ISRCTN64925094 https://doi.org/10.1186/ISRCTN64925094

Study to assess whether the amount of drugs that reach the blood circulation, are metabolised and eliminated after the intake by healthy volunteers under fasting conditions of one new capsule containing both ramipril and furosemide, is the same as after the intake of two separate tablets Triatec (ramipril) and Lasix (furosemide)

Submission date	Recruitment status	[_] Prospectively registered
11/05/2021	No longer recruiting	[_] Protocol
Registration date	Overall study status	[_] Statistical analysis plan
18/05/2021	Completed	[_] Results
Last Edited	Condition category	[_] Individual participant data
18/05/2021	Other	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Neopharmed Gentili S.p.A. developed a fixed dose combination of ramipril and furosemide, which are often co-prescribed for the treatment of chronic heart failure. The present randomised cross-over, two-stage bioequivalence study aims at demonstrating the bioequivalence (similar effects on and processing by the body) of the novel fixed combination (10 mg of ramipril/25 mg of furosemide) vs. the extemporaneous combination of 2 marketed reference products.

Who can participate?
Healthy men and women volunteers aged 18 - 55 years

What does the study involve?
A single oral dose of test (T) and reference (R) treatments, both combining ramipril 10 mg and furosemide 25 mg, will be administered to healthy male and female volunteers under fasting conditions in two study periods according to a randomised 2-way cross-over design, with a wash-out interval of at least 5 days between consecutive administrations.
During the study, blood samples will be collected from participants for the measurement of ramipril and furosemide in the bloodstream. The subject heart rate and blood pressure will be measured, ECG will be recorded and laboratory tests on blood and urine will be performed to test the safety of the medications.

What are the possible benefits and risks of participating?
No specific benefits for the participants in the current study are foreseen. Their remuneration will be paid after study completion. The remuneration covers loss of time and any inconvenience caused by the participation in the study.
No particular risks are expected for the study subjects originating from the ramipril and furosemide dose regimen scheduled in the present study, considering that both ramipril and furosemide are well known drugs that have been used for decades. Undesired effects which may occur frequently during treatment with ramipril (defined as common untoward effects which occur at a frequency <1/10, but ≥1/100) include headache, dizziness, hypotension, orthostatic blood pressure decrease, syncope, non-productive tickling cough, bronchitis, sinusitis, dyspnoea, gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting, elevation in blood potassium, rash in particular maculopapular, muscle spasms, myalgia, chest pain and fatigue. Common undesired events that may occur with furosemide treatment include haemoconcentration, electrolytes imbalance (hyponatremia, hypochloremia, hypokalaemia, hepatic encephalopathy (in patients with hepatocellular insufficiency), arterial pressure reduction, including orthostatic hypotension (after intravenous infusion), and polyuria. According to the literature, no drug-drug interaction between ramipril and furosemide is known; however, as both drugs tested in the present study lower blood pressure, there is the risk of severe hypotension and renal function impairment.

Where is the study run from?
Neopharmed Gentili S.p.A. (Italy)

When is the study starting and how long is it expected to run for?
March 2019 to May 2020

Who is funding the study?
Neopharmed Gentili S.p.A., Italy

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CRO-PK-19-336 - Sponsor code NG8707/C03

Study information

Scientific Title
Bioequivalence study of a new ramipril 10 mg/furosemide 25 mg hard capsule fixed dose combination (Neopharmed Gentili S.p.A.) versus a free combination of ramipril 10 mg tablets (Triatec®, Sanofi-Aventis) and furosemide 25 mg tablets (Lasix®, Sanofi-Aventis) in healthy male and female volunteers under fasting conditions

Study objectives
To investigate the bioequivalence of ramipril and furosemide, when administered in single dose in 2 consecutive cross-over periods as a fixed combination (ramipril 10 mg/furosemide 25 mg hard capsules) versus a free combination of ramipril 10 mg tablets (Triatec®) and furosemide 25 mg tablets (Lasix®) to healthy male and female volunteers under fasting conditions.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/04/2019, Cantonal Ethics Committee Canton Ticino (c/o Health Office, Via Orico 5, 6501 Bellinzona, Switzerland; +41 (0)91 8143057; dss-ce@ti.ch), ref: 2019-00541 CE 3461

Study design
Single dose open-label randomized two-period cross-over two-stage bioequivalence study

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Bioequivalence study in healthy volunteers

Interventions
A single dose of test (T) and reference (R) treatments, both combining ramipril 10 mg and furosemide 25 mg, will be administered to healthy male and female volunteers under fasting conditions in two study periods according to a randomised 2-way cross-over design, with a wash-out interval of at least 5 days between consecutive administrations.

Both test and reference treatments will be orally administered in the morning of study Day 1, at 8:00±1 h. One hard capsule of fixed dose combination of ramipril 10 mg/furosemide 25 mg (T) or one tablet of Triatec®, 10 mg ramipril + one tablet of Lasix®, 25 mg furosemide (R) will be swallowed with 150 mL of still mineral water by the subjects.

