A Phase 1, Single-Center, Randomized, 3-Period Crossover Study in Healthy Volunteers to Evaluate the Absorption of WTX101 After Single Dose Administration of an Enteric Coated Formulation with and without food and a Non-Coated Formulation Coadministered with a Proton Pump Inhibitor without Food

Unique Protocol ID:	WTX101-102
NCT Number:	NCT05319912
Date of Protocol:	24 February 2014

16. Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Celerion Project No.: CA13895

Sponsor Project No.: WTX101-102

US IND No.: 119,006

A Phase 1, Single-Center, Randomized, 3-Period Crossover Study in Healthy Volunteers to Evaluate the Absorption of WTX101 After Single Dose Administration of an Enteric Coated Formulation with and without food and a Non-Coated Formulation Coadministered with a Proton Pump Inhibitor without Food

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

All information concerning the Investigational Product supplied by Wilson Therapeutics in connection with this study, and not previously published, is considered confidential and proprietary information. This information includes the Investigator's Brochure, protocol and case report forms. This confidential information shall remain the sole property of Wilson Therapeutics, shall not be disclosed to others without prior written consent from Wilson Therapeutics, and shall not be used except in the performance of this study.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Wilson Therapeutics in connection with the development of the Investigational Product. This information may be disclosed as deemed necessary by Wilson Therapeutics.

The Investigator is obliged to provide Wilson Therapeutics with complete test results and all data derived from this study. Only Wilson Therapeutics may make information obtained during this study

available to the physicians and to the regulatory agencies, except as required by regulation.

1 PROTOCOL REVISION HISTORY

24 Feb 2014 By PPD	Final Version

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Phase 1, Single-Center, Randomized, 3-Period Crossover Study in Healthy Volunteers to Evaluate the Absorption of WTX101 After Single Dose Administration of an Enteric Coated Formulation with and without food and a Non-Coated Formulation Coadministered with a Proton Pump Inhibitor without Food

SPONSOR:

Wilson Therapeutics USA, Inc.
P.O. Box 17757
Urbana, Illinois 61803 - USA

Wilson Therapeutics, AB
Västra Trädgårdsgatan 15
11453 Stockholm, Sweden

SPONSOR'S REPRESENTATIVE:

PPD
11 Ridgefield Road
Winchester, Massachusetts, 01890, USA
Tel.: PPD
E-mail:
PPD

The clinical trial pro PPD pproved by the Sponsor:

27 FEB 2014
Date

CELERION PRINCIPAL INVESTIGATOR AND CLINICAL SITE:

PPD
621 Rose Street
Lincoln, Nebraska 68502, USA
Tel.: PPD
Fax:
E-mail: PPD

Investigator's Statement:

I have read and understood the information in this protocol and agree to conduct the trial according to the protocol (subject to any amendments). Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of subjects.

I agree to conduct in person or to supervise the trial.

I agree to ensure that all that assist me in the conduct of the study are aware of their obligations.

PPD

26 Feb 2014
Date

3 ADDITIONAL KEY CONTACTS FOR THE STUDY

Protocol Author	PPD to Wilson Therapeutics AB Västra Trädgårdsgatan 15 S-11153 Stockholm, Sweden Tel: PPD E-mail: PPD
Clinical Contact	PPD Wilson Therapeutics AB Västra Trädgårdsgatan 15 S-11153 Stockholm, Sweden Tel: PPD Fax: PPD E-mail: PPD
Certified Clinical Laboratory	Celerion 621 Rose Street Lincoln, Nebraska 68502, USA Contact: PPD Tel.: PPD Fax: PPD
Certified Bioanalytical Laboratory	QPS Netherlands B.V. Petrus Campersingel 123 NL-9713 AG Groningen The Netherlands Telephone: PPD FAX: PPD Email: PPD
Pharmacokinetic and Statistical Analyses	PPD Kramer Consulting LLC 14313 Outpost Way North Potomac, Maryland 20878-4352, USA

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5 SYNOPSIS

Compound:	WTX101
Clinical Indication:	Wilson Disease (WD)
Study Phase and Type:	Phase 1 – Drug absorption and food-effect
Study Objectives:	The primary objectives of the study are to evaluate: • The effect of dosing with an Enteric coated (EC) tablet versus dosing with the current non-coated capsule administered with a proton pump inhibitor (PPI; omeprazole) under fasting conditions on the absorption of WTX101. • The effect of dosing an EC tablet with and without food on the absorption of WTX101 • The safety and tolerability of WTX101.
Summary of Study Design:	This will be a single-center, open-label, randomized, 3-period, 3-treatment, 6-sequence crossover study evaluating the absorption of WTX101 after single doses in healthy subjects based on the measurement of plasma total molybdenum (Mo). This study consists of a screening phase, three periods with similar procedures, and an end-of-study (EOS) visit. Screening of subjects will occur within 28 days prior to the first WTX101 dose. Subjects randomized to receive PPI in Period 1 (Treatment C) will report to the Clinical Research Unit (CRU) on Day -5, i.e. 5 days prior to first dosing with WTX101, to receive a morning dose of omeprazole under fasting conditions. These subjects will be given a container with omeprazole doses and will continue once daily (QD) administration of omeprazole under fasting conditions on an outpatient basis, until their return to the CRU for check-in on Day -1. To ensure that the planned number of subjects are dosed with WTX101 on Day 1 of Period 1, stand-by subjects will also receive QD doses of omeprazole, as described above. Should any subject withdraw from the study after omeprazole administration, but before receiving WTX101 in Period 1, they will be replaced with a stand-by subject. Subjects randomized to receive PPI in Periods 2 or 3 will receive the container with omeprazole doses prior to discharge from the CRU after the 192-hour post-dose procedures in Period 1 or Period 2, as appropriate. These subjects will initiate

	QD administration of omeprazole under fasting conditions at home the following day and continue until their return to the CRU for their next admission. In each of the 3 periods, all subjects (Treatments A, B, and C) will be admitted to the CRU on Day -1, and will receive WTX101 EC tablets alone under fasting conditions (Treatment A); WTX101 EC tablets alone under fed conditions (Treatment B); or, omeprazole under fasting conditions followed by WTX101 non-coated capsules under fasting conditions (Treatment C). Pharmacokinetic (PK) sampling (for the measurement of plasma concentrations of total elemental Molybdenum (Mo)) will be obtained at the following timepoints while subjects remain in the CRU: Time 0 (within 1 hour predose), and then 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 14, 16, 24, 36, and 48 hours postdose. Subjects will be discharged on Day 3 following the 48 hours postdose procedures, unless medically necessary to extend confinement to 72 hours. Subjects will be required to return to the CRU for outpatient visits on 6 consecutive days (Days 4, 5, 6, 7, 8 and 9) in each period, for subsequent PK sampling and procedures at: 72, 96, 120, 144, 168, and 192 hours postdose. The exact time points for collection of PK samples may be amended following evaluation of the data from the ongoing Study WTX101-101. If this is required it will be confirmed prior to study start. However, the total volume of blood taken for PK sample analysis will not be increased from that stated in Section 11.1.5.3 The washout between WTX101 doses in each period will be at least 14 days. Subjects will return to the CRU 14 days (+/-2 days) after the final study medication administration for an EOS visit with follow-up procedures, and to determine if any adverse event (AE) has occurred since the last study visit. Subjects who terminate the study early should be seen and assessed by an Investigator, whenever possible, to undergo the procedures associated with the EOS visit. Safety will be monitored throughout the study.
Study Duration:	Subjects who complete the study may be involved in the study for up to 48 days excluding screening (Day -5 of period one to the EOS visit). The study has a screening phase (Day -28 to Day -5 of Period 1); three study periods (Periods 1, 2, and 3 comprised of Day -5 to Day 9); and, an EOS visit 14 days (+/- 2 days) following the final administration of WTX101. Each period will be separated by a washout of at least 14 days

	between administrations of WTX101. The entire study is expected to last 48 days from the first subject dosed to last subject-last visit (LSLV).
Blinding:	This is an open-label study.
Number of Subjects:	Eighteen (18) healthy, non-tobacco using adult male and female subjects between 19 and 55 years of age (inclusive).
Dosage, Dosage Form, Route, and Dose Regimen:	WTX101 will be supplied as non-coated capsules or EC tablets for oral administration. Each WTX101 non-coated capsule (hydroxypropyl methylcellulose [HPMC]) contains 30 mg of bis-choline tetrathiomolybdate and the following excipients: anhydrous di-calcium phosphate and anhydrous sodium carbonate. Each WTX101 EC tablet contains 30 mg of bis-choline tetrathiomolybdate and the following excipients: tri-calcium phosphate, sodium carbonate, sodium starch glycolate, magnesium stearate. WTX101 EC Tablets are coated with Opadry 03K19229 Clear and Acryl-Eze White. Dose regimens are described as follows: Treatment A: 60 mg WTX101 (2 x WTX101 EC tablets, 30mg) at Hour 0 on Day 1 following an overnight fast. Treatment B: 60 mg WTX101 (2 x WTX101 EC tablets, 30mg) at Hour 0 on Day 1, 30 minutes after the start of a high-fat breakfast, preceded by an overnight fast. Treatment C: 20 mg omeprazole (1 x 20 mg delayed-release capsule) QD on the mornings of Days -5 to -1 following an overnight fast, 20 mg omeprazole capsule at Hour -1 on Day 1 following an overnight fast, and 60 mg WTX101 (2 x WTX101 non-coated capsules, 30mg) at Hour 0 on Day 1 All study medications (WTX101 non-coated capsules, WTX101 EC tablets and Omeprazole) should be administered orally with approximately 240 mL of room temperature water. The EC Tablets and non-coated capsules must be swallowed whole.
Stopping Rules	Safety-related individual- and study-specific stopping criteria are detailed below: Dosing will be discontinued for an individual subject experiencing any National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (CTCAE v. 4.0) Grade 3 or higher event that is assessed as treatment-related.* The study will be stopped if:

	• 2 or more subjects experience an NCI CTCAE v. 4.0 Grade 3 or higher event that is assessed as treatment-related*, or if • 1 or more subjects experience a Grade 4 or higher event that is assessed as treatment-related*. *Treatment-related is defined as likely, probably, or possibly related per Section 11.1.6.3 of the protocol.
Key Assessments:	**Pharmacokinetics:** The plasma concentrations of WTX101 will be measured by plasma concentrations of total elemental Mo. The following PK parameters will be calculated for total Mo in plasma: AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, λz, $t_{½}$, CL/F, and Vz/F. Descriptive statistics will be computed for all parameters. The parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} will be compared among treatments using an analysis of variance (ANOVA) on the ln-transformed values. T_{max} will be compared among treatments using non-parametric statistic, i.e. Wilcoxon Rank Sum. **Safety:** Safety will be monitored through physical examinations, vital sign measurements, electrocardiograms (ECGs), AEs and clinical laboratory tests. Summary statistics for the laboratory safety tests, ECGs, and/or vital signs will be computed and provided.

6 STUDY EVENTS FLOW CHART

Study Procedures[a]	S[b]					C-I[c]		Study Days in Each Period[d]																												EOS or ET[e]
Days →	-28	-5	-4	-3	-2	-1		1																					2	3	4	5	6	7	8	9	
Hours →						AM	PM	Pre dose	0[f]	1	2	3	3.5	4	4.5	5	6	7	7.5	8	8.5	9	9.5	10	12	14	16[g]	24	36	48	72	96	120	144	168	192	
Administrative Procedures																																					
Informed Consent	x																																			
Inclusion/Exclusion Criteria	x						x																													
Medical History	x																																			
Randomization[h]									x																											
Safety Evaluations / Others																																					
Physical Examination[i]	x						x																													x
Height	x																																			
Weight	x						x																													x
12-Lead ECG	x						x	x		x				x						x					x			x								x
Vital Signs (HR, BP, RR & T)	x						x	x		x				x						x					x			x								x
Hem, Chem, UA, and Coag[j]	x						x																						x							x
Serum Cp and Cu	x																																			
Serum Preg (females only)	x						x																													x
FSH (postmen females only)	x																																			
Urine Alcohol and Drug Screen	x						x																													
HIV/Hepatitis Screen	x																																			
AE Monitoring		<----------x---------->																																		
ConMeds		<----------x---------->																																		
Study Medication Administration / PK samples																																					
PPI Administration[k]		x	x	x	x	x		x																													
WTX101 Administration									x																												
Blood for Plasma Total Mo (PK)[l]								x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Other Procedures																																					
High-Fat Breakfast[m]								x																													
Confinement in the CRU								<----------x---------->																												
Return Visits		x																													x	x	x	x	x	x	x

a. For details on study procedures, refer to Section 11.

b. Within 28 days of WTX101 first administration.

c. Subjects will be admitted to the CRU at least 10 hours prior to WTX101 dosing.

d. Each period will be separated by a washout of at least 14 days between WTX101 doses.

e. Subjects will be required to return to the CRU approximately 14 days (±2 days) following the final dose of study medication for an EOS evaluation. In the event of early termination, the procedures listed at the end of the study will be performed prior to subject discharge.

f. Hour 0 corresponds to the time of WTX101 administration. Unless stated otherwise, times listed are in relation to WTX101 dosing.

g. The 16-hour time point following WTX101 dosing on Day 1 will be either on Day 1 or Day 2, depending on the time of dosing on Day 1.

h. Please refer to Section10.5.2 for randomization details.

i. A full physical examination will be performed at screening, check-in, and at the end of the study or upon early termination. A symptom-driven physical examination may be performed at other times, at the Principal Investigator's (PI) discretion.

j. Samples for serum chemistry will be obtained following a fast of at least 8 hours at screening, and of at least 6 hours at check-in. In case of dropouts, rechecks and postdose serum chemistry, subjects may not have fasted for 6 or 8 hours before the serum chemistry sample is taken.

k. Subjects randomized to receive Treatment C in Period 1 will be required to come to the CRU in the morning of Day -5 of Period 1 to receive their first dose of PPI (omeprazole). They will receive a properly labeled container which will contain omeprazole doses to be self-administered at home on Days -4 to -1. At the end of Periods 1 and 2, subjects will receive a container with omeprazole doses for self-administration of doses on Days -5 to -1, if they are randomized to receive Treatment C in the next period. Each omeprazole dose self-administered should be taken under fasting conditions, at a time corresponding to Hour -1 relative to the time of dosing WTX101 on Day 1 (Hour 0). Subjects will be given paper diaries to record their self-administered omeprazole doses and whether the dose was administered with food and must return the container (empty or not) and diary at the next visit. The data from the diary will then be transcribed into the eCRF. Home dosing will be monitored daily via attempted contacts (phone calls, texts or emails) whereupon subjects will be reminded to take their medication and queried about AE occurrence.

l. The exact time points for collection of PK samples may be amended following evaluation of the data from the ongoing Study WTX101-101. If this is required it will be confirmed prior to study start. However, the total volume of blood taken for PK sample analysis will not be increased from that stated in Section 11.1.5.3

m. Subjects randomized to receive Treatment B will receive breakfast, to be initiated at Hour -0.5 and consumed entirely within the 30 minutes prior to dosing.

Abbreviations: AE = Adverse Event, BP = Blood Pressure, Chem = Serum Chemistry, C-I = Check-in, Coag = Coagulation, ConMeds = Concomitant Medication Monitoring, Cp = Cerulplasmin, CRU = Clinical Research Unit, Cu = Copper, ECG = Electrocardiogram, EOS/ET = End of Study or Early Termination, FSH = Follicle Stimulating Hormone, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart Rate, Mo = Molybdenum, PI = Principal Investigator, PK = Pharmacokinetics, Postmen = Postmenopausal, PPI = Proton Pump Inhibitor, RR = Respiration Rate, S = Screening, Serum Preg = Serum Pregnancy Test, T = Temperature, UA = Urinalysis.

7 ABBREVIATIONS

aPTT	Activated partial thromboplastin time
ADL	Activity of daily living
AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the plasma concentration versus time curve
AUC_{0-t}	Area under the plasma concentration versus time curve to the last measurable concentration (t)
AUC_{0-inf}	Area under the plasma concentration versus time curve to infinity
BMI	Body Mass Index
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent oral clearance
cm	Centimeter
C_{max}	Maximum measured plasma concentration
Cp	Ceruloplasmin
CRU	Clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
Cu	Copper
CV	Coefficient of variation
EC	Enteric Coated
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End-of-study
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GLSM	Geometric least-squares means
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus

HIV	Human immunodeficiency virus
HPMC	Hydroxypropyl methylcellulose
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICP-MS	Inductively-coupled plasma mass spectrometry
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
λz	Apparent terminal elimination rate constant
kg	Kilogram
LSLV	Last subject-last visit
µg	Microgram
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
Mo	Molybdenum
MTD	Maximum tolerated dose
N	Number of subjects
NCI	National Cancer Institute
No.	Number
NOAEL	No observed adverse effect level
oz	Ounce
PI	Principal Investigator
PK	Pharmacokinetic(s)
PKAP	Pharmacokinetic Analysis Plan
PPI	Proton pump inhibitor
PT	Prothrombin Time
QA	Quality assurance
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
t_{max}	Time of the maximum measured plasma concentration

$t_{½}$	Apparent terminal elimination half-life
US	United States
USA	United States of America
Vz/F	Apparent oral volume of distribution
WD	Wilson Disease

8 BACKGROUND AND RATIONALE

8.1 Background

WTX101 (bis-choline tetrathiomolybdate) is being developed by Wilson Therapeutics for the treatment of Wilson Disease (WD). WD is a rare autosomal-recessive disorder caused by mutations in the ATP7B gene, resulting in a disturbed copper (Cu) metabolism. In the affected patients, Cu accumulates in the liver and in other tissues including the central nervous system. Left untreated, morbidity is progressive and the condition is eventually fatal.

The mechanism of action of tetrathiomolybdate differs in several aspects from currently existing WD therapeutics:

- The tetrathiomolybdate anion binds Cu^{2+} with high affinity and has high selectivity to Cu compared with other divalent cations.
- Thiomolybdates can enter hepatocytes and bind and remove Cu from metallochaperones (e.g., metallothionein).
- Tetrathiomolybdate binds Cu *via* the formation of Cu-tetrathiomolybdate-protein complexes, which are rapidly excreted, primarily *via* bile.

Published data suggest that this differentiated mechanism of action could translate into an improved clinical profile. Previous clinical studies with ammonium tetrathiomolybdate in WD patients indicate that tetrathiomolybdate might lower non-ceruloplasmin [Cp]-bound Cu faster than D penicillamine (Cuprimine®, Depen®) and trientine hydrochloride (Syprine®), which are orally administered chelating agents currently used to treat WD, as well as be associated with a reduced risk of neurologic deterioration after initiation of treatment in WD patients with neurologic disease.[1, 2, 3]

Tetrathiomolybdate has previously been investigated in several clinical trials. Initially, researchers at University of Michigan used ammonium tetrathiomolybdate in trials in WD patients. In addition, there have been a number of clinical trials in other indications; mainly in oncology patients but also including patients with macular degeneration or primary biliary cirrhosis. Some of these studies in non-WD patients were conducted with ammonium tetrathiomolybdate, while some studies conducted by Attenuon LLC (later renamed to Tactic Pharma LLC) used bis-choline tetrathiomolybdate due to the stability issues identified with the ammonium salt form. Based on its better stability, bis-choline tetrathiomolybdate is more suitable for clinical development and commercialization.

The majority of the non-clinical studies were conducted using ammonium tetrathiomolybdate. To support the clinical use of the bis-choline salt form, the comparability of the two salt forms was established in both in vitro and in vivo non-clinical studies. Bridging data suggest that the cation has neither an influence on the mechanism of action of the drug nor any appreciable effect on its pharmacokinetics (PK). Therefore, studies performed with ammonium tetrathiomolybdate can support the use of bis-choline tetrathiomolybdate in the planned clinical development for WTX101.

8.1.1 Non-clinical Safety and Toxicology Summary and Conclusion

The non-clinical package includes data collected using both ammonium and bis-choline tetrathiomolybdate, with the main toxicology studies being carried out with the ammonium tetrathiomolybdate. The active moiety, tetrathiomolybdate anion, is identical for both compounds, the chemical structure is well defined, and no substantial biological effect of the cationic moiety have been observed based on comparability studies in rodents and dogs. In summary, these studies show no substantial differences between the two salt forms that would indicate that non-clinical data obtained using the ammonium tetrathiomolybdate is different from data obtained using bis-choline tetrathiomolybdate.

In accordance with regulatory guidelines, 6-month (rat) and 9-month (dog) repeated-dose studies were performed under Good Laboratory Practice (GLP) conditions. In these studies, ammonium tetrathiomolybdate was administered by gavage to normal rats up to the maximally tolerated dose (MTD). These repeated-dose toxicity studies as well as shorter term studies included separate groups including Cu supplementation of the diet of rats and dogs in an attempt to differentiate the effects induced by tetrathiomolybdate independent of the pharmacologic effects, namely, Cu depletion. Nevertheless, it is emphasized that Cu metabolism is not necessarily comparable between healthy animals, artificially Cu supplemented animals, and WD patients. It is assumed that short-term supplemented Cu is not handled in the same physiological way as long-term excess brought on by patients with WD. Thus, although the safety data collected in healthy animals or even in artificially Cu-supplemented animals is useful in defining a toxicity profile for tetrathiomolybdate, the quantitative dose response extrapolation to humans, and particularly to WD patients, is of limited relevance.

In rats, 4 mg/kg ammonium tetrathiomolybdate (i.e., equivalent to 6.8 mg/kg bis-choline tetrathiomolybdate) administered for 6 months caused minimal anemia, increases in total bilirubin, total bile acids, albumin, and cholesterol as well as degenerate spermatocytes and sperm granuloma in the epididymis, and tibial bone cysts. The anemia, changes in total bilirubin, albumin and cholesterol, as well as tibial cysts were reversible as they were not observed after a one-month recovery period. The increase in total bile acids was partially reversed at the end of the recovery period. Liver and pancreas histopathological changes were observed in a 90-day study without Cu supplements in males dosed at 10 mg/kg but was not accompanied by changes in plasma liver enzyme concentrations.

Anemia, increases in total bile acids and cholesterol were not observed in Cu-supplemented (22 and 110 mg/kg) rats administered 4 mg/kg/day tetrathiomolybdate. Also, a lower incidence and/or severity of the degenerate spermatocytes and tibial cysts were observed in Cu-supplemented rats. These results are interpreted to indicate that these specific pathologic findings are secondary to Cu deprivation, i.e., secondary to the pharmacologic action of tetrathiomolybdate. In Cu-supplemented animals, the no-observed adverse effect level (NOAEL) was established at or above the highest tested dose (>10 mg/kg).

In a 9-month repeat-dose toxicology study in dogs, no signs of local or systemic toxicity were noted up to the highest tested dose of 3 mg/kg. The initial pathology report further points to histopathological findings in the liver of mid and high dosed animals, defining the NOAEL at 0.3 mg/kg, the lowest tested dose. Since similar findings were not noted in rats and the findings were not correlated with any liver enzyme changes, Wilson Therapeutics requested a re-evaluation of the liver slides. According to the re-evaluation (conducted by

two independent pathologists) the only histologic finding in the liver that was attributed to the test item (with or without Cu supplementation), was hemosiderin deposition, which is considered non-adverse and not indicative of hepatocellular injury.

In a shorter term study in dogs, ammonium tetrathiomolybdate at doses of 10 mg/kg and higher were lethal.

Segment I (fertility) and II (developmental) reproductive toxicity studies were conducted in rats and rabbits. The results indicated effects on male fertility; no effects were observed in Cu-supplemented animals and thus, these effects on fertility were considered secondary to Cu deprivation rather than due to an intrinsic effect by the drug. Developmental toxicity was observed in rats and rabbits including malformations in rabbits at 20 mg/kg ammonium tetrathiomolybdate (equimolar to 34 mg/kg bis-choline tetrathiomolybdate); (human equivalent dose 5.5 mg/kg; 330 mg/subject [body weight 60 kg]). The NOAEL (6 mg/kg ammonium tetrathiomolybdate, equimolar to 10.2 mg/kg of bis-choline tetrathiomolybdate) based on teratogenicity and maternal toxicity is equivalent to 1.6 mg/kg bis-choline tetrathiomolybdate in humans (100 mg/human subject).

The full standard package of genotoxicity studies as per regulatory guidance has been conducted. An Ames test was negative and excluded any mutagenic potential for bis-choline tetrathiomolybdate up to the highest tested concentration (5000 µg). An *in vitro* mouse lymphoma assay suggests genotoxic activity at high (cytotoxic) concentrations of ammonium tetrathiomolybdate. However, *in vivo* micronuclei evaluation of bone marrow cells were included in the rat chronic toxicity studies conducted with ammonium tetrathiomolybdate. There was no increase in micronuclei at the highest dose tested (with and without Cu supplementation); 4 mg/kg/day (equimolar to 6.8 mg/kg/day bis-choline tetrathiomolybdate) in rats or 3 mg/kg/day in dogs *in vivo* (equimolar to 5.1 mg/kg/day bis-choline tetrathiomolybdate); available data on bone marrow distribution and toxicity support that the drug reaches the bone marrow.

In summary, the safety profile is acceptable for the proposed single dose healthy volunteer clinical study.

8.1.2 Summary of Safety in Oncology Studies with Bis-Choline Tetrathiomolybdate

Over 150 oncology patients have been treated with bis-choline tetrathiomolybdate, alone or in combination, at doses up to 330 mg/day, for periods of up to 6 months. Overall, bis-choline tetrathiomolybdate was well tolerated in this population. The most frequently reported (Adverse Events) AEs during bis-choline tetrathiomolybdate treatment (initial dose 120-330 mg/day; maintenance dose titrated for toxicity and/or Cp) were fatigue, dizziness, myelosuppression (anemia, leukopenia, neutropenia, lymphocytopenia and/or thrombocytopenia), and gastrointestinal complaints (nausea, vomiting, diarrhea, constipation, flatulence, sulphur eructations, anorexia). Concomitant medication with a proton pump inhibitor (PPI) was found to overcome the gastrointestinal problems.[4]

Dose-limiting toxicities were myelosuppression (anemia and/or neutropenia) and fatigue, and the MTD was defined as 300 mg/day. The degree of myelosuppression appears to be related to dose and duration of high-dose loading, but not to Cp level. Fatigue coincided often with anemia, and the degree of fatigue appeared to be loading dose-dependent and

only Grade 1-2 fatigue was seen at the MTD. Fatigue responded rapidly to dose reductions. These adverse effects are to be expected if copper levels are reduced to below-normal levels. As discussed by Lin *et al*,[5] neutropenia has been described in copper-deficient patients and may be due to arrested development of granulocytes.[6] It is also well established that copper deficiency is essential for iron metabolism and erythropoiesis and copper-deficient animals and humans develop iron deficiency anemia.

