



Clinical trial results:

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

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2016-003876-29 |
| Trial protocol | DK DE GB AT IT BE |
| Global end of trial date | 18 January 2022 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 09 August 2023 |
| First version publication date | 09 August 2023 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | GMPO-131-002 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|--------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03539952 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | EudraCT Number: 2016-003876-29 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Orphalan SA |
| Sponsor organisation address | 226 Boulevard Voltaire, Paris, France, 75011 |
| Public contact | Clinical Trials Information, Orphalan SA, 33 1 42 49 82 64, naseem.s.amin@orphalan.com |
| Scientific contact | Clinical Trials Information, Orphalan SA, 33 1 42 49 82 64, naseem.s.amin@orphalan.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 04 October 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 January 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of trientine tetrahydrochloride compared with penicillamine in stable adult Wilson disease patients tolerant to penicillamine. In this non-inferiority randomised trial, the primary endpoint to determine efficacy is the mean difference of non-ceruloplasmin copper (NCC) in serum between the two treatment groups.

Protection of trial subjects:

Home visits were implemented to reduce the intensity of the 4-weekly post-randomization period (week 12-36) compared to 1 to 2 times a year for standard of care visits

Background therapy:

Eligible patients were adults aged between 18 and 75 years receiving penicillamine for at least one year for the treatment of Wilson's disease and on a stable dose for at least 4 months prior to enrolment.

Evidence for comparator:

Comparator:

The other approved chelator, penicillamine, is effective but known to be associated with a high frequency of adverse reactions. It is reported that approximately 30% of Wilson's disease patients prescribed penicillamine will experience adverse reactions; in the first 1-3 weeks of the treatment, this includes hyper-sensitivity reactions with fever, rash, lymphadenopathy, neutropenia, thrombocytopenia or total aplasia and proteinuria (Sternlieb and Schienberg, 1968), with long-term use associated with side effects including bone marrow toxicity, nephrotoxicity and lupus-like syndrome and dermatopathies (Gibbs and Walshe, 1966; Walshe, 1973; Walshe, 1989; Kumagi et al, 2004; Medici et al, 2007; Weiss et al, 2011).

| | |
|---|------------------|
| Actual start date of recruitment | 09 February 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Poland: 12 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Denmark: 2 |
| Country: Number of subjects enrolled | France: 11 |
| Country: Number of subjects enrolled | Germany: 17 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | United States: 2 |
| Country: Number of subjects enrolled | Brazil: 17 |

| | |
|------------------------------------|----|
| Worldwide total number of subjects | 77 |
| EEA total number of subjects | 54 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 73 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients were recruited by selected WD centers. The randomization target was set at 55. Recruitment took place over a period of almost 2 years and ended December 2019

Pre-assignment

Screening details:

WD patients who are considered to be stable by the site investigator, on their standard-of-care penicillamine chelation therapy for at least 1 year, are eligible and once eligible for the study, will enter a 12-week Penicillamine Baseline Period comprising of 1 month (4 weeks) run-in period followed by a 2 month (8 weeks) evaluation period.

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 77 |
| Number of subjects completed | 77 |

Period 1

| | |
|------------------------------|-----------------------------------|
| Period 1 title | Screen and baseline run-in period |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Adjudication to confirm baseline eligibility before randomization were blinded to subject number and site number

Arms

| | |
|-----------|----------------------------|
| Arm title | Screen and run-in failures |
|-----------|----------------------------|

Arm description:

All subject that were screened, and failed to meet the enrolment criteria between screening and randomization

| | |
|--|-----------------|
| Arm type | Baseline run-in |
| Investigational medicinal product name | Penicillamine |
| Investigational medicinal product code | |
| Other name | D-penicillamine |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

The total daily dose in milligrams of penicillamine to be administered from Day 1 onwards is the same total daily dose in milligrams as the patient's maintenance dose of penicillamine prior to enrolment in the study.

From Day 1 onwards, the total daily dose is to be administered as two divided doses (BID). If the dose does not divide equally then the higher number of capsules should be taken at the first administration of the day.

| Number of subjects in period 1 | Screen and run-in failures |
|--------------------------------|----------------------------|
| Started | 77 |
| Completed | 53 |
| Not completed | 24 |
| Eligibility criteria not met | 17 |
| Consent withdrawn by subject | 4 |
| Physician decision | 1 |
| Lost to follow-up | 2 |

Period 2

| | |
|------------------------------|----------------------------------|
| Period 2 title | Post randomization phase W12-W36 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Penicillamine arm |

Arm description:

All patients in the penicillamine arm will receive following treatments:

Period 1: penicillamine

Period 2: penicillamine

Period 3: penicillamine

Period 4: TETA 4HCl

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Penicillamine |
| Investigational medicinal product code | |
| Other name | D-penicillamine |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Each patient will receive its individual daily dose , given as twice daily

| | |
|------------------|----------------------------------|
| Arm title | Trientine tetrahydrochloride arm |
|------------------|----------------------------------|

Arm description:

All patients in the trientine tetrahydrochloride arm will receive following treatments:

Period 1: penicillamine

Period 2: TETA 4HCl

Period 3: TETA 4HCl

Period 4: TETA 4HCl

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | TETA 4HCl |
| Investigational medicinal product code | |
| Other name | trientien tetrahydrochloride, Cuprior |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The total daily dose in milligrams of trientine base has been the same total daily dose in milligrams of

penicillamine administered at the end of the Penicillamine Baseline Period at Week 12, rounded to the nearest 150 mg of trientine base. Each patient will receive its individual daily dose, given as twice daily

| Number of subjects in period 2 | Penicillamine arm | Trientine tetrahydrochloride arm |
|--------------------------------|-------------------|----------------------------------|
| | | |
| Started | 27 | 26 |
| Completed | 26 | 26 |
| Not completed | 1 | 0 |
| Consent withdrawn by subject | 1 | - |

Period 3

| | |
|------------------------------|----------------------------|
| Period 3 title | 1st Extension phase W36-60 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Penicillamine arm |

Arm description:

All patients in the penicillamine arm will receive following treatments:

Period 1: penicillamine

Period 2: penicillamine

Period 3: penicillamine

Period 4: TETA 4HCl

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Penicillamine |
| Investigational medicinal product code | |
| Other name | D-penicillamine |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Each patient will receive its individual daily dose , given as twice daily

| | |
|------------------|----------------------------------|
| Arm title | Trientine tetrahydrochloride arm |
|------------------|----------------------------------|

Arm description:

All patients in the trientine tetrahydrochloride arm will receive following treatments:

Period 1: penicillamine

Period 2: TETA 4HCl

Period 3: TETA 4HCl

Period 4: TETA 4HCl

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------------------------------|
| Investigational medicinal product name | TETA 4HCl |
| Investigational medicinal product code | |
| Other name | trientine tetrahydrochloride, Cuprior |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The total daily dose in milligrams of trientine base was the same total daily dose in milligrams of penicillamine administered at the end of the Penicillamine Baseline Period at Week 12, rounded to the nearest 150 mg of trientine base. Each patient will receive its individual daily dose, given as twice daily

| Number of subjects in period 3 | Penicillamine arm | Trientine tetrahydrochloride arm |
|--------------------------------|-------------------|----------------------------------|
| | | |
| Started | 26 | 26 |
| Completed | 19 | 23 |
| Not completed | 7 | 3 |
| Consent withdrawn by subject | 3 | 1 |
| Adverse event, non-fatal | 1 | 1 |
| Other: not further specified | 3 | 1 |

Period 4

| | |
|------------------------------|--------------------------------|
| Period 4 title | 2nd Extension phase W60 ≤ W108 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Penicillamine arm |

Arm description:

All patients in the penicillamine arm will receive following treatments:

Period 1: penicillamine

Period 2: penicillamine

Period 3: penicillamine

Period 4: TETA 4HCl

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | TETA 4HCl |
| Investigational medicinal product code | |
| Other name | trientine tetrahydrochloride, Cuprior |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The total daily dose in milligrams of trientine base to be administered will be the same total daily dose in milligrams of penicillamine administered at the end of the Penicillamine previous Period at Week 60, rounded to the nearest 150 mg of trientine base. Each patient will receive its individual daily dose, given as twice daily

| | |
|------------------|----------------------------------|
| Arm title | Trientine tetrahydrochloride arm |
|------------------|----------------------------------|