Regarding the randomisation procedure, subjects will be assigned to one sequence of treatments (TR or RT), according to the randomisation list, to receive one of the two treatments (T or R) during period 1 and the other treatment during period 2 or vice versa. Randomisation number will be given to the subjects on study Day -1, Period 1, and will be used to assign the subject to one treatment sequence.

During the interventional phase, blood samples will be collected for pharmacokinetic analysis at pre-dose (0) and 10, 20, 30, 40, 50 min and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8 and 12 h post-dose in each of the 2 study periods. Each sample will be processed for the determination of the concentration of ramipril and furosemide in plasma.
Safety and general tolerability of the investigational products will be based on adverse events, ECG, physical examinations including body weight, vital signs and routine haematology, blood chemistry and urinalysis laboratory tests.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
ramipril, furosemide

Primary outcome(s)
Bioequivalent rate (Cmax) and extent (AUC0-t) of absorption of ramipril and furosemide calculated from plasma concentrations after single dose administration of T and R treatments (where Cmax = Maximum plasma concentration and AUC0-t = Area under the concentration-time curve from administration to the last observed concentration time t, calculated with the linear trapezoidal method)

Key secondary outcome(s))

1. The plasma pharmacokinetic profile of ramipril and furosemide in terms of AUC0-t, tmax, t1/2 and Frel calculated from plasma concentrations after single dose administration of T and R treatments (where AUC0-t = Area under the concentration-time curve extrapolated to infinity, calculated, if feasible, as AUC0-t + Ct/λz, where Ct is the last measurable drug concentration and λz = Terminal elimination rate constant, calculated, if feasible, by log-linear regression using at least 3 points, where tmax = Time to achieve Cmax, where t1/2 = Half-life, calculated, if feasible, as ln2/λz, where Frel = Relative bioavailability, calculated as ratio AUC0-t (test)/ AUC0-t (reference))
2. Safety and tolerability data of test and reference treatments after single dose administration measured using adverse events, vital signs (blood pressure and heart rate), body weight, ECG, laboratory parameters taken from case report forms

Completion date
18/05/2020

Eligibility

Key inclusion criteria
1. Informed consent: signed written informed consent before inclusion in the study
2. Sex and Age: males/females, 18 - 55 year old inclusive
3. Body Mass Index: 18.5 - 28 kg/m² inclusive
4. Vital signs: systolic blood pressure 100 - 139 mmHg, diastolic blood pressure 60 - 89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting position
5. Body temperature: 35.7 - 37.5° C at screening
6. Full comprehension: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study
7. Contraception and fertility (women): women of child-bearing potential must be using at least one of the following reliable methods of contraception:
7.1. Hormonal oral, implantable, transdermal or injectable contraceptives for at least 2 months before the screening visit
7.2. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
7.3. A male sexual partner who agrees to use a male condom with spermicide
7.4. A sterile sexual partner
Female participants of non-child-bearing potential or in post-menopausal status for at least one year will be admitted.
For all women, pregnancy test result must be negative at screening and Day -1.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit

18 years

Sex
All

Total final enrolment
48

Key exclusion criteria
1. Electrocardiogram (12-lead ECG in supine position): clinically significant abnormalities
2. Physical findings: clinically significant abnormal physical findings indicative of physical illness
3. Laboratory analyses: clinically significant abnormal laboratory values indicative of physical illness
4. Virology: positive result of serum virology assays
5. Allergy: ascertained or presumptive hypersensitivity to the active principles and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may affect the outcome of the study
6. Hypotension and heart rate: during the screening procedures or history of orthostatic hypotension or syncope/fainting or heart rate <50 bpm
7. Diseases: significant history of renal, hepatic, cardiovascular, respiratory, skin, haematological, endocrine, neurological, psychiatric and in particular gastrointestinal diseases that may interfere with the aim of the study. History of heart failure. Raynaud's syndrome. Events of haemorrhage (e.g. epistaxis) for 90 days before the day of screening
8. Medications: any medications, including over the counter medications, herbal remedies and vitamins for 2 weeks before the start of the study. Organ-toxic drugs (e.g. any drug with a well-defined potential for toxicity to a major organ or system such as chloramphenicol, which may cause bone marrow suppression) and systemic drugs known to alter hepatic metabolism within 3 months before first dosing. Any prescription systemic treatment within 28 days before first dosing. Hormonal contraceptives for women will be allowed.
9. Investigative drug studies: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
10. Blood donation: blood donations for 3 months before this study
11. Drug, alcohol, caffeine, tobacco: history of drug, alcohol (>1 drink/day for women and >2 drinks/day for men, defined according to the USDA Dietary Guidelines 2015-2020), caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
12. Drug test: positive result at the drug test at screening
13. Alcohol test: positive alcohol breath test at Day -1
14. Diet: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians
15. Pregnancy (women only): positive or missing pregnancy test at screening or Day -1, pregnant or lactating women

Date of first enrolment
25/10/2019

Date of final enrolment
24/11/2019

Locations

Countries of recruitment
Switzerland

Study participating centre
CROSS Research S.A. - Phase I Unit
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Sponsor information

Organisation
Neopharmed Gentili S.p.A.

Funder(s)

Funder type
Industry

Funder Name
Neopharmed Gentili S.p.A.

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes