ISRCTN35244287 https://doi.org/10.1186/ISRCTN35244287

Bioequivalence study of a new capsule containing ramipril 10 mg and bisoprolol fumarate 5 mg (Neopharmed Gentili S.r.l.) versus the simultaneous administration of ramipril 10 mg tablets (Triatec®, Sanofi-Aventis) and bisoprolol fumarate 5 mg film coated tablets (Congescor®, Daiichi Sankyo) in healthy male and female volunteers under fasting conditions

Submission date
05/12/2018

Recruitment status
No longer recruiting

Registration date
18/04/2019

Overall study status
Completed

Last Edited
18/04/2019

Condition category
Other

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
NG 8706 is a new fixed dose combination containing ramipril and bisoprolol, developed by Neopharmed Gentili S.r.l., Italy. Ramipril and bisoprolol are frequently prescribed in association for the treatment of essential hypertension (high blood pressure). Ramipril is used to treat hypertension and congestive heart failure. Ramipril works by relaxing the smooth muscles of small blood vessels, which in turn reduces blood pressure (BP). Bisoprolol's effects include a reduction of heart rate, cardiac output, BP and possibly reflex orthostatic hypotension. Bisoprolol is used for the secondary prevention of myocardial infarction, heart failure, angina pectoris and mild to moderate hypertension. Neopharmed Gentili S.r.l., Italy, has developed 6 strength combinations as immediate release capsules. The proposed 6 strength combinations cover the majority of the needs of patients in terms of combined therapy. The aim of this study is to compare the new fixed combination at the highest dose (10 mg of ramipril/5 mg of bisoprolol) with the combination of two marketed reference products.

Who can participate?
Healthy volunteers aged 18-55

What does the study involve?
A single dose of the test product and of the reference products, both corresponding to ramipril 10 mg and bisoprolol fumarate 5 mg, is given to healthy volunteers under fasting conditions in two study periods, with a break of at least 14 days. Vitals signs are checked and blood samples are collected at specific timepoints.

What are the possible benefits and risks of participating?
Both ramipril and bisoprolol are well known drugs which have been used for decades. No specific benefits for the participants in the current study were foreseen, except for the physical examination as part of the study procedures and a possible, although not certain, positive wellbeing effect.

Where is the study run from?
CROSS Research SA (Switzerland)

When is the study starting and how long is it expected to run for?
July 2017 to October 2017

Who is funding the study?
Neopharmed Gentili S.r.l. (Italy)

Who is the main contact?
Dr Francesco Gianese, Medical Director

Contact information

Type(s)
Scientific

Contact name
Dr Francesco Gianese

Contact details
Via San Giuseppe Cottolengo
Milan
Italy
20143

Additional identifiers

Protocol serial number
Study CRO-PK-17-324 - Sponsor code NG8706-C01

Study information

Scientific Title
Bioequivalence study of a new ramipril 10 mg/bisoprolol fumarate 5 mg hard capsule fixed dose combination (Neopharmed Gentili S.r.l.) versus a free combination of ramipril 10 mg tablets (Triatec®, Sanofi-Aventis) and bisoprolol fumarate 5 mg film coated tablets (Congescor®, Daiichi Sankyo) in healthy male and female volunteers under fasting conditions

Acronym
Ramipril/bisoprolol BE

Study objectives
The objective of the study was to assess the bioequivalence of ramipril and bisoprolol, when administered in single dose in 2 consecutive study periods as a fixed combination (ramipril 10 mg /bisoprolol fumarate 5 mg hard gel capsule) versus a free combination of ramipril 10 mg tablet (Triatec®) and bisoprolol fumarate 5 mg film-coated tablet (Congescor®) to healthy male and female volunteers under fasting conditions.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Cantonal Ethics Commitee Ticino, 12/09/2017, project ID 2017-01417 / CE 3259

Primary study design
Interventional

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

Study type(s)
Other

Health condition(s) or problem(s) studied
Not applicable

Interventions
The study protocol foresaw 2 periods separated by a wash-out interval of at least 14 days between consecutive administrations.
The following visits were performed:

Screening phase
- Screening – visit 1: between Day -14 and Day -2
- Period 1 – visit 2: Day -1

Interventional phase
- Period 1 – visit 3: Days 1-3
- Wash-out interval of at least 14 days
- Period 2 – visit 4: Day -1
- Period 2 – visit 5: Days 1-3

Final phase
- Final visit/early termination visit (ETV). In case of early discontinuation, discontinued subjects underwent an early termination visit (ETV)

A single dose of the test fixed dose combination or of the reference extemporaneous combination, both corresponding to ramipril 10 mg and bisoprolol fumarate 5 mg, was 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 14 days between consecutive administrations.

Both test and reference treatments were orally administered in the morning of study Day 1, at 08:00±1h.

One hard capsule of fixed dose combination of ramipril 10 mg / bisoprolol fumarate 5 mg (test treatment) or one tablet of Triatec®, 10 mg + one tablet of Congescor®, 5 mg (reference treatment) were swallowed with 150 mL of still mineral water by the subjects.
Vital signs were checked and blood samples for PK analysis were collected at specific timepoints.

TEST (T): IMP Ramipril 10 mg / Bisoprolol fumarate 5 mg hard capsules (NG8706), Neopharmed Gentili S.r.l., Italy
REFERENCE (R) IMP: Triatec®, 10 mg ramipril tablets + Congescor®, 5 mg bisoprolol fumarate film-coated tablets

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Ramipril, bisoprolol fumarate

Primary outcome(s)
The bioequivalent rate (Cmax) and extent (AUC0-t) of absorption of ramipril and bisoprolol (plasma concentrations evaluated using an LC/MS-MS assay) after single dose administration of test and reference products

Key secondary outcome(s)
1. The plasma PK profile (0-48 hours) of ramipril and bisoprolol after single dose administration of test and reference products
2. Safety and tolerability of test and reference products after single dose administration

Completion date
21/10/2017

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 (BMI): 18.5-28 kg/m2 inclusive
4. Vital signs: systolic blood pressure (SBP) 100-139 mmHg, diastolic blood pressure (DBP) 60-89 mmHg, heart rate (HR) 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 (females): females of child-bearing potential had to 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 [IUD] 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 1 year will be admitted. For all female subjects, pregnancy test result must be negative at screening.
8. Contraception (males): males with partners of childbearing potential will either be sterile or agree to use one of the following approved methods of contraception from the first study drug administration until at least 45 days after the last administration:
8.1. A male condom with spermicide
8.2. A sterile sexual partner or a partner in post-menopausal status for at least 1 year
8.3. Use by the female sexual partner of an IUD, a female condom with spermicide, a contraceptive sponge with spermicide, a diaphragm with spermicide, a cervical cap with spermicide, or hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit
9. Male subjects had to accept to inform their partners of the participation in the clinical study

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
All

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 considered could affect the outcome of the study
6. Hypotension and heart rate: during the screening procedures or history of orthostatic hypotension or syncope/fainting or HR<50 bpm

7. Diseases: significant history of renal, hepatic, cardiovascular, respiratory, skin, haematological, endocrine, neurological, psychiatric and in particular gastrointestinal diseases that could 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 (OTC) medications and 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 females were 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 females and >2 drinks/day for males, 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 (females only): positive or missing pregnancy test at screening or day -1, pregnant or lactating women

Date of first enrolment
25/09/2017

Date of final enrolment
29/09/2017

Locations

Countries of recruitment
Switzerland

Study participating centre
CROSS Research SA Phase I Unit
Via F.A. Giorgioli 14
Arzo
Switzerland
6864

Sponsor information

Organisation

Neopharmed Gentili S.r.l.

Funder(s)

Funder type
Industry

Funder Name
Neopharmed Gentili S.r.l.

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and analysed during the current study will be available upon request from Neopharmed Gentili S.r.l. The results are not currently available since the sponsor is performing additional analysis.

IPD sharing plan summary
Available on request