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Study to assess the distribution in the blood of healthy volunteers of a new formulation of losartan compared with the marketed formulation Cozaar® administered under fasting conditions

Submission date
14/04/2022

Recruitment status
No longer recruiting

Registration date
22/04/2022

Overall study status
Completed

Last Edited
26/04/2022

Condition category
Other

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
This study is designed to compare the bioavailability of losartan after a single oral dose of a losartan potassium modified-release 100 mg test formulation (T) with the reference losartan 100 mg formulation (Cozaar®) (R) when administered under fasting conditions to healthy male volunteers.
The bioavailability is the amount of the active substance of a medicine that reaches the blood flow, while the pharmacokinetics profile describes the way the medicine behaves inside the body, after administration (i.e. the absorption, distribution, metabolism and elimination of the substance).
The secondary objective of the study is to investigate and compare the pharmacodynamics of losartan potassium after single-dose administration of T and R to healthy male volunteers and to evaluate the safety and tolerability of T and R. Pharmacodynamics is the study of the biochemical and physiologic effects of drugs on the body. In particular, this study is designed to evaluate losartan potassium's pharmacodynamic effects on plasma renin activity, angiotensin II and aldosterone plasma values.

Who can participate?
Healthy men aged 18-55 years old inclusive

What does the study involve?
Participants will receive a single oral dose of a losartan potassium modified-release 100 mg test formulation (T) and of the reference losartan 100 mg formulation (Cozaar®) (R) that will be administered under fasting conditions in two subsequent study periods with a break of at least 5 days between administrations. The formulation to be tested is not yet available on the market in Switzerland and should therefore be considered a trial product. Participants will have blood samples taken and vital parameters recorded at regular intervals.

What are the possible benefits and risks of participating?
Participating in this study will not bring any direct benefit to participants, with the exception of the medical tests that will be performed during it. No particular risks are expected for the participants from the single dose of losartan considering the favourable safety profile of the drug. However, as with all products, the appearance of allergic reactions or side effects that are known or not yet known cannot be ruled out.

Where is the study run from?
CROSS Research S.A. Phase I Unit Clinical Centre (Switzerland)

When is the study starting and how long is it expected to run for?
July 2020 to August 2020

Who is funding the study?
DPL Pharma S.p.A. (Italy)

Who is the main contact?
Dr Milko Radicioni
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Contact information

Type(s)
Principal investigator

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Additional identifiers

Protocol serial number
DPL-739-01-2020

Study information

Scientific Title

Bioavailability and proof of concept study of a new modified release losartan formulation versus the marketed formulation Cozaar® administered to healthy volunteers under fasting conditions

Study objectives
This study is designed to compare the bioavailability of losartan after a single oral dose of a losartan potassium modified-release 100 mg test formulation (T) with the reference losartan 100 mg formulation (Cozaar®) (R) when administered under fasting conditions to healthy male volunteers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/04/2020, Canton Ticino Ethics commitee (c/o Ufficio di sanità, Via Orico 5, 6501 Bellinzona, Switzerland; +41(0)91 814 30 57; beatrice.giberti-gai@ti.ch), ref: 2020-00420 / CE 3590

Primary study design
Interventional

Study design
Single-centre single-dose open-label two-way cross-over randomized bioavailability and pharmacodynamic pilot study

Study type(s)
Other

Health condition(s) or problem(s) studied
Bioavailability of a new formulation of losartan

Interventions
TEST (T): Losartan potassium 100 mg modified-release tablets, Doppel Farmaceutici S.r.l., Italy
REFERENCE (R): Cozaar®, 100 mg losartan potassium film-coated tablets, Merck Sharp & Dohme Corp., USA

A single 100 mg oral dose of T and R will be administered under fasting conditions in two subsequent study periods according to the study randomised cross-over design, with a wash-out interval of at least 5 days between consecutive administrations.

The randomisation list was computer-generated by the Biometry Unit of the Clinical Contract Research Organization (CRO), using the PLAN procedure of the SAS® version 9.3 (TS1M1). The randomisation list was supplied to the study site before study start.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)

Losartan potassium

Primary outcome(s)
Bioavailability of losartan, AUC0-t, Cmax and Tmax of losartan calculated from the relative plasma concentrations after single dose administration of T and R under fasting conditions. Blood samplings were made on Days 1 & 2 of the two study periods at the following timepoints: pre-dose (0), 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h post-dose.

Key secondary outcome(s)
1. Plasma renin activity, angiotensin II and aldosterone plasma levels after single dose administration of T and R under fasting conditions. Blood samplings were made on Day1&2 of the two study periods at the following timepoints :pre-dose (0), 3, 6, 9, 12, 16 and 24 h post-dose
2. Safety and tolerability data after single dose administration of T and R under fasting conditions. reatment-emergent adverse events recordings throughout the study duration.
3. Vital signs: subjects blood pressure (BP) and heart rate (HR) were measured by the Investigator or his deputy after 5 min at rest (in sitting position) at: screening visit, day 1 of each period: pre-dose (0), 3, 6, 9, 12 and 16 h post-dose, day 2 of each period: 24 h post-dose. Period 2, 24-h post-dose check was considered as the final study assessment. They were measured at Early Termination Visit, if applicable.
4. Electrocardiograms: 12-Leads ECGs were performed (in supine position) at screening, on day -1 of both study periods and before leaving the clinical centre on day 2 or at ETV in case of premature discontinuation.
5. Body weight: it was recorded at screening and final visit/ETV. BMI was recorded at screening visit only. Subjects were weighed (kg) lightly clothed without shoes. Height was measured at screening only and BMI will be recorded. BMI was calculated as weight [kg]/(height [m] x height [m]).
6. Laboratory parameters: Samples of blood (12.5 mL) and urine were collected. The following laboratory analyses were performed at the screening visit:
6.1 HAEMATOLOGY
Leukocytes and leukocyte differential count (percentage values and absolute values), erythrocytes, haemoglobin (conv. units), haemoglobin (IS units), haematocrit, MCV, MCH, MCHC, thrombocytes.
6.2 BLOOD CHEMISTRY
Electrolytes: sodium, potassium, calcium, chloride, inorganic phosphorus
Enzymes: alkaline phosphatase, γ-GT, AST, ALT
Substrates/metabolites: total bilirubin, creatinine, glucose, urea, uric acid, total cholesterol, triglycerides
Proteins: total proteins
6.3 URINE ANALYSIS
Urine chemical analysis (stick): pH, specific weight, appearance, colour, nitrites, proteins, glucose, urobilinogen, bilirubin, ketones, haematic pigments, leukocytes
Urine sediment (analysis performed only if positive): leukocytes, erythrocytes, flat cells, round cells, crystals, cylinders, mucus, bacteria
6.4 SERUM VIROLOGY
Hepatitis B (HBs antigen), Hepatitis C (HCV antibodies), HIV 1/2 (HIV Ag/Ab combo).
The same analyses, with the exception of virology, were performed at the final visit/ETV.

Completion date
14/08/2020

Eligibility

Key inclusion criteria
1. Informed consent: signed written informed consent before inclusion in the study
2. Men, 18-55 years old inclusive
3. Body Mass Index: 18.5-30 kg/m² inclusive
4. Vital signs: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting position
5. 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

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
Male

Total final enrolment
16

Key exclusion criteria
1. Electrocardiogram (ECG, 12-leads, supine position): clinically significant abnormalities
2. Physical findings: clinically significant abnormal physical findings which could interfere with the objectives of the study
3. Laboratory analyses: clinically significant abnormal laboratory values indicative of physical illness
4. Allergy: ascertained or presumptive hypersensitivity to the active principle 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
5. Diseases: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study. Known renal dysfunction
6. Medications: medications, including over the counter medications and herbal products for 2 weeks before the start of the study
7. 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
8. Blood donation: blood donations for 3 months before this study

9. Drug, alcohol, caffeine, tobacco: history of drug, alcohol (>2 drinks/day, defined according to the USDA Dietary Guidelines 2015-2020), caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
10. Drug test: positive result at the drug test at screening or day -1 (all study periods)
11. Alcohol test: positive alcohol breath test at day -1 (all study periods)
12. Diet: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians

Date of first enrolment
29/07/2020

Date of final enrolment
31/07/2020

Locations

Countries of recruitment
Italy

Switzerland

Study participating centre
CROSS Research S.A., Phase I Unit
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Arzo
Switzerland
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Sponsor information

Organisation
DPL Pharma S.p.A.

Funder(s)

Funder type
Industry

Funder Name
DPL Pharma 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?
Basic results		26/04/2022	26/04/2022	No	No