Arm description:

All patients in the trientine tetrahydrochloride arm will receive following treatments:

Period 1: penicillamine

Period 2: TETA 4HCl

Period 3: TETA 4HCl

Period 4: TETA 4HCl

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | TETA 4HCl |
| Investigational medicinal product code | |
| Other name | trientine tetrahydrochloride, Cuprior |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Each patient will receive its individual daily dose , given as twice daily

| Number of subjects in period 4 | Penicillamine arm | Trientine tetrahydrochloride arm |
|---------------------------------------|-------------------|----------------------------------|
| | | |
| Started | 19 | 23 |
| Completed | 19 | 21 |
| Not completed | 0 | 2 |
| Adverse event, serious fatal | - | 1 |
| Consent withdrawn by subject | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|-----------------------------------|
| Reporting group title | Screen and baseline run-in period |
| Reporting group description: - | |

| Reporting group values | Screen and baseline run-in period | Total | |
|---|-----------------------------------|-------|--|
| Number of subjects | 77 | 77 | |
| Age categorical | | | |
| Age was defined to be between 18 and 75 years (extremes included), at the time of consent | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 73 | 73 | |
| From 65-84 years | 4 | 4 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 42.9 | | |
| standard deviation | ± 14.50 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 38 | 38 | |
| Male | 39 | 39 | |

Subject analysis sets

| | |
|---|----------------------------------|
| Subject analysis set title | Penicillamine arm |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All subjects randomized to Penicillamine treatment | |
| Subject analysis set title | Trientine tetrahydrochloride arm |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All subjects randomized to TETA 4HCl treatment | |

| Reporting group values | Penicillamine arm | Trientine tetrahydrochloride arm | |
|---|-------------------|----------------------------------|--|
| Number of subjects | 27 | 26 | |
| Age categorical | | | |
| Age was defined to be between 18 and 75 years (extremes included), at the time of consent | | | |
| Units: Subjects | | | |
| In utero | 0 | | |

| | | | |
|---|---------|---|--|
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 51 | | |
| From 65-84 years | 2 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 43.6 | | |
| standard deviation | ± 14.49 | ± | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 28 | | |
| Male | 25 | | |

End points

End points reporting groups

| | |
|---|----------------------------------|
| Reporting group title | Screen and run-in failures |
| Reporting group description: All subject that were screened, and failed to meet the enrolment criteria between screening and randomization | |
| Reporting group title | Penicillamine arm |
| Reporting group description: All patients in the penicillamine arm will receive following treatments: Period 1: penicillamine Period 2: penicillamine Period 3: penicillamine Period 4: TETA 4HCl | |
| Reporting group title | Trientine tetrahydrochloride arm |
| Reporting group description: All patients in the trientine tetrahydrochloride arm will receive following treatments: Period 1: penicillamine Period 2: TETA 4HCl Period 3: TETA 4HCl Period 4: TETA 4HCl | |
| Reporting group title | Penicillamine arm |
| Reporting group description: All patients in the penicillamine arm will receive following treatments: Period 1: penicillamine Period 2: penicillamine Period 3: penicillamine Period 4: TETA 4HCl | |
| Reporting group title | Trientine tetrahydrochloride arm |
| Reporting group description: All patients in the trientine tetrahydrochloride arm will receive following treatments: Period 1: penicillamine Period 2: TETA 4HCl Period 3: TETA 4HCl Period 4: TETA 4HCl | |
| Reporting group title | Penicillamine arm |
| Reporting group description: All patients in the penicillamine arm will receive following treatments: Period 1: penicillamine Period 2: penicillamine Period 3: penicillamine Period 4: TETA 4HCl | |
| Reporting group title | Trientine tetrahydrochloride arm |
| Reporting group description: All patients in the trientine tetrahydrochloride arm will receive following treatments: Period 1: penicillamine Period 2: TETA 4HCl Period 3: TETA 4HCl Period 4: TETA 4HCl | |
| Reporting group title | Penicillamine arm |
| Reporting group description: All patients in the penicillamine arm will receive following treatments: Period 1: penicillamine Period 2: penicillamine Period 3: penicillamine Period 4: TETA 4HCl | |
| Reporting group title | Trientine tetrahydrochloride arm |
| Reporting group description: All patients in the trientine tetrahydrochloride arm will receive following treatments: Period 1: penicillamine Period 2: TETA 4HCl Period 3: TETA 4HCl Period 4: TETA 4HCl | |
| Subject analysis set title | Penicillamine arm |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All subjects randomized to Penicillamine treatment | |
| Subject analysis set title | Trientine tetrahydrochloride arm |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All subjects randomized to TETA 4HCl treatment | |

