Clinical Study Protocol

Trientine tetrahydrochloride (TETA 4HCl) for the treatment of Wilson's disease

Study Number:	GMPO-131-002 (CHELATE STUDY)
Version / Date:	Version 6.0 / 27 May 2020
Investigational Drug:	Trientine tetrahydrochloride (gmp-orphan)
Comparator:	Standard-of-care penicillamine
Phase:	3
Sponsor:	gmp-orphan SA Pépinière Paris Santé Cochin 27-29 rue Faubourg Saint-Jacques 75014 Paris France
EudraCT number:	2016-003876-29
IND number:	128103

GCP statement

The experimental protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the Institutional Review Board and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, the ICH E6 (R1) guidelines of Good Clinical Practice, 21 CFR 21.50 Protection of Human Subjects and 21 CFR 21.56 Institutional Review Boards, and all applicable regulatory authority requirements.

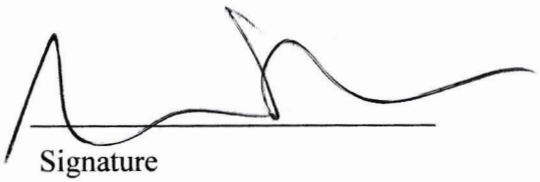
1. Signatures and agreement with protocol

Protocol Approval

Study title: CHELATE STUDY: Trientine tetrahydrochloride (TETA 4HCl) for the treatment of Wilson's disease

Sponsor's Representative
Laurence Skillern,
MD FRCOG FFPM,
Chief Medical Officer

27/5/2020
Date


Signature

Investigator Signature page

Study title: CHELATE STUDY: Trientine tetrahydrochloride (TETA 4HCl) for the treatment of Wilson's disease

I agree to conduct this study according to the Study Protocol.

I agree that the study will be carried out in accordance with Good Clinical Practice (GCP), with the Declaration of Helsinki (with amendments) and with the laws and regulations of the countries in which the study takes place.

Investigator

Date Signature

Address

2. Study synopsis

Title of the study: CHELATE STUDY: Trientine tetrahydrochloride (TETA 4HCl) for the treatment of Wilson's disease	
Sponsor: gmp-orphan SA	**Protocol code:** GMPO-131-002 (CHELATE) **EudraCT number:** 2016-003876-29 **IND number:** 128103
Investigator(s): Coordinating investigator: Professor Michael Schilsky, Yale University, USA	
Study center(s): Estimated 18-20 study sites	
Phase of development: Phase 3	
Planned study period: Each patient will participate in the initial part of the study for approximately 9 months, which may be followed by an extension phase	
Objectives: To evaluate the efficacy of TETA 4HCl compared to penicillamine. The safety of TETA 4HCl compared to penicillamine will also be evaluated.	
Clinical hypotheses: The efficacy of TETA 4HCl is not inferior to penicillamine, as assessed by the level of serum non-ceruloplasmin bound copper (NCC). TETA 4HCl is well tolerated.	
Study design: Multicenter, randomized, open label study with an active standard-of-care comparator. Stable patients who are already considered to be stable on their penicillamine chelation therapy for at least 1 year will enroll in the study and enter the 12-week Penicillamine Baseline Period comprising of a 1 month (4 weeks) run-in period followed by a 2 month (8 weeks) evaluation period. During this time all patients will continue to take their current penicillamine under study conditions. At the end of the Penicillamine Baseline Period, patients who fulfill the protocol definition of being adequately controlled and tolerating penicillamine, as confirmed by the independent Adjudication Committee, will be randomized in a 1:1 ratio to receive either TETA 4HCl or to continue to receive penicillamine. There is then a 24-week Post-randomization Phase comprising of a 1 month (4 weeks) run-in period for both treatment arms followed by a 5 month (20 weeks) evaluation period. Scheduled study visits (clinic or telephone) will occur at screening/enrolment (clinic), Week 4 (clinic), Week 8 (telephone), Week 12 (clinic), Week 16 (clinic), Week 20 (telephone), Week 24 (clinic), Week 28 (telephone), Week 32 (telephone) and Week 36 (clinic) – see figure below. For the telephone visits, the necessary lab samples will be collected directly from the patient. Note that the designated telephone visits are permitted to be performed at the clinic, but the reverse is not the case i.e. a designated clinic visit cannot be a telephone visit, unless circumstances arising from the Coronavirus disease 2019 (COVID-19) crisis are preventing the execution of planned visits at the clinic. Patients who successfully complete the 24-week Post-randomization Phase of the study will have the opportunity to enter an Extension Phase of maximally up to 18 months (72 weeks). Initially they will continue on their allocated treatment (penicillamine or TETA 4HCl) for a	

further 24 weeks. Thereafter patients may receive TETA 4HCl for a further 24 or 48 weeks. Study clinic visits will occur every 6 months (24 weeks), i.e. at Weeks 60, 84 and 108. An additional visit for patients who were previously allocated to the penicillamine treatment arm will occur at Week 64 (i.e. 4 weeks after starting to receive TETA 4HCl).

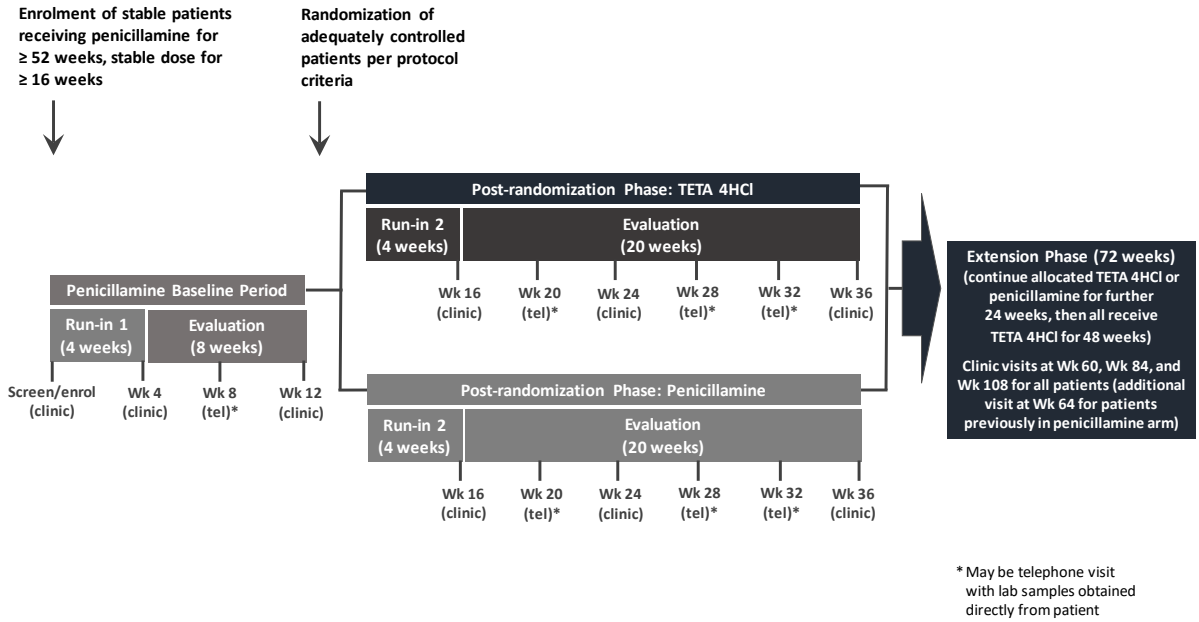
From protocol version 6.0 onwards all patients reaching Week 60, 64, 84 and 108 will terminate the study at their first visit, i.e.:

- all patients that have previously completed the Week 36 visit will terminate at their Week 60 visit; Patients initially randomized to the penicillamine arm and willing to switch to TETA 4HCl will finish the study at the Week 64 visit.
- all patients that have previously completed the Week 60 visit will stop the trial at the next visit, either Week 84 visit, or an earlier unscheduled visit agreed between the patient and investigator and
- all patients that have previously completed the Week 84 visit will stop the trial at the next visit either Week 108 visit or an earlier unscheduled visit agreed between the patient and the investigator

Upon stopping all patients will have their end of treatment visit assessments to complete the study.

In case local circumstances arising from the COVID-19 crisis are preventing the execution of the extension phase visits at the clinic, the scheduled assessments may be performed in part by telephone, in combination with collection of lab samples and vital signs obtained directly from the patient at home.

The Adjudication Committee will review data up to and including Week 36 and Week 60 to confirm patients are well controlled and clinically stable post randomisation.



Planned number of subjects:

The target is to have 55 patients randomized.

Medical condition or disease under investigation:
Patients with Wilson's disease adequately controlled and tolerating penicillamine

Inclusion criteria

1. Patient is able to provide, and has provided, written informed consent
2. Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable, including:
    a. For US sites: Authorization for Use and Release of Health Research Study Information
    b. For EU sites: Data Protection Consent
3. Male or female, aged ≥ 18 and ≤ 75 years of age at time of consent
4. Patient has a diagnosis of Wilson's disease, as defined by a prior or current Leipzig score of ≥ 4
5. Patient's Wilson's disease is clinically stable, in the opinion of the investigator, and being treated with penicillamine for at least 1 year (52 weeks) prior to the screening/enrolment visit
6. Patient is on a stable dose and regimen of penicillamine for at least 4 months (16 weeks) prior to the screening/enrolment visit (other prescribed treatments for Wilson's disease not permitted during this period)
7. No anticipated need that patient will require additional pharmacological therapies other than study medication, including prescribed zinc therapy, for the management of copper levels during the study
8. Patient must be willing to maintain stable diet throughout the study, and avoid foods with high copper content, including the Penicillamine Baseline Period
9. Patient considered suitable to receive therapy with both TETA 4HCl and penicillamine administered twice a day
10. Negative central laboratory tests for HIV and viral hepatitis (results will be available after start of run-in period)
11. For female patients of childbearing potential, negative urine pregnancy test (at screening/enrolment visit and prior to randomization)
12. For females of childbearing potential, use of a reliable form of contraceptive
13. Patient is considered as able to complete study requirements and attend the study visits, in the opinion of the investigator

Additional inclusion criteria following receipt of Screening laboratory results

14. Patient is adequately controlled and tolerating penicillamine therapy as defined by fulfilment of all of the following:
    a. Serum non-ceruloplasmin bound copper (NCC) level between ≥ 25 and ≤ 150 μg/L*
    b. 24-hour urinary copper excretion of between ≥ 100 and ≤ 900 μg/24 hours*
    c. Alanine transaminase (ALT) < 2 times upper limit of normal*
    d. No other laboratory or clinical findings that would prevent continuation of maintenance therapy, in the opinion of the investigator

* Based on results from screening/enrolment visit samples for which can be taken within ± 7 days of visit. Result should be within the assay limits of quantification for the sample. The ranges in μmol of copper are 0.40 to 2.38 μmol/L for NCC and 1.59 to 14.29 for 24-hour urinary copper excretion (using division by 63 of value in μg per Walshe, 2011).

In the event that one or more of the above lab values fall outside the specified range, it can be repeated, including at the Week 4 and Week 8 visits.

Additional inclusion criteria at Week 12 visit (end of Penicillamine Baseline Period) and prior to randomization

15. Patient is adequately controlled and tolerating penicillamine therapy as defined by fulfilment of all of the following criteria:

a. Serum non-ceruloplasmin bound copper (NCC) level between ≥ 25 and ≤ 150 μg/L*
b. 24-hour urinary copper excretion of between ≥ 100 and ≤ 900 μg/24 hours**
c. Alanine transaminase (ALT) < 2 times upper limit of normal*
d. No other laboratory or clinical findings that would prevent continuation of maintenance therapy, in the opinion of the investigator

* Based on lab values from Week 8 visit; ** Based on lab value from Week 4 visit as routinely not performed at Week 8 visit, however can also be based on value at Week 8 visit if a repeat (unscheduled) urinary copper excretion was performed at this visit. Result should be within the assay limits of quantification for the sample. The ranges in μmol of copper are 0.40 to 2.38 μmol/L for NCC and 1.59 to 14.29 for 24-hour urinary copper excretion (using division by 63 of value in μg per Walshe, 2011).

In the event that one or more of the above lab values fall outside the specified range, it can be repeated. The repeat value(s) must be available prior to randomization at Week 12 and, if within specified range, the patient can continue to randomization. If a patient fails this additional criterion at the end of the Penicillamine Baseline Period, the patient can return to the start of the run-in period i.e. Day 1 (but only once).

A negative urinary pregnancy test is also required prior to randomization for females of childbearing potential.

Exclusion criteria

1. Patient is in 'de-coppering' phase of treatment for Wilson's disease, in the opinion of the investigator

2. Patient evidence of uncontrolled liver disease, including but not limited to:

a. Modified Nazer score of > 4 (result may not be available until after start of run-in period since based on lab results*)
b. decompensated cirrhosis
c. acute hemolytic anemia
d. acute hepatitis
e. hepatic malignancy
f. evidence of acute liver failure

3. Cause of patient's liver disease is due to another condition, in the investigator's opinion

4. Patient has severe anemia defined as hemoglobin of ≤ 9 g/dL (result will be available

after start of run-in period*)

5. Patient has experienced a gastrointestinal bleed within 6 months (24 weeks) prior to screening/enrolment visit
6. Patient has renal impairment defined as creatinine clearance of ≤ 30 mL/min (result may not be available until after start of run-in period*), or patient has nephritis or nephrotic syndrome, in the opinion of the investigator
7. Patient has neurological disease that prevents swallowing of study medication (e.g. requires a nasogastric feeding tube) or requires intensive in-patient medical care
8. Patient is currently taking medication containing trientine for management of Wilson's disease or has taken it within 4 months (16 weeks) of screening/enrolment visit
9. Patient is currently receiving prescribed zinc therapy for management of Wilson's disease or has taken it within 4 months (16 weeks) of screening/enrolment visit
10. Patient is taking any of the following concomitant therapies: gold therapy, antimalarial therapy, cytotoxic drugs, oxyphenbutazone, phenyl butazone
11. Patient has a known intolerance, allergy or sensitivity to penicillamine (that is uncontrolled) or to TETA 4HCl, including any component of the study medication
12. For female patients of childbearing potential, planning a pregnancy during study period or currently nursing
13. For female patients of childbearing potential, unable or unwilling to use a reliable form of contraceptive throughout the study
14. Patient is currently participating in another therapeutic study, or has previously participated in a therapeutic study within 30 days of screening/enrolment visit (or longer, if local requirements specify this)
15. Patient has any condition or in any situation which, in the investigator's opinion, puts the patient at significant risk, could confound study results, or may interfere significantly with the patient's participation in the study

* Samples for screening/enrolment labs can be taken within ± 7 days of visit. In the event that lab value is above the specified threshold, it can be repeated, including at the Week 4 and Week 8 visits, with the result available prior to randomization at Week 12.

Test product, dose and mode of administration:
TETA 4HCl tablets
Each tablet contains 150 mg of trientine base.

Reference product, dose and mode of administration:
Penicillamine (each patient's current therapy)

Duration of treatment:
Each patient will receive chelation therapy (penicillamine/TETA 4HCl) for the duration of the study.

Dosage, dose regimen:

Day 1 to Week 12 (Penicillamine Baseline Period):

- All patients continue to receive their current penicillamine therapy.

- The total daily dose in milligrams (mg) is to be the same as the patient's current maintenance dose of penicillamine. This will be administered as 2 divided doses for all patients (BID).
- In the event that the total daily dose needs to be changed, this is permitted during the 4-week run-in period and subsequently, if deemed clinically necessary (see dose modification criteria)

Week 12 to Week 36 (24-week Post-randomization Phase)

- Patients are randomized to receive TETA 4HCl or to continue to receive their current penicillamine therapy
- For patients randomized to TETA 4HCl the total daily dose in mg of trientine base will be the same as the patient's total daily dose of penicillamine in mg at the end of the Penicillamine Baseline Period at Week 12, rounded to the nearest 150 mg, administered as 2 divided doses for all patients (BID)
- For patients randomized to penicillamine the total daily dose in mg will be the same as at the end of the Penicillamine Baseline Period at Week 12. This will be administered as 2 divided doses for all patients (BID)
- In the event that the total daily dose needs to be changed, this is permitted during the 4-week run-in period and subsequently, if deemed clinically necessary (see dose modification criteria)

Week 36 to Week 60 (first 24 weeks of Extension Phase)

- All patients continue to receive their allocated TETA 4HCl or penicillamine therapy according to their randomized allocation
- The total daily dose will be the continuation of the patient's total daily dose in mg (trientine base or penicillamine) at the end of the 24-week Post-randomization Phase at Week 36. This will continue to be administered as 2 divided doses for all patients (BID)
- In the event that the total daily dose needs to be changed, this is permitted, if deemed clinically necessary, during the Extension Phase (see dose modification criteria)

Week 60 to Week 108 (last 48 weeks of Extension Phase)

- All patients receive TETA 4HCL
- The total daily dose in mg of trientine base will be the same as the total daily dose the patient is receiving at the end of Week 60, rounded to the nearest 150 mg if the patient had been in the penicillamine arm. This will be administered as 2 divided doses for all patients (BID)
- In the event that the total daily dose needs to be changed, this is permitted at any time during the extension phase (see dose modification criteria)

Dose modification:

The investigator may modify (increase or decrease) the total daily dose of penicillamine or TETA 4HCl by protocol-defined increments if the patient is no longer fulfilling the protocol criteria of being adequately controlled and tolerating the chelation therapy. The investigator's decision therefore includes the evaluations of serum NCC, 24-hour urinary copper excretion, alanine transaminase (ALT) level, and any safety parameters that could warrant a change in dose; the investigator will also take into account other factors e.g. compliance with study medication. See protocol for full details.

Criteria for evaluation:

Efficacy measures:

Primary:

- Serum NCC concentration

Secondary:

- 24-hour urinary copper excretion
- Clinical stability assessment by independent Adjudication Committee
- Clinical Global Impression of Change (CGIC) rating scale

Other:

- Unified Wilson's Disease Rating Scale (UWDRS), neurological scale
- Serum total copper and serum ceruloplasmin concentrations

Safety measures:

- Adverse events and serious adverse events
  - Clinically significant laboratory abnormalities and significant changes in neurological signs/symptoms will be reported as AEs
- Hematology, biochemistry and coagulation analysis
- Urinalysis
- Neurological signs and symptoms (using the relevant UWDRS items)
- Cognitive assessment using the semantic verbal fluency test
- Modified Nazer score
- Vital signs (heart rate, blood pressure, respiration rate, body temperature)
- Urine pregnancy test (for females of childbearing potential)

Pharmacokinetic measures:

- Plasma samples will be obtained at designated sites/visits for patients who receive TETA 4HCl for subsequent pharmacokinetic evaluation of plasma concentrations of trientine and the metabolites N1-acetyltriethylenetetramine (MAT) and N1, N10-diacetyltriethylenetetramine (DAT)

Statistical methods:

The intention-to-treat population will consist of all randomized patients.

All safety analyses will be performed using the safety population, consisting of all patients who received at least one dose penicillamine in the Penicillamine Baseline Period.

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

Efficacy: The primary efficacy measure of the study is serum NCC concentration. The absolute values at screening/enrolment, Weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36, will be analysed using a restricted maximum likelihood (REML) based general linear model for correlated data. The model will be used to test if there is a difference between the absolute values of serum NCC in the two treatment groups at Week 36. Non-inferiority of TETA 4HCl compared to penicillamine will be declared if the limit of the one-sided 97.5% confidence interval of the difference in mean serum NCC level under these two treatments excludes the non-inferiority margin.

The same model will be used for the repeatedly measured 24-hour urinary copper excretion absolute values. In addition, the proportion of patients with serum NCC levels below certain thresholds at Week 36 will be summarised as will be the proportion of patients with 24-hour urinary copper excretion above certain thresholds, as will the proportion of patients remaining within the entry criteria ranges of serum NCC and urinary copper excretion.

The outcome of the adjudication will state whether patients are well controlled and clinically stable. The proportion of clinically stable patients at Week 36 and at Week 60 will be computed and reported with their 95% confidence intervals.

The results of the UWDRS neurological scale will also be presented, including graphical representation e.g. within-patient shifts.

Efficacy data for the Extension Phase will be summarized separately.

Safety: AEs will be summarized by system organ class (SOC), preferred term (PT), and treatment group as the number and percentage of patients with an event. The following subsets of AEs will also be summarized by treatment group: AEs related to study treatment, severe AEs, AEs leading to treatment withdrawal and SAEs.

Categorical endpoints will be summarized by frequencies and percentages, continuous endpoints by summary statistics.

Safety data for penicillamine will be tabulated separately for the following 4 periods: screening/enrolment visit to Week 12 visit (i.e. Penicillamine Baseline Period), Week 12 visit +1 day to Week 36 visit (i.e. 24-week Post-randomization Phase), Extension Phase from Week 36 visit +1 day up to Week 60 visit, Extension Phase from Week 60 visit +1 day to Week 108 visit, or end of treatment visit, whichever is earlier.