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Study to assess the amount of drug that reach the blood circulation after the intake of ibuprofen arginine as tablets versus granules for oral solution by healthy volunteers

Submission date
12/10/2023

Recruitment status
No longer recruiting

Registration date
13/10/2023

Overall study status
Completed

Last Edited
20/10/2023

Condition category
Other

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

Plain English summary of protocol

Background and study aims
Ibuprofen arginine is a well-known anti-inflammatory drug, widely used in the treatment of mild to moderate pain and inflammation. The Sponsor has recently developed a new formulation of ibuprofen arginine 600 mg film-coated tablets to provide an alternative to the already approved ibuprofen arginine 600 mg sachet for oral solution. This study aims to evaluate the bioequivalence (similar effect on the body) of the new ibuprofen arginine 600 mg film-coated tablet formulation (test product) versus ibuprofen arginine 600 mg sachet (reference product) after single dose administration in healthy men and women.

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

What does the study involve?
Each participant will receive a single oral dose of ibuprofen arginine 600 mg film-coated tablet (test product) and a single oral dose of ibuprofen arginine 600 mg granules for oral solution (reference product), under fasting conditions, in two study periods separated by at least 3 days. During the study, blood samples will be collected from participants for the measurement of ibuprofen arginine in the bloodstream. In addition, their vital signs will be measured and laboratory tests will be performed on blood to investigate the safety of the medicinal products.

What are the possible benefits and risks of participating?
No specific benefits for the participants in the current study are foreseen. The participants will be reimbursed after study completion. The remuneration covers loss of time and any inconvenience caused by participation in the study.
About the possible risks, ibuprofen is a safe product for the treatment of pain with a well-known safety profile which has remained consistent in the last few years. It is well tolerated and is one of the safest anti-inflammatory drugs during long-term treatments. Undesired reactions are mainly of a gastrointestinal type. In detail, very common (defined as untoward effects which

occur at a frequency ≥1/10) undesired reactions include dyspepsia (indigestion) and diarrhoea. Common (from ≥1/100 to <1/10) undesired reactions are abdominal pain, nausea, flatulence, headache, dizziness, skin disorder and rash.
Undesired effects reported with ibuprofen arginine were similar to those observed in the group of subjects who received ibuprofen. The most frequent undesired reactions were of a gastrointestinal nature (mainly nausea and vomiting). Blood sampling for laboratory analyses with cannula insertion may cause minor discomfort. The risks associated with blood draws include pain, bleeding and bruising.

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

When is the study starting and how long is it expected to run for?
June 2022 to October 2022

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

Who is the main contact?
Veronica Di Fonzo, Veronica.DiFonzo@ZambonGroup.com

Contact information

Type(s)
Public, Scientific

Contact name
Mrs Veronica Di Fonzo

Contact details
via Lillo del Duca 10
Bresso
Italy
20091
+39 (0)2 66 52 41
veronica.difonzo@zambongroup.com

Type(s)
Principal investigator

Contact name
Mr Milko Radicioni

Contact details
Via F.A. Giorgioli 14
Arzo
Switzerland
6864
+41 (0)91 64 04 450
clinic@croalliance.com

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Z7100J02

Study information

Scientific Title
Bioequivalence study of a new ibuprofen arginine 600 mg tablet formulation versus ibuprofen arginine 600 mg sachet in healthy volunteers

Study objectives
To investigate the bioequivalence of the new ibuprofen arginine 600 mg film-coated tablet and the marketed ibuprofen arginine 600 mg sachet after single-dose administration of the two products in healthy men and women under fasting conditions

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 09/08/2022, Cantonal Ethics Committee Canton Ticino (c/o Health Office, Via Orico 5, Bellinzona, CH-6501, Switzerland; +41 (0)918143057; dss-ce@ti.ch), ref: 2022-01317 CE 4138

Study design
Single-centre single-dose open-label randomized two-way two-stage cross-over bioequivalence study

Primary study design
Interventional

Study type(s)
Other, Treatment

Health condition(s) or problem(s) studied
Bioequivalence study of a new ibuprofen arginine 600 mg tablet formulation versus ibuprofen arginine 600 mg sachet

Interventions
A single oral dose of 600 mg of ibuprofen arginine, as a film-coated tablet (test product) and granules for oral solution (reference product), will be administered to healthy men and women, under fasting conditions, in two study periods, according to a randomised two-way, cross-over design, with a wash-out of at least 3 days between the administrations.

Both test and reference products will be orally administered in the morning of study Day 1, at 8: 00±1 h, as follows:
1. Test: one film-coated tablet of ibuprofen arginine 600 mg film-coated tablet will be swallowed by the subject with 150 ml of still mineral water
2. Reference: the entire content of one sachet of ibuprofen arginine 600 mg granules for oral solution will be dispersed in 100 ml of still mineral water until complete dissolution and drunk by the subject. Afterwards, the glass will be rinsed with a further 50 ml of still mineral water and the rinse drunk.

Participants will be assigned to one of the two sequences of treatments (test/reference; reference/test) according to the randomisation list, to receive one of the two treatments (test or reference) during period 1 and the other one during period 2.

The randomisation number will be given to the subjects on study Day -1, period 1, and will be used to assign the treatment sequence.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Ibuprofen as L-arginine salt

Primary outcome(s)
The rate (Cmax, maximum plasma concentration) and extent (AUC0-t, area under the concentration-time curve from administration to the last observed concentration time t, calculated with the linear trapezoidal method) of absorption of ibuprofen S-enantiomer calculated from plasma concentrations after a single oral dose of test and reference products. Plasma concentrations of ibuprofen S-enantiomer will be measured using a fully validated chiral LC-MS/MS method at pre-dose (0) and at 5, 10, 20, 30, 40, 50 min and 1, 1.5, 2, 3, 4, 6, 9, 12 h post-dose in each of the two study periods.

Key secondary outcome(s))
1. tmax (time to achieve the maximum plasma concentration), Frel (relative bioavailability, calculated as ratio AUC0-t [test]/AUC0-t [reference]) and, if feasible, %AUCextra (percentage of the residual area extrapolated to infinity in relation to the total AUC0-inf calculated, if feasible, as 100×[Ct/ λZ]/AUC0-inf), AUC0-inf (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), t1/2 (half-life calculated, if feasible, as ln2/λz) and λZ (terminal elimination rate constant, calculated, if feasible, by log-linear regression using at least 3 points) of plasma ibuprofen S-enantiomer after single oral dose of test and reference products
2. Cmax, AUC0-t, tmax, Frel and, if feasible, %AUCextra, AUC0-inf, t1/2 and λZ of plasma ibuprofen R-enantiomer after a single oral dose of test and reference products
3. Cmax, AUC0-t, tmax, Frel and, if feasible, %AUCextra, AUC0-inf, t1/2 and λZ of total ibuprofen, calculated as the sum of ibuprofen S-enantiomer and R-enantiomer concentrations, after a single oral dose of test and reference products
4. Treatment-emergent adverse events during the whole clinical study, vital signs (blood pressure and heart rate, measured at screening visit, on Day -1 of each study period, On Day 1 at 12 h post-dose of each study period and at early termination visit), physical examinations (at

screening and at final visit/early termination visit), body weight (at screening and at final visit /early termination visit), clinical laboratory parameters (at screening, on Day -1 of each study period and at final visit/early termination visit).
Plasma concentrations of ibuprofen S-enantiomer and ibuprofen R-enantiomer will be measured using a fully validated chiral LC-MS/MS method at pre-dose (0) and at 5, 10, 20, 30, 40, 50 min and 1, 1.5, 2, 3, 4, 6, 9, 12 h post-dose in each of the two study periods.

Completion date
12/10/2022

Eligibility

Key inclusion criteria
1. Informed consent: subjects able to complete and sign the informed consent before inclusion in the study
2. Sex and age: men and women, 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 60-89 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 cooperate with the Investigator and to comply with the requirements of the entire study
6. Contraception and fertility (women only): women of child-bearing potential must be using at least one of the following reliable methods of contraception:
6.1. Hormonal oral, implantable, transdermal or injectable contraceptives for at least 2 months before the screening visit
6.2. 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
6.3. A male sexual partner who agrees to use a male condom with spermicide
6.4. 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 women, pregnancy test results 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

Upper age limit
55 years

Sex

All

Total final enrolment
24

Key exclusion criteria
1. Subjects: subjects younger than 18 years or older than 55 years, subjects unable to give informed consent, subjects with cognitive impairment and otherwise non-healthy subjects
2. SARS-CoV-2 test: positive on COVID-19 Antigen Rapid Test at screening or Day -1
3. Electrocardiogram (12-lead ECG in supine position): clinically significant abnormalities
4. Physical findings: clinically significant abnormal physical findings which could interfere with the objectives of the study
5. Laboratory analyses: clinically significant abnormal laboratory values indicative of physical illness
6. Allergy: ascertained or presumptive hypersensitivity to the active principle or formulations' ingredients or both; history of anaphylaxis to drugs or allergic reactions in general (in particular to NSAIDs), which the Investigator considers may affect the outcome of the study
7. Diseases: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine, immunological or neurological diseases that may interfere with the aim of the study
8. Medications: medications, including over-the-counter (OTC) medications, herbal remedies and vitamins, for 2 weeks before the start of the study. 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 2020-2025], caffeine (>5 cups coffee/tea/day) or tobacco abuse (>10 cigarettes/day)
12. Drug test: positive result at the drug test at screening or Day -1
13. Alcohol test: positive alcohol test on 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
21/09/2022

Date of final enrolment
27/09/2022

Locations

Countries of recruitment
Switzerland

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

Sponsor information

Organisation
Zambon (Italy)

ROR
https://ror.org/04zzq8d03

Funder(s)

Funder type
Not defined

Funder Name
Zambon 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		16/10/2023	20/10/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 1.0	08/07/2022	12/10/2023	No	No