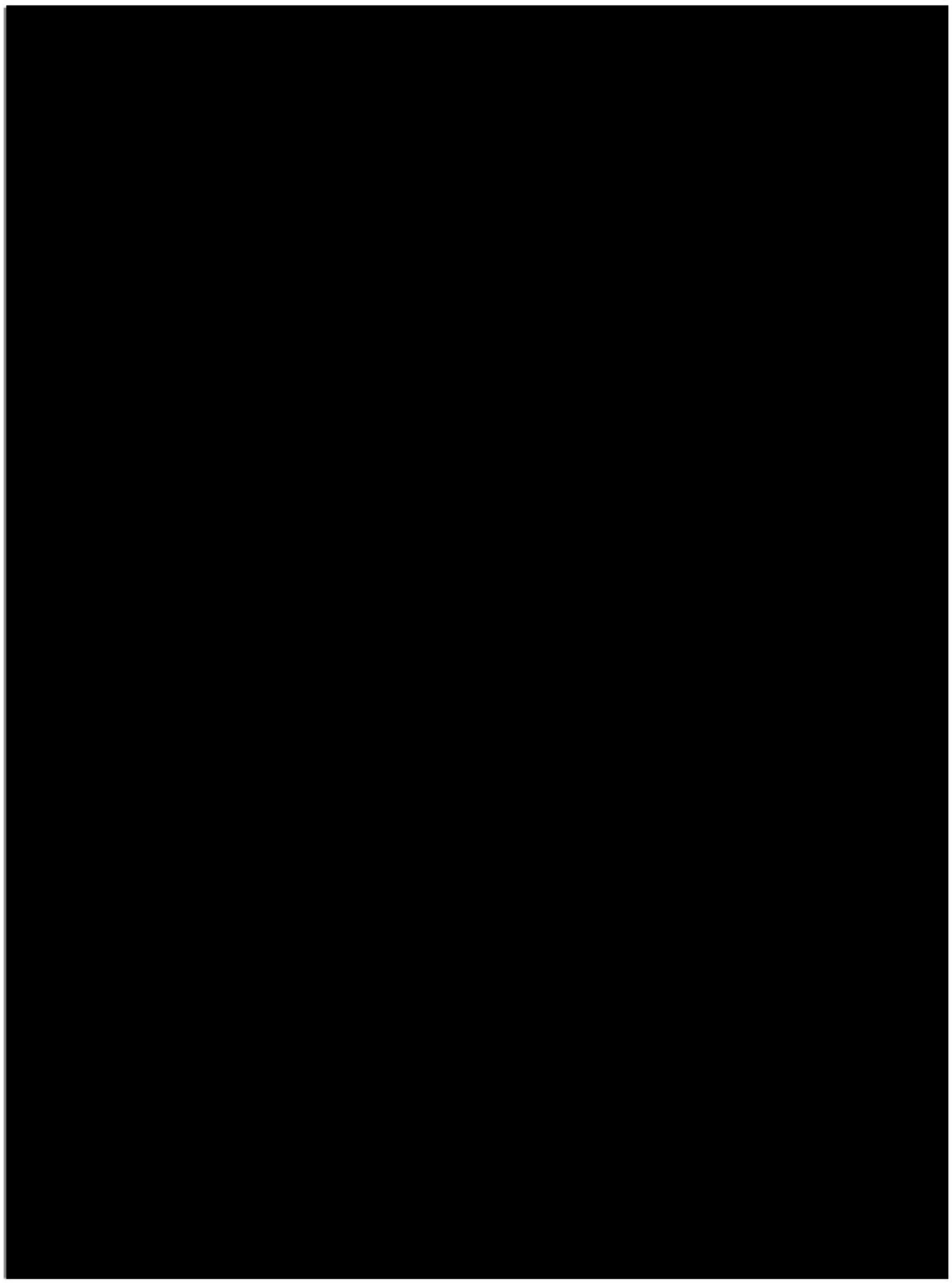


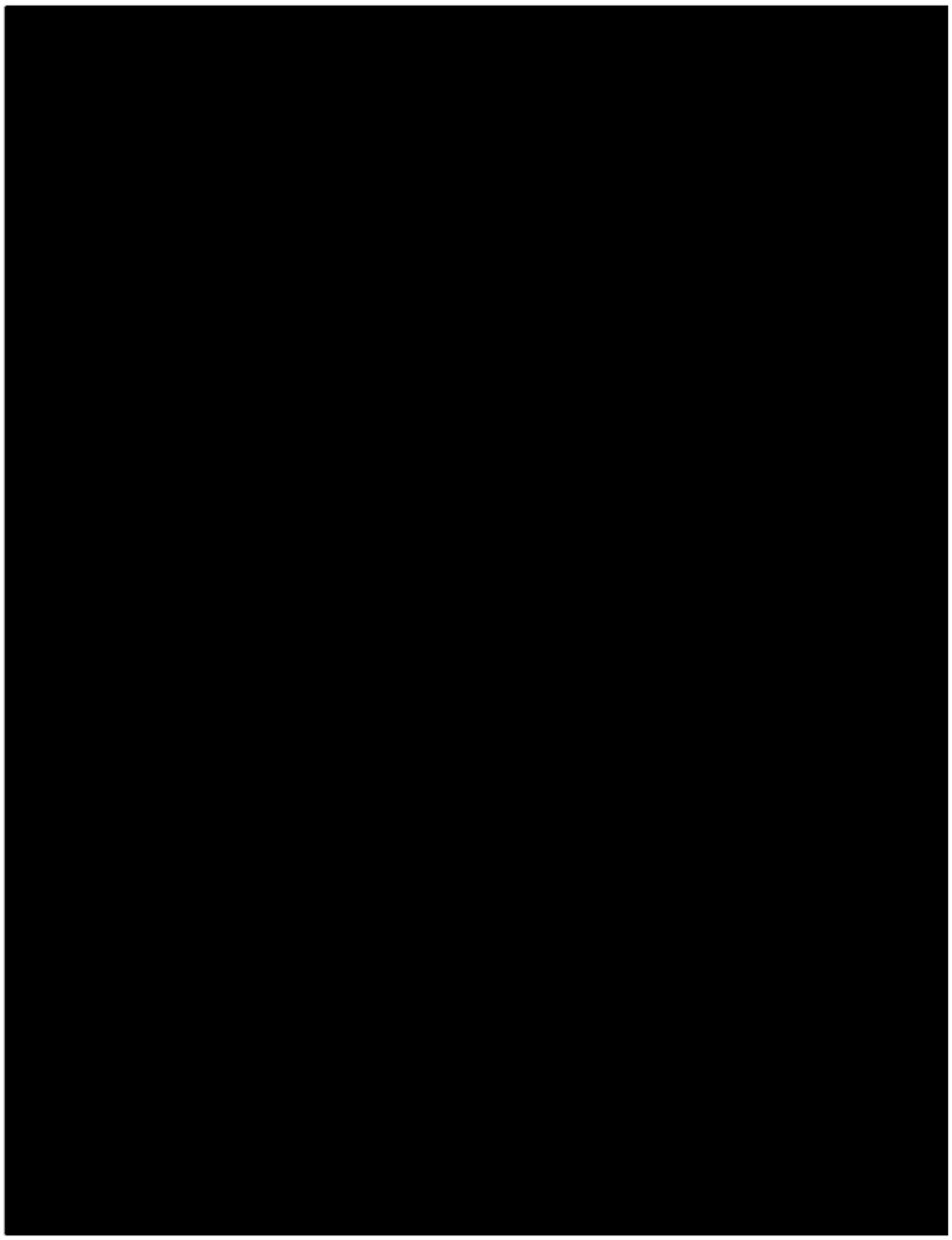












GTW_SummarySimulations_Responder_Updtmodel_210203 01-Feb-2021

17.3 Low-copper Diet

Low-copper diet, from Schilsky et al, 2022 (AASLD): Foods with very high concentrations of copper (shellfish, nuts, chocolate, mushrooms, and organ meats) generally should be avoided, at least in the first year of treatment. Diets deficient in copper may delay the onset of the disease and control disease progression, but dietary management is not sufficient to treat patients.