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Preliminary study with the aim to assess the effect on humans and the amount of a drug that reaches the blood circulation when using a newly developed plaