TRIENTINE DIHYDROCHLORIDE VS. TETRAHYDROCHLORIDE: A PHASE 1, SINGLE CENTER, RANDOMIZED, INTERVENTIONAL, SINGLE DOSE, OPEN-LABEL, CROSSOVER STUDY IN ADULT HEALTHY MALE AND FEMALE SUBJECTS TO EVALUATE THE PHARMACOKINETICS AND THE SAFETY, TOLERABILITY OF TWO DIFFERENT ORAL FORMULATIONS

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Iron and trace metal metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON42700

Source
ToetsingOnline

Brief title
GMPO-131-001

Condition

- Iron and trace metal metabolism disorders

Synonym
excessive copper accumulation, Wilsons disease

Research involving
Human

Sponsors and support

Primary sponsor: GMP-Orphan SAS
Source(s) of monetary or material Support: GMP-Orphan SAS

Intervention

Keyword: CROSSOVER, PHARMACOKINETICS, PHASE 1, RANDOMIZED

Outcome measures

Primary outcome

To assess and compare the plasmatic PK profiles of single doses of trientine

dichlorhydrate (TETA•2HCl) and trientine tetrachlorhydrate

(TETA•4HCl) in adult heathy volunteers.

Secondary outcome

Safety analyses will be conducted on all subjects who have received at least

one dose of TETA•2HCl or TETA•4HCl

Study description

Background summary

Wilson*s disease (WD) is a life-threatening inborn error of copper metabolism leading to an excessive copper accumulation, mainly in the liver or brain, causing hepatic and neurologic severe symptoms (Gitlin 2003). The gene responsible for WD, ATP7B, was identified on chromosome 13 (Tanzi 1993). The gene ATP7B is highly expressed in the liver, kidney, and placenta. The product

of ATP7B is a copper-transporting P-type ATPase responsible for transporting copper from intracellular chaperone proteins into the secretory pathway, both for excretion into bile and for incorporation into apoceruloplasmin for the synthesis of the functional plasma protein ceruloplasmin (Tao 2003). More than 500 distinct mutations have been described in the Wilson gene, from which 380 have a confirmed role in the pathogenesis of the disease (refer to the WD mutation database).

Normal dietary consumption and absorption of copper, approximately 1 to 2 mg per day , exceeds the metabolic need, approximately 0.75 mg daily, and homeostasis of this element is maintained exclusively by the biliary excretion of copper (Ala 2007).
The most common presentations are with liver disease or neuropsychiatric disturbances.
In about 40% of WD patients, hepatic symptoms are highly variable, from asymptomatic, with only biochemical abnormalities, to overt cirrhosis with all its complications, or acute hepatic failure sometimes associated with Coombs-negative hemolytic anemia, acute renal failure or chronic hepatic disease. Indeed, WD accounts for 6-12% of all patients with acute liver failure who are referred for emergency transplantation.
About one-third of all WD patients initially present with psychiatric abnormalities, like declining school performance, personality changes, impulsiveness, labile mood, sexual exhibitionism, inappropriate behavior, paranoia, schizophrenia or depression.
The neurological abnormalities, which usually present in the third decade of life, are the initial symptoms of WD in approximately 40-50 % of patients (Yarze 1992). Those neurologic disturbances can be classified as akinetic-rigid syndrome similar to Parkinson*s disease, pseudosclerosis dominated by tremor, ataxia, and dystonic syndrome.
The main ophthalmologic changes are Kayser-ayseres o rings, caused by deposition of copper in Descemets membrane of the cornea, present in 95% of patients with neurologic symptoms and somewhat over half of those without neurologic symptoms. Other ophthalmologic changes are rare and include sunflower cataracts, which are caused by deposits of copper in the center of the lens.

Less common presentations include gigantism, lunulae, renal abnormalities including aminoaciduria and nephrolithiasis, hypercalciuria and nephrocalcinosis, cardiomyopathy, myopathy, chondrocalcinosis and osteoarthritis, hypoparathyroidism, pancreatitis, infertility or repeated miscarriages.

Untreated WD, or in case of a poor adherence to drug therapy (when a patient starts skipping doses daily for months), is universally fatal, with most patients dying from liver disease and a minority from complications of progressive neurologic disease. WD is therefore chronically debilitating and life threatening.

In general, prognosis for survival depends on the severity of liver and neurological disease, and compliance with drug treatment, to avoid the recurrence of symptoms and progression of the disease (Ala 2007)

Trientine, also referred to as triethylene tetramine, is an organic compound with the formula [CH2NHCH2CH2NH2]2. This oily liquid is colorless but, like many amines, assumes a yellowish color due to impurities resulting from air-oxidation. It is soluble in polar solvents and exhibits the reactivity typical for amines. In terms of activity, trientine exhibits chelating properties.

The first trientine salt developed was a dihydrochloride (also referred to as trientine hydrochloride). It is a registered drug in United Kingdom (marketing authorization number PL 41626/0001 delivered on 8 August 1985, renewed on 16 April 1996), authorized in WD patients who are intolerant to D-penicillamine.

GMP-orphan has formulated a different already known trientine salt, trientine tetrahydrochloride (TETA•4HCl) for the treatment of WD. TETA•4HCl has largely been used over more than two decade in France through a named-patient program for WD patients intolerant to D-penicillamine, and has been therefore integrated in the French guidelines for the management of WD patients (refer to Haute Autorite* de Sante* (or French National Authority for Health), French guidelines in WD.

Trientine is a chelating agent with a polyamine structure chemically, distinct from D-penicillamine, which chelates copper by the formation of stable complexes with the four constituent nitrogens in a planar ring (Ala 2007, Boiocchi 2005). Like D-penicillamine, trientine promotes urinary copper excretion.

The rationale for developing this tetrahydrochloride salt is that, unlike the dihydrochloride, TETA•4HCl is stable at room temperature, has been developed as a convenient pharmaceutical formulation for adults as well as children, and will improve WD patients* access throughout EU.

Study objective

The principal aim of this study is to evaluate the PK parameters of both oral formulations in adult healthy volunteers in order to propose for Marketing Authorization Application an adequate strength for TETA•4HCl (i.e. a strength providing a PK profile similar to TETA•2HCl)

Study design

This is a single center, randomized, interventional, single dose, cross-over study to explore the safety, tolerability and PK of both oral formulations

(capsules of TETA•2HCl and tablets of TETA•4HCl) in adult healthy male and female subjects.

Intervention

Single dose of 900 mg of TETA•2HCl (i.e. 3 capsules of 300 mg containing each 225 mg of trientine base) or 1200 mg TETA•4HCl (i.e. 4 tablets of 300 mg containing each 150 mg of trientine base) will be given (crossover design)

Study burden and risks

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Contacts

Public
GMP-Orphan SAS

rue du Pasteur Wagner 7
Paris 75011
FR
Scientific
GMP-Orphan SAS

rue du Pasteur Wagner 7
Paris 75011
FR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy male and female volunteers aged 18 to 45 years

Exclusion criteria

Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study, including bowel, gastrointestinal, renal, pulmonary, pancreatic, hepatic, hematological, immunological, or neurological disorder

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-06-2015
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	TETA•4HCl
Product type:	Medicine

Brand name:	Trientine
Generic name:	Trientine dihydrochloride capsules 300 mg

Ethics review

Approved WMO Date:	04-06-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-06-2015
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-002199-25-NL
CCMO	NL53662.056.15