8.1.3 Summary of Safety in Wilson Disease Studies with Ammonium Tetrathiomolybdate

In the published, completed studies for ammonium tetrathiomolybdate treatment of WD (N=80), the most commonly reported AEs were changes in hematologic parameters (bone marrow suppression), attributed by the Investigators to overtreatment and resultant Cu deficiency. Also, transient and dose dependent elevation in liver transaminase levels, usually after 4 to 6 weeks, was reported.[1, 2, 3.] These two main side effects were readily reversible by decreasing the dose or giving a drug holiday (data on file at Wilson Therapeutics).

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

This study is designed to meet the objectives outlined in Section 9.

WTX101 is an oral de-coppering agent. It is a bis-choline salt of tetrathiomolybdate, bis[(2-hydroxyethyl)trimethylammonium] tetrathiomolybdate.

In previous studies, coadministration of PPIs has been shown to increase the bioavailability of tetrathiomolybdate (as a consequence of increased gastric pH) and to reduce gastrointestinal side effects.[4] An Enteric Coated (EC) tablet formulation would be expected to offer the same benefits of increased bioavailability and reduced gastrointestinal side effects while avoiding the need to coadminister a PPI.

This study will be conducted as a crossover study, aimed at evaluating the absorption of WTX101 from the EC tablet under fed and fasted conditions and compared to the current non-coated capsule administered with a proton pump inhibitor (under fasting conditions) in order to Confirm the in vivo performance characteristics, including the absorption profile, and food effect of the EC tablet in man.

Subjects will be randomized to one of six treatment sequences to minimize assignment bias. A crossover design is used to control the variability between subjects. The washout period between WTX101 doses is considered sufficient to prevent carryover effects of the treatments.

8.2.2 Rationale for the Dose Selection

The 60 mg WTX101 dose selected for this healthy subject study is well within the dose range demonstrated to be safe in humans. In oncology indications, doses of up to 300 mg WTX101 coadministered with PPIs were well tolerated in studies of up to 6 months in

duration. The oncology patient experience, which identified appropriate measures for safety monitoring, is relevant to healthy subjects as both populations have normal baseline Cu conditions. For these reasons, single doses of 60 mg in healthy subjects are not anticipated to cause any safety issues in this Phase 1 study.

The 60mg WTX101 dose has been used in the ongoing WTX101-101 Phase I study evaluating the bioavailability of WTX101 in healthy subjects after single dose administration of a non-coated capsule with and without a PPI and with a PPI with and without food. The WTX101-101 study is a 3 way cross-over study and healthy subjects have received 60mg doses of WTX101 on 3 occasions. Evaluation of interim safety data in this ongoing study has been performed and no safety concerns have been identified to date.

A once daily (QD) dose of 20 mg omeprazole is consistent with the dosage and administration recommendations for various gastrointestinal conditions.[7]

8.2.3 Rationale for Endpoints

The primary endpoints will be the AUCs and C_{max}, as these PK parameters are the most relevant to characterize the rate and extent of exposure following WTX101 administration - from the treatments to be tested.

Other parameters will also be presented, including: t_{max}, λz, and $t_{½}$, CL/F, and Vz/F.

9 STUDY OBJECTIVES, AND ENDPOINTS

9.1 Study Objectives

The primary objectives of the study are to evaluate:

- The effect of dosing with an EC tablet versus dosing with the current non-coated capsule coadministered with a proton pump inhibitor (PPI; omeprazole) under fasting conditions, on the absorption of WTX101.
- The effect of dosing an EC tablet with and without food on the absorption of WTX101.
- The safety and tolerability of WTX101.

9.2 Study Endpoints

The primary endpoints are:

- Plasma concentrations and PK parameters (e.g., $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, t_{max}, λz, and $t_{½}$, CL/F, and Vz/F) for total Molybdenum (Mo) following WTX101 EC tablet administration under fasting and fed conditions and WTX101 non coated capsule coadministered with a PPI under fasting conditions
- Safety and tolerability will be evaluated based on physical examinations, vital sign measurements, Electrocardiogram (ECGs), AEs, and clinical laboratory tests.

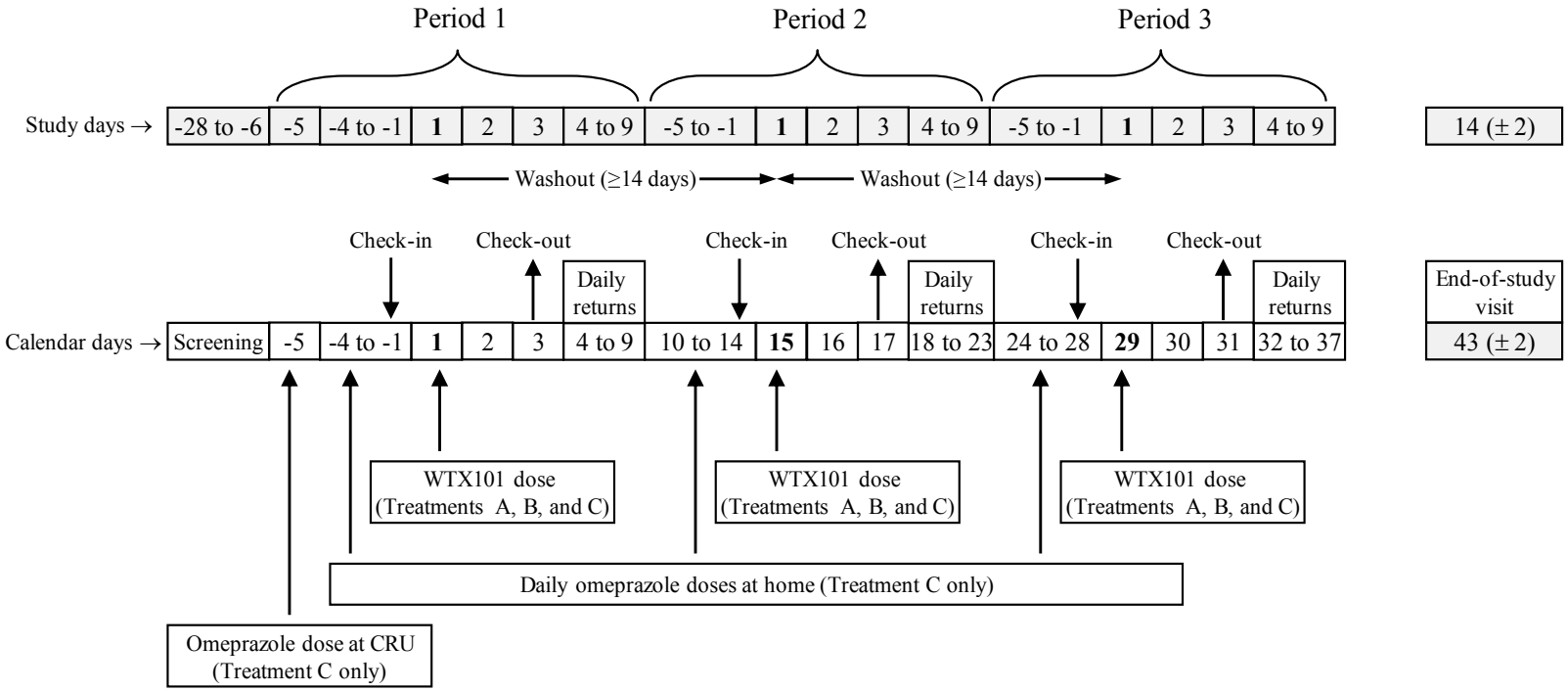
10 INVESTIGATIONAL PLAN

10.1 Overall Study Design and Plan

This will be a single-center, open-label, randomized, 3-period, 3-treatment, 6-sequence crossover study evaluating the PK of single doses of WTX101 in healthy subjects based on the measurement of plasma total Mo.

Please refer to the next page for the Study Diagram.

Figure 1 Study Diagram



Eighteen (18) healthy, non-tobacco using adult male and female subjects who complete the study screening assessments and meet all eligibility criteria will be enrolled. These subjects will receive the corresponding product, according to a randomization scheme generated at Celerion. To ensure that the planned number of subjects are dosed with WTX101 on Day 1 of Period 1, additional 'stand-by' subjects (who also complete the study screening assessments and meet all eligibility criteria) will also be enrolled. Subjects will be considered randomized when they receive the first dose of WTX101 on Day 1 of Period 1.

Subjects randomized to receive PPI in Period 1 (Treatment C) will report to the Clinical Research Unit (CRU) on Day -5, i.e. 5 days prior to first dosing with WTX101, to receive a morning dose of omeprazole under fasting conditions. These subjects will be given a container with omeprazole doses and continue QD administration of omeprazole under fasting conditions at home, until their return to the CRU for check-in on Day -1. To ensure that the planned number of subjects are dosed with WTX101 on Day 1 of Period 1, stand-by subjects will also receive QD doses of omeprazole, as described above. Should any subject withdraw from the study after omeprazole administration, but before receiving WTX101 in Period 1, they will be replaced with a stand-by subject.

Subjects randomized to receive PPI in Periods 2 or 3 will receive the container with omeprazole doses prior to discharge from the CRU after the 192-hour postdose procedures in Period 1 or Period 2, as appropriate. These subjects will initiate QD administration of omeprazole under fasting conditions at home the following day and continue until their return to the CRU for their next admission. For details on self-administration of omeprazole doses, see Section 10.5.1.

In each of the 3 periods, all subjects (Treatments A, B, and C) will be admitted to the CRU on Day -1, and will receive WTX101 EC tablet alone under fasting conditions (Treatment A); WTX101 EC tablet under fed conditions (Treatment B); or, omeprazole under fasting conditions followed by WTX101 non-coated capsule under fasting conditions (Treatment C). PK sampling will be obtained at the following timepoints while subjects remain in the CRU: Time 0 (within 1 hour predose), and then 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 7.5 8, 8.5, 9, 9.5,10, 12, 14, 16, 24, 36, and 48 hours postdose. Subjects will be discharged on Day 3 following the 48 hours postdose procedures, unless medically necessary to extend confinement to 72 hours.

Subjects will be required to return to the CRU for outpatient visits on 6 consecutive days (Days 4, 5, 6, 7, 8 and 9) in each period, for subsequent PK sampling and procedures at: 72, 96, 120, 144, 168, and 192 hours postdose.

Dose regimens are described as follows:

Treatment A: 60 mg WTX101 (2 x WTX101 EC tablets, 30 mg) at Hour 0 on Day 1 following an overnight fast.

Treatment B: 60 mg WTX101 (2 x WTX101 EC tablets, 30 mg) at Hour 0 on Day 1, 30 minutes after the start of a high-fat breakfast, preceded by an overnight fast.

Treatment C: 20 mg omeprazole (1 x 20 mg delayed-release capsule) QD in the morning of Days -5 to -1 following an overnight fast, 20 mg omeprazole delayed-release capsule at Hour -1 on Day 1 following an overnight fast, and 60 mg WTX101 (2 x WTX101 non-coated capsules, 30 mg) at Hour 0 on Day 1.

Appropriately trained employees of the study site will administer the study treatment. Each dose will be administered with approximately 240 mL of room temperature water. The date and time of administration will be recorded in the source notes and witnessed by a second person from the clinical facility.

The washout between WTX101 doses in each period will be at least 14 days.

Subjects will return to the CRU approximately 14 days (+/-2 days) after the final study medication administration for an end-of-study (EOS) visit with follow-up procedures, and to determine if any AE has occurred since the last study visit. Subjects who terminate the study early should be seen and assessed by an Investigator, whenever possible, to undergo the procedures associated with the EOS visit.

Subjects may be replaced at the discretion of the Sponsor.

10.1.1 Confinement and Return Visits

During each of the 3 periods, subjects will be housed from at least 10 hours before dosing until after the 48-hour blood draw on Day 3. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Principal Investigator (PI). Subjects will return for 6 consecutive days (Days 4, 5, 6, 7, 8 and 9) for the subsequent PK sampling. A final return visit will be required 14 days (+/-2 days) following the final administration of WTX101 for conduct of EOS procedures.

10.1.2 Study Duration

Subjects who complete the study may be involved in the study for up to 48 days excluding screening (Day -5 of period 1 to the EOS visit). The entire study is expected to last approximately 48 days from the first subject dosed (Omeprazole) to last subject-last visit (LSLV).

The study has a screening phase (Day -28 to Day -5 of Period 1); three study periods (Periods 1, 2, and 3 comprised of Day -5 to Day 9); and an EOS visit 14 days (+/-2 days) following the final study medication administration. There is a 14 day minimum washout period between each dose of WTX101.

10.2 Risks and/or Benefits to Subjects

The dose of WTX101 administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study. The single doses to be administered in each of the 3 periods are well within the dose range demonstrated to be safe in humans, (data on file at Wilson Therapeutics). The dose of omeprazole administered in this study corresponds to dosing recommendations found in the full prescribing information for Prilosec®.[7]

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, 12-lead ECG, hematology, serum chemistry, urinalysis, and AE questioning) are

adequate to protect the subjects' safety and should detect all expected treatment-emergent AEs.

There will be no direct health benefit for study participants from receipt of study medication. An indirect health benefit to the healthy subjects enrolled in this trial is the free medical tests received at screening and during the study.

10.3 Selection of Study Population

10.3.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study, unless otherwise specified:

1. Healthy, adult, male or female, 19-55 years of age, inclusive.

2. Continuous non-smoker who has not used nicotine-containing products for at least 3 months prior to the first WTX101 dose.

3. Medically healthy with no clinically significant laboratory profiles, vital signs or ECGs, as deemed by the PI.

4. Body Mass Index (BMI) ≥ 18 and ≤ 32.0 kg/m^2.

5. Adequate venous access in the left or right arm to allow collection of a number of blood samples.

6. Willing and able to fast per the study requirements.

7. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first WTX101 dose and throughout the study or be using one of the following acceptable birth control methods:

    a. intrauterine device in place for at least 3 months prior to the first WTX101 dose and throughout the study.
    b. barrier methods (e.g., condom or diaphragm) with spermicide for at least 14 days prior to the first WTX101 dose and throughout the study.
    c. surgical sterilization of the partner (vasectomy for 6 months minimum).
    d. hormonal contraceptives for at least 3 months prior to the first WTX101 dose of the study and throughout the study.

    A female subject who claims to be sexually inactive, but becomes sexually active during the course of the study must agree to use a barrier method (e.g., condom, diaphragm) with spermicide from the time of the start of sexual activity through to the completion of the study.

    In addition, female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 28 days following the last dose.

8. A female of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to the first WTX101 dose:

   a. hysteroscopic sterilization;

   b. bilateral tubal ligation or bilateral salpingectomy;

   c. hysterectomy;

   d. bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to the first WTX101 dose and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status.

9. A non-vasectomized, male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 90 days beyond the last dose of study medication. (No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to study start. A male who has been vasectomized less than 4 months prior to study start must follow the same restrictions as a non-vasectomized male).

10. If male, must agree not to donate sperm from the first WTX101 dose until 90 days after the final WTX101 dosing.

11. Understands the study procedures in the informed consent form (ICF), and willing and able to comply with the protocol.

10.3.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Subject is mentally or legally incapacitated or has significant emotional problems at the time of screening visit or expected during the conduct of the study.

2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the PI.

3. History of any illness that, in the opinion of the PI, might interfere with drug absorption (e.g., chronic diarrhea), might confound the results of the study or poses an additional risk to the subject by their participation in the study.

4. History or presence of hypersensitivity or idiosyncratic reaction to the study medications, study medication excipients (including anhydrous di-calcium phosphate, anhydrous sodium carbonate, etc.), to PPIs, or to related compounds.

5. History or presence of alcoholism or drug abuse within the past 2 years.

6. Female subjects who are pregnant or lactating.

7. Regularly drinks more than 2 units (1 unit = 265 mL beer, 100 mL wine, or 1 measure of spirits) of alcohol per day or may have difficulty abstaining from alcohol during the

48 hours prior to WTX101 administration and until completion of blood sampling in each period.

8. Positive urine drug and alcohol results at screening or check-in.

9. Positive results at screening for Human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg) or Hepatitis C virus (HCV).

10. Seated blood pressure less than 90/60 mmHg or greater than 140/90 mmHg at screening.

11. Serum Cp value outside of the normal range at screening.

12. Serum Cu values outside of the normal range at screening.

13. Unable to refrain from or anticipates the use of any drug, including recreational drugs, prescription and non-prescription (over-the-counter) medications, herbal remedies, or vitamin supplements beginning approximately 14 days prior to WTX101 first dosing and throughout the study. Hormonal contraceptives and hormone replacement therapy will not be excluded. Acetaminophen (up to 2 g per 24 hour period) may be permitted during the study.

14. Have been on a diet incompatible with the on-study diet within the 28 days prior to the first WTX101 dose and throughout the study.

15. Hemoglobin level below the lower limit of normal at screening.

16. Unable to consume the contents of a high-fat breakfast.

17. Donation of blood or significant blood loss within 56 days prior to the first WTX101 dose.

18. Plasma donation within 7 days prior to the first WTX101 dose.

19. Involvement in the planning or the conduct of the study.

20. Participation in another clinical trial within 28 days prior to the first WTX101 dose. The 28-day window will be derived from the date of the last study procedure (such as last blood collection or dosing) in the previous study to Day 1 of Period 1 of the current study.

21. Participation in a previous clinical trial with WTX101.

10.3.3 Stopping Rules

Safety-related individual- and study-specific stopping criteria are detailed below:

- Dosing will be discontinued for an individual subject experiencing any National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0 Grade 3 or higher event that is assessed as treatment-related.*

- The study will be stopped if 2 or more subjects experience an NCI CTCAE v. 4.0 Grade 3 or higher event that is assessed as treatment-related*, or if 1 or more subjects experience a Grade 4 or higher event that is assessed as treatment-related.*

*Treatment-related is defined as likely, probably, or possibly related (see Section 11.1.6.3)

10.3.4 Removal of Subjects from the Study

Subjects are free to withdraw from the study at any time for any reason. Subjects who discontinue will be asked about the reason(s) for their discontinuation and the presence of any AEs.

In addition, subjects may be withdrawn from the study by the PI or sub-Investigator in consultation with the Sponsor for the following reasons:

- NCI CTCAE v. 4.0 Grade 3 or higher event that is assessed as treatment-related (see Section 10.3.3.)
- AEs.
- Difficulties in blood collection.
- Safety reasons, as judged by the PI and/or the Sponsor.
- Protocol violation (may include severe non-compliance to the protocol or development of exclusion criterion).
- Incorrect enrollment (i.e., the subject does not meet the required inclusion/exclusion criteria).
- Subject lost to follow-up.

Whenever possible, discontinued subjects should be seen and assessed by an Investigator. Discontinued subjects should undergo the study procedures outlined at the end-of-study visit. AEs should be followed up as detailed in Section 11.1.6

The clinical report will include reasons for subject withdrawals as well as details relevant to the subject withdrawal.

10.4 Study Restrictions

10.4.1 Prohibitions and Concomitant Therapy

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 24 hours before first dosing (PPI or WTX101) in each period and throughout the period of sample collection (small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz. decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz chocolate bar, per day, would not be considered a deviation to this restriction);

- Alcohol: 48 hours before first dosing (PPI or WTX101) in each period and throughout the period of sample collection;
- Grapefruit/Seville orange: 14 days before first WTX101 dosing and throughout the period of sample collection.

Subjects may not donate either blood or plasma throughout the duration of the study.

No subject may take medication (including over-the-counter products), herbal products or vitamin supplements for 14 days prior to WTX101 first dosing and throughout the study, except as required for the study. Hormonal contraceptives and hormone replacement therapy are not part of this prohibition.

During the study, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI. The subjects will be instructed that no additional medication will be allowed without the prior consent of the Investigator. If deviations occur, the PI will decide on a case-by-case basis whether the subject may continue participation in the study based on the time the study medication was administered and its pharmacology.

Any medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator(s). All medications taken by subjects during the course of the study will be recorded in the source documents and in the appropriate sections of the electronic Case Report Form (eCRF). If a medication is associated with an AE, the AE will also be recorded in the source documents and in the appropriate sections of the eCRF.

Subjects may not participate in another clinical trial until they have completed their end-of-study visit.

10.4.2 Meals

Days - 5 to -1:

For Treatment C, subjects will be required to fast for at least 10 hours before, and for at least 1 hour following Omeprazole administration.

Days -1 to 1:

For Treatments A and C, subjects will be required to fast overnight for at least 10 hours before WTX101 dosing and for at least 4 hours thereafter.

For Treatment B, subjects will be required to fast overnight for at least 10 hours until approximately 30 minutes prior to their scheduled dosing times (Hour -0.5), when they will be given a standard high-fat breakfast which will be entirely consumed within 30 minutes. An example of a high-fat breakfast would be 2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash brown potatoes, and 240 mL of whole milk. Subjects will fast for at least 4 hours following dosing.

All days:

For Treatments A, B, and C, water will not be permitted from 1 hour before until 1 hour after WTX101 dosing, except for water and/or fluids given at dosing. Water will be allowed ad

libitum at all other times. On all days that subjects are confined to the CRU, standard meals will be provided at approximately 4 and 9 hours after dosing, and at appropriate times thereafter.

Except for the high-fat breakfast in Treatment B, each meal and/or snack served at the CRU will be standardized and will be similar in caloric content and composition (especially for dietary Cu) and will be taken at approximately the same time in each period.

10.4.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours following WTX101 administration, except when they are supine or semi-reclined for study procedures.

However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports, at any time from screening until completion of the study.

10.5 Treatments

10.5.1 Treatments Administered

All subjects will be given properly labeled containers with the requisite number of omeprazole doses for at home administration. Subjects will be given paper diaries to record their self-administered omeprazole doses, and will be instructed in the CRU on: self-administration under fasting conditions, and on recording of doses and timing of doses in their diary. Written instructions will be provided for the subjects to take home. Each omeprazole dose self-administered should be taken under fasting conditions, at a time corresponding to Hour -1 relative to the time of dosing WTX101 on Day 1 (Hour 0). Subjects must return the container (empty or not) and their diary at the next visit. Self-administered dosing will be monitored daily by attempted contacts (phone calls, texts, or emails) to remind subjects to take these doses.

Subjects randomized to receive PPI in Period 1 (Treatment C) will report to the Clinical Research Unit (CRU) on Day -5, i.e. 5 days prior to first dosing with WTX101, to receive a morning dose of omeprazole under fasting conditions. Prior to release from the CRU on Day -5 of Period 1, subjects will receive a container with omeprazole doses which will be self-administered by subjects at home. Subjects randomized to receive PPI in Periods 2 or 3 will receive the container with omeprazole doses prior to discharge from the CRU after the 192-hour postdose procedures in Period 1 or Period 2, as appropriate. These subjects will initiate QD administration of omeprazole under fasting conditions at home the following day and continue until their return to the CRU for their next admission. Each self-administered dose of omeprazole should be taken under fasting conditions, at a time corresponding to Hour -1 relative to the time of dosing WTX101 on Day 1 (Hour 0).

Treatments A, B, and C are described as follows:

Treatment A: 60 mg WTX101 (2 x WTX101 EC tablets, 30 mg) at Hour 0 on Day 1 following an overnight fast.

Treatment B: 60 mg WTX101 (2 x WTX101 EC tablets, 30 mg) at Hour 0 on Day 1, 30 minutes after the start of a high-fat breakfast, preceded by an overnight fast.

Treatment C: 20 mg omeprazole (1 x 20 mg delayed release capsule) QD in the morning of Days -5 to -1 following an overnight fast, 20 mg omeprazole capsule at Hour -1 on Day 1 following an overnight fast, and 60 mg WTX101 (2 x WTX101 non-coated capsules, 30mg) at Hour 0 on Day 1.

Subjects randomized to receive Treatment C in Period 1 will be required to come to the CRU in the morning of Day -5 of Period 1 to receive their first dose of PPI (omeprazole). They will receive a properly labeled container which will contain omeprazole doses to be self-administered at home on Days -4 to -1. At the end of Periods 1 and 2, subjects will receive a container with omeprazole doses for self-administration of doses on Days -5 to -1, if they are randomized to receive Treatment C in the next period. Each self-administered dose of omeprazole should be taken under fasting conditions, at a time corresponding to Hour -1 relative to the time of dosing WTX101 on Day 1 (Hour 0).

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject and for each study period, as per the randomization scheme.

All study medications should be taken orally with approximately 240 mL of water.

Subjects will be instructed not to crush, split or chew the study medication, the WTX101 non-coated capsules and WTX101 EC tablets should be swallowed whole.

The date and exact clock time of dosing will be recorded on on-site dosing days.

Home dosing will be monitored via attempted contacts (phone calls, texts or emails) as subjects will be reminded to take their omeprazole dose and queried about the occurrence of AEs.

10.5.2 Method of Randomizing Subjects to Treatment Groups

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will receive the corresponding product, according to a randomization scheme generated at Celerion. To ensure that the planned number of subjects are dosed with WTX101 on Day 1 of Period 1, additional, stand-by subjects (who also complete the study screening assessments and meet all eligibility criteria) will also receive QD doses of omeprazole. Subjects will be considered randomized when they receive the first dose of WTX101 on Day 1 of Period 1.

Subjects will receive each treatment on one occasion. The sequences to be used in the randomization will be ABC, ACB, BAC, BCA, CAB, and CBA.

Subjects may be replaced at the discretion of the Sponsor.

10.5.3 Blinding

This is an open-label study. The randomization scheme will not be available to bioanalytical laboratory personnel.

10.5.4 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses, for doses administered at the CRU. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study medication. Once a subject has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study medication was ingested.

Compliance to at home omeprazole dosing will be reinforced by instructions and attempted daily contact with subjects. At home omeprazole dosing containers must be returned by the subjects to the CRU whether or not they are empty. A qualified designee will be responsible for accountability procedures.

10.5.5 Diary

Subjects will self-administer omeprazole at home on the days designated as home-dosing according to the Study Events Flow Chart (Section 6).

A paper diary and omeprazole medication for at home dosing will be supplied to subjects before release from the CRU. The diary will capture subject identification, dose taken, actual date and time of dose taken, a check that the dose was accompanied or not by food, any missed doses, and a comment section should the subject have a comment. Subjects must return the diary when they return to the CRU at the next visit. The data will be transcribed from the patient diary into the eCRF.

11 STUDY PROCEDURES

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI and/or the Sponsor for reasons related to subject safety.

For this study, the blood collection for total Mo is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

11.1 Safety Assessment

11.1.1 Screening

Within 28 days prior to WTX101 dosing, medical and surgical history and demographic data, including name, sex, date of birth, race, ethnicity, body weight (kg), height (cm), BMI, history of tobacco use, and alcohol use (including number drinks consumed per day) will be recorded. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG and the laboratory tests of hematological, hepatic and renal function, as well as the additional tests as noted in Section 11.1.5.1.

11.1.2 Physical Examination

A full physical examination will be performed as per the Study Events Flow Chart (Section 6). The physical examination should include general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, respiratory system, abdomen and a neurological examination. A symptom driven physical examination may be performed at any time at the PI's discretion.

11.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 6).

Blood pressure and heart rate measurements will be performed on subjects after at least 2 minutes in the supine position. Vital signs may be taken at any other times, if deemed necessary. Additional blood pressure and heart rate measurements will be performed with subjects in a supine position except when subjects are reclined, semi-reclined or in a seated position because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the PI.

Blood pressure and heart rate will be measured within 2 hours prior to Day 1 dosing of each period for the predose time point. Postdose vital signs will be performed within approximately 10 minutes of the scheduled time point.

11.1.4 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6).

ECGs will be performed on subjects after at least 2 minutes in supine position. All ECG tracings will be reviewed by the Study Physician or his/her designee. The following ECG variables will be collected and transcribed into the eCRF; HR, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval and overall interpretation

ECGs will be measured within 2 hours prior to Day 1 dosing of each period for the predose time point. When scheduled, postdose ECGs will be performed within approximately 20 minutes of the scheduled time point.

A subject will be withdrawn from the study by the Study Physician if, in their medical judgment, ECG findings are present which make continued study participation not in the subject's best interest.

11.1.5 Blood Sampling for Safety and Pharmacokinetic Analyses

11.1.5.1 Safety Laboratory Tests

All tests listed below will be performed as per Study Events Flow Chart (Section 6). Clinical laboratory results will be used during screening by the PI to establish eligibility for enrollment. Any deviation in laboratory values that are confirmed on re-examination to be clinically significant by the PI that would jeopardize the safety of the subject or impact the validity of the study results will result in exclusion of that subject. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI.

Hematology
- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

Serum Chemistry*
- Blood urea nitrogen (BUN)
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose (fasting)
- Creatinine**

Urinalysis
- pH
- Specific gravity
- Protein***
- Glucose
- Ketones
- Bilirubin
- Blood***
- Nitrite***
- Urobilinogen
- Leukocyte esterase***

Additional Tests
- HIV test
- HBsAg
- HCV
- Urine drug screen
  - Opiates
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for post-menopausal females only)
- Prothrombin Time (PT) / International Normalized Ratio (INR), and activated Partial Thromboplastin Time (aPTT)
- Cp (Screening)
- Total Cu (Screening)

* Samples for serum chemistry will be obtained following a fast of at least 8 hours at screening, and of at least 6 hours at check-in. In case of dropouts, rechecks and postdose serum chemistry, subjects may not have fasted for 6 or 8 hours before the serum chemistry sample is taken.

** At screening, creatinine clearance will be calculated using Cockcroft-Gault formula.

*** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a

microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

11.1.5.2 Pharmacokinetic Assessment Sampling and Processing

For all subjects, blood samples for the determination of plasma total Mo will be collected and processed at scheduled time points as delineated in the Study Events Flow Chart (Section 6). A total of approximately 1512 samples (84 per subject) will be collected for PK analysis as per the target sample times (times blood will be drawn in relation to dosing).

The exact time points for collection of PK samples may be amended following evaluation of the data from the ongoing Study WTX101-101. If this is required it will be confirmed prior to study start. However, the total volume of blood taken for PK sample analysis will not be increased from that stated in Section 11.1.5.3.

Details on the sample collection process will be included in the central laboratory manual. The predose blood sample should be taken within 60 minutes prior to dosing. Samples up to and including the 8 hour postdose samples will be collected within 3 minutes of the scheduled time, thereafter all postdose samples will be collected within 30 minutes of the scheduled time. The actual blood collection date and time will be recorded in the source documents. All deviations outside the range allowed above will be documented as protocol deviations. In all such cases, appropriate time corrections, for the actual time of sample collection will be incorporated at the time of data analysis.

The actual sample date and times (date and times samples actually taken) will be recorded in the source notes and will be entered at the time of or as soon as possible after sampling. All times must be recorded in the 24 hour format. An explanation must be given for any blood sample taken outside of the set sampling times.

Sample Processing: The Sponsor will provide a laboratory manual that will detail the handling of PK blood samples.

Analytical Methodology: Plasma samples will be assayed by a validated inductively coupled plasma mass spectrometry (ICP-MS) method, which is specific for the determination of Mo. A validation study will be conducted by the appointed bioanalytical laboratory to establish validity. This study will be appended to the final report.

Samples from all subjects enrolled in the study including drop-outs for AEs will be analyzed. The criteria for repeat analysis as defined in the respective in-house procedure will be followed.

11.1.5.3 Blood Volume Drawn for Study Assessments

Table 1 Blood Volume during the Study

Sample Type	Number of Timepoints	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology, Cp, and Cu), FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only).	1	23	23
On-study hematology	7	4	28
On-study serum chemistry and serum pregnancy (for female subjects only) when scheduled at the same time	7	8.5	59.5
PT, INR, and aPTT	8	4.5	36
Blood for total Mo (PK)	84	6	504
		Total Blood Volume (mL)→	650.5**

** Additional volume, up to 50 mL may need to be collected due to unforeseen circumstances.

11.1.6 Adverse Events

11.1.6.1 Adverse Event Definition

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

11.1.6.2 Monitoring

Subjects will be monitored throughout confinement, and also during a home omeprazole dosing, for adverse reactions to the study formulations and/or procedures. At the time of release, subjects will be asked how they are feeling. At the time of subsequent sample collections in each study period and at the beginning of the second and third period subjects will be queried with an open-ended question such as: ‘How have you been feeling since your last visit?’

All symptoms will be evaluated by the PI before the next dose is administered.

Regardless of the relationship of the AE to the study drug the AE must be recorded in the eCRF. Any subject who reports an AE (whether serious or non-serious) or has a clinically significant abnormal laboratory test value(s) will be evaluated by the PI and will be treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as

judged by the PI. Treatment of serious adverse events (SAEs) will be performed by a physician, either at Celerion or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

11.1.6.3 Reporting

AEs (including SAEs) will be recorded beginning with the first dose of study medication, either omeprazole or WTX101 (as per randomization), and through the EOS visit. AEs will be followed for 14 days after the last dosing with WTX101; or until the event resolves or stabilizes, whichever is earlier. All AEs that occur during this period will be recorded.

The PI will review each event and assess its relationship to drug treatment (likely, probably, possibly, unlikely or unrelated). Each sign or symptom reported will be graded on NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5).[8]

The following definitions will be used for rating the severity of AEs:

AE Severity	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Note 1: A semi-colon indicates 'or' within the description of the grade.

Note 2: Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The date of onset, time of onset, and outcome of each event will be noted. Additional variables to be recorded are as follows:

- Date and time when the AE started and stopped
- Maximum intensity
- Action taken
- Whether or not the AE is serious

- Whether or not the AE caused the subject to discontinue the study
- Outcome

11.1.6.4 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered AEs, it is the responsibility of PIs or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 14 days of completing the trial. All subjects or female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes must be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

11.1.6.5 Serious Adverse Event

If any of the above AEs are serious (SAEs), as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor within one working day and followed by written reports within five working days for non-expedited reports and three working days for expedited reports, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and 21 CFR 314.80 for marketed drugs (15-day alerts). The institutional review board (IRB) will be notified by Celerion of the Alert Reports as per FDA regulations; FDA will be notified by the Sponsor or their designee.

SAEs will be followed until either the event is considered stable or resolved.

The following is the definition for a SAE as per FDA regulations:

A Serious Adverse Event (SAE) is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, in-patient hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may or may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If a SAE occurs to a subject on this study, contact the Sponsor's clinical representatives; PPD PPD Tel.: PPD E-mail: PPD and PPD Tel: PPD E-mail: PPD listed in Section 2 and 3.

12 DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of Good Clinical Practices.

12.1 Pharmacokinetic Parameters

PK parameters for plasma total Mo will be calculated as follows:

AUC_{0-t}:	The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.
AUC_{0-inf}:	The area under the plasma concentration versus time curve from time 0 to infinity. AUC_{0-inf} is calculated as the sum of AUC_{0-t} plus the ratio of the last measurable plasma concentration to the elimination rate constant.
C_{max}:	Maximum measured plasma concentration over the time span specified.
t_{max}:	Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.
λz:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations), beginning with the last non-zero concentration.
$t_{½}$:	Apparent first-order terminal elimination half-life will be calculated as $0.693/\lambda z$.
CL/F	Apparent oral clearance
Vz/F	Apparent oral volume of distribution

No value for λz, AUC_{0-inf}, $t_{½}$, CL/F, or Vz/F will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

AUC and C_{max} parameters will not be calculated for subjects with only 2 or less timepoints with detectable concentrations.

12.2 Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by

Celerion and agreed upon with the Sponsor. This SAP will not include any pharmacokinetic analysis. Additionally, a separate Pharmacokinetic Analysis Plan (PKAP) will be prepared by Kramer Consulting LLC and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP/PKAP.

12.2.1 Determination of Sample Size

The sample size chosen for this study was selected without statistical considerations. It has been determined adequate to meet the study objectives.

12.2.2 Descriptive Statistics

Arithmetic means, standard deviations (SD), sample size, coefficient of variation (CV), median, minimum and maximum values will be calculated for the plasma concentrations and the PK parameters listed in Section 12.1. Geometric means will be calculated only for AUC and C_{max} parameters.

12.2.3 Analysis of Variance

An analysis of variance (ANOVA) will be performed on the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}. The ANOVA model will include sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Sequence will be tested using subject nested within sequence as the error term at a 10% level of significance. Each ANOVA will include calculation of geometric least-squares means (GLSM), the difference between treatment GLSM, and the standard error associated with this difference. The above statistical analyses will be done using SAS® PROC GLM.

12.2.4 Ratios and Confidence Intervals

Ratios of GLSM will be calculated using the exponentiation of the difference between treatment GLSM from the analyses on the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. These ratios will be expressed as a percentage relative to the reference treatment.

Consistent with the two one-sided test for bioequivalence,[9] 90% (Confidence Interval) CIs for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment GLSM resulting from the analyses on the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. The CIs will be expressed as a percentage relative to the reference treatment.

The comparisons of interest are as follows:

- Treatment B compared with Treatment A
- Treatment A compared with Treatment C.

12.3 Safety Evaluation

All subjects who receive at least one dose of WTX101 will be included in the safety evaluation, and safety data will be populated in individual eCRFs. All safety data will be listed by subject.

Safety data including physical exams, ECGs, vital signs assessments, clinical laboratory evaluations, and AEs will be summarized by treatment group and point of time of collection, when applicable.

Descriptive statistics (arithmetic mean, SD, sample size, CV, median, minimum, maximum, and number) will be calculated for quantitative safety data as well as for the difference to baseline, when appropriate. In addition, a shift table describing out of normal range shifts will be provided for clinical laboratory results. A normal-abnormal shift table will also be presented for physical exam results and ECGs.

WTX101 and omeprazole dosing dates and times will be listed by subject.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 16.1 and summarized by treatment group for the number of subjects reporting the AE and the number of AEs reported. A by-subject AE data listing including (but not limited to) verbatim term, coded term, treatment group, severity, and relationship to treatment will be provided.

All concomitant medications recorded during the study will be listed by subject and coded with the WHO Dictionary Version 01Sep2013. Medical history will be listed by subject, and coded using the 16.1 version of MedDRA® dictionary.

13 STUDY ADMINISTRATION

13.1 Ethics

13.1.1 Institutional Review Board

This protocol and ICF will be reviewed by an institutional review board and the study will not start until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The board is International Conference on Harmonisation (ICH) compliant. If it is necessary for the protocol to be amended, the amendment and/or a new version of the protocol, along with an updated ICF (if needed) must be provided to the IRB for approval, before implementation.

13.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, Good Clinical Practice (GCP), 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

13.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an informed consent form summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. If a protocol amendment requires a change to the ICF, then subjects will be required to sign and date the updated ICF upon approval by the IRB.

Subjects will be given a copy of their informed consent form(s).

13.2 Termination of the Study

Celerion reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to terminate the study or a study site at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence and severity of AES in this or other studies with WTX101 indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- GCP is not being maintained and/or adequately followed.
- Administrative reasons.
- Reasons unrelated to the study.

13.3 Study Documentation and Recordkeeping

13.3.1 Source Documents

The Investigator must maintain detailed records of all study participants who are enrolled in the study or who undergo screening. Source documents include subject medical records and Investigator's subject study files, as well as all test results. Information required for study purposes and any data recorded in the eCRF must be supported by appropriate source documentation.

13.3.2 Data Monitoring and Handling

Data collection and maintenance will be conducted through Electronic Data Capture. Celerion standard eCRFs will be supplied. Validation checks will be built into the live system to capture data errors, and data clarification queries will be generated at the time of data monitoring. One hundred percent source data verification against the source documents at the site will be performed prior to locking of the study database. Following the completion of source data verification, a thorough review of data will be completed manually by the clinical data managers to ensure data consistency and to identify and request correction of any remaining data errors. All queries will be resolved or closed with written documentation providing reasons for irresolvable queries. Additional manual validation checks will be performed as needed. Statistical analysis will be performed based on a predefined statistical analysis plan.

The study site will be monitored according to GCP and standard operating procedures. Prior to initiation of the study, representatives from the Sponsor or its designee will review with the site personnel information about the investigational product, protocol requirements, randomization procedures, training on data collection and entry, monitoring requirements, and reporting of AEs. During and after the study, periodic site visits will be made to monitor for compliance, including verification of the accuracy and completeness of data recorded on the eCRFs, source documents, and drug accountability records.

The eCRFs for each subject must be reviewed and signed by the Investigator. This should be done as soon as possible after the subject has completed the study and all data queries have been resolved.

13.4 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for implementing and maintaining quality assurance and quality control systems to ensure that the trial is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the quality assurance (QA) department and the QA audit certificate will be included in the study report.

13.5 Direct Access to Source Data/Documents

Celerion will ensure that the Sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). Celerion will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at his or her center. The purpose of Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP guidelines, and any applicable regulatory requirements. In the event that other trial-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

13.6 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of WTX101 to allow completion of this study. WTX101 will be supplied in two different formulations:

WTX101 non-coated capsule, 30 mg:

A size 1 white opaque hydroxypropyl methylcellulose (HPMC) capsule, each capsule contains 30 mg of bis-choline tetrathiomolybdate and the following excipients: 475 mg anhydrous di-calcium phosphate and 25 mg anhydrous sodium carbonate.

The capsules are manufactured in accordance with the principles of cGMP at:

Pharmatek Laboratories, Inc.
7330 Carroll Road, Suite 200
San Diego, CA 92121
USA

WTX101 30 mg non-coated capsule will be supplied by the Sponsor in blisters containing capsules in accordance with all applicable regulatory requirements. Labels will be in accordance with all applicable regulatory requirements for the labeling of active pharmaceutical ingredients and with Annex 13 of GMP. Labels will contain the drug name (Capsules of WTX101, 30mg), protocol number, lot number, storage conditions and a caution that the drug is for clinical investigational use only.

WTX101 EC tablets, 30 mg:

A white round tablet containing 30 mg of WTX101 and the following excipients: tri-calcium phosphate, sodium carbonate, sodium starch glycolate, magnesium stearate, Opadry clear coat, Acryl-eze white enteric coat.

The WTX101 EC tablets, 30 mg are manufactured in accordance with the principles of cGMP at:

Pharmatek Laboratories, Inc.
7330 Carroll Road, Suite 200
San Diego, CA 92121
USA

WTX101 EC tablet, 30 mg will be supplied by the Sponsor in amber glass bottles containing tablets and dessicant in accordance with all applicable regulatory requirements. Labels will be in accordance with all applicable regulatory requirements for the labeling of active pharmaceutical ingredients and with Annex 13 of GMP. Labels will contain the drug name; (Tablets of WTX101, 30 mg), protocol number, lot number, storage conditions and a caution that the drug is for clinical investigational use only.

Omeprazole will be sourced by Celerion. The lot numbers and expiration dates (where available) of the study medications supplied will be recorded in the final report.

13.6 Study Drug Handling, Storage and Return/Disposal

All material supplied is for use only in this clinical study and should not be used for any other purpose. Only subjects enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer study drug. All study drug supplies will be stored refrigerated at 2-8^{o}C (36-46^{o}F), and in a secure area with access limited to the Investigator and authorized staff and under the physical conditions that are consistent with the study drug–specific requirements.

Study drug supplies will be stored securely under the appropriate conditions at the clinical study facility according to the State and Commonwealth Laws.

Standard Operating Procedures will be followed for the receipt, handling and accountability of the study formulations.

The Investigator is responsible for the investigational product accountability, reconciliation and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. This person will document the amount of investigational product received from the Sponsor, the amount supplied and/or administered to and returned by subjects, if applicable.

A Drug Dispensing Log must be kept current and will contain the following information:

- the identification of the subject to whom the drug was dispensed.
- the date(s), time(s) and quantity of the drug dispensed to the subject.
- the identification of the dispenser.

Doses will be dispensed in accordance with the study-specific randomization schedule.

At the conclusion of the study, any unused study medications will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. Records shall be maintained by the Investigator of any such alternate disposition of the test drug. These records must show the identification and quantity of each unit disposed of, the

method of destruction (taking into account the requirements of local law), and the person who disposed of the test substance. Such records must be submitted to the Sponsor. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

13.7 Data Handling and Record Keeping

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by Celerion until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in a ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

13.8 Training of Staff

The PI is responsible for the conduct of the study at this study site, including delegation of specified study responsibilities, and training of study staff. The PI shall ensure that the study is carried out in accordance with the protocol, ICH/GCP guidelines, and regulations.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

13.9 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

13.10 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor’s written consent to publish the article.

14 REFERENCES

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