Primary: Serum Non-ceruloplasmin bound copper (NCC) concentration

| | |
|-----------------|--|
| End point title | Serum Non-ceruloplasmin bound copper (NCC) concentration |
|-----------------|--|

End point description:

Summary statistics

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Week 36

| End point values | Penicillamine arm | Trientine tetrahydrochloride arm | | |
|--------------------------------------|-------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 26 | | |
| Units: µg/L | | | | |
| arithmetic mean (standard deviation) | 46.5 (± 5.69) | 58.7 (± 5.54) | | |

Statistical analyses

| | |
|----------------------------|-------------------------|
| Statistical analysis title | Serum NCC Concentration |
|----------------------------|-------------------------|

Statistical analysis description:

The primary endpoint was the assessment of the non-inferiority of TETA 4HCl in relation to D-penicillamine. The non-inferiority assessment was made on the basis of the mean serum NCC level at Week 36

| | |
|---|--|
| Comparison groups | Penicillamine arm v Trientine tetrahydrochloride arm |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Mean difference (net) |
| Point estimate | -9.2 |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| lower limit | -50 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 7.49 |

Notes:

[1] - The primary efficacy analysis utilized the serum NCC values from all study visits that were analyzed up to week 36 using a restricted maximum likelihood based general linear model for correlated data. The correlation due to repeated measures was modeled by specifying the variance covariance matrix. Considering a comparison of means in both treatment arms (D-penicillamine minus TETA 4HCl) at the 1-sided 2.5% level of Type 1 error, a noninferiority margin of 50 µg/L was used

Secondary: 24-hour Urinary Copper Excretion (UCE)

| | |
|-----------------|--|
| End point title | 24-hour Urinary Copper Excretion (UCE) |
|-----------------|--|

End point description:

24-hour urinary copper excretion (µg/ 24 hr) from urine collected by the patient over a 24-hour period, at week 12 (end of Baseline) and at week 36 (end of period 2, post randomization)

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 36

| End point values | Penicillamine arm | Trientine tetrahydrochloride arm | | |
|--------------------------------------|-------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 26 | | |
| Units: µg/24 hours | | | | |
| arithmetic mean (standard deviation) | 510.8 (± 47.77) | 274.5 (± 45.59) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

To allow for a direct comparison between treatments, only treatment emergent adverse events from week 12 to 36 and from week 36 to 60 are reported.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 21.1 |

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Penicillamine arm (W12-36) |
|-----------------------|----------------------------|

Reporting group description:

WD patients that were adequately controlled and tolerating penicillamine at the end of the baseline period and being randomized to the penicillamine arm to continue in the 24 week post randomization phase (period 1) on penicillamine. Only (S)AEs reported during the 24 post randomization phase are reflected

| | |
|-----------------------|------------------------|
| Reporting group title | TETA 4HCl arm (W12-36) |
|-----------------------|------------------------|

Reporting group description:

WD patients that were adequately controlled and tolerating penicillamine at the end of the baseline period and being randomized to the TETA 4HCl arm to continue in the 24 week post randomization phase (period 1) on TETA 4HCl. Only (S)AEs reported during the 24 post randomization phase are reflected

| | |
|-----------------------|----------------------------|
| Reporting group title | Penicillamine arm (W36-60) |
|-----------------------|----------------------------|

Reporting group description:

WD patients that were adequately controlled and tolerating penicillamine at the end of the 24 week post randomization phase (period 1) on penicillamine continued on the same treatment in the 1st extension after the post randomization phase (period 1), i.e., penicillamine. Only (S)AEs reported during the 1st extension (W36-60) are reflected

| | |
|-----------------------|------------------------|
| Reporting group title | TETA 4HCl arm (W36-60) |
|-----------------------|------------------------|

Reporting group description:

WD patients that were adequately controlled and tolerating TETA 4HCl at the end of the 24 week post randomization phase (period 1) continued on the same treatment in the 1st extension after the post randomization phase (period 1), i.e., TETA 4HCl. Only (S)AEs reported during the 1st extension (W36-60) are reflected.

| Serious adverse events | Penicillamine arm (W12-36) | TETA 4HCl arm (W12-36) | Penicillamine arm (W36-60) |
|---|----------------------------|------------------------|----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 0 / 26 (0.00%) | 0 / 24 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cholangiocarcinoma | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 26 (0.00%) | 0 / 24 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic cancer | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 26 (0.00%) | 0 / 24 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 26 (0.00%) | 0 / 24 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------------|--|--|
| Serious adverse events | TETA 4HCl arm (W36-60) | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cholangiocarcinoma | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic cancer | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 25 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Penicillamine arm (W12-36) | TETA 4HCl arm (W12-36) | Penicillamine arm (W36-60) |
|---|-------------------------------|---------------------------|-------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 27 (33.33%) | 6 / 26 (23.08%) | 3 / 24 (12.50%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 26 (7.69%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 26 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 5 / 27 (18.52%) | 2 / 26 (7.69%) | 1 / 24 (4.17%) |
| occurrences (all) | 8 | 4 | 1 |
| Dizziness | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 26 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 26 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastrointestinal disorders | | | |

| | | | |
|--|---------------------|-----------------------|---------------------|
| Abdominal pain alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 4 / 26 (15.38%) 12 | 0 / 24 (0.00%) 0 |
| Abnormal faeces alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 2 / 26 (7.69%) 3 | 0 / 24 (0.00%) 0 |
| Dry mouth alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 2 / 26 (7.69%) 2 | 0 / 24 (0.00%) 0 |
| Constipation alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 2 / 26 (7.69%) 2 | 0 / 24 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Alopecia alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 2 / 26 (7.69%) 2 | 0 / 24 (0.00%) 0 |
| Renal and urinary disorders Urinary tract infection alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 26 (0.00%) 0 | 2 / 24 (8.33%) 2 |
| Psychiatric disorders Mood swings alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 2 / 26 (7.69%) 2 | 0 / 24 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia alternative assessment type: Systematic | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 3 / 27 (11.11%) 3 | 1 / 26 (3.85%) 1 | 0 / 24 (0.00%) 0 |
| Infections and infestations Gastroenteritis viral alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 2 / 26 (7.69%) 2 | 0 / 24 (0.00%) 0 |

| | | | |
|---|--|--|--|
| Non-serious adverse events | TETA 4HCl arm (W36-60) | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 1 / 25 (4.00%) | | |
| Investigations Alanine aminotransferase increased alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | | |
| Injury, poisoning and procedural complications Fall alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | | |
| Nervous system disorders Headache alternative assessment type: Systematic subjects affected / exposed occurrences (all) Dizziness alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 | | |
| General disorders and administration site conditions Pyrexia alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | | |
| Gastrointestinal disorders | | | |

| | | | |
|---|--|--|--|
| <p>Abdominal pain</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>0 / 25 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Abnormal faeces</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>0 / 25 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Dry mouth</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>0 / 25 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Constipation</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>0 / 25 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Alopecia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>0 / 25 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Renal and urinary disorders</p> <p>Urinary tract infection</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>1 / 25 (4.00%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Psychiatric disorders</p> <p>Mood swings</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>0 / 25 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>alternative assessment type: Systematic</p> | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | | |
| Infections and infestations Gastroenteritis viral alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36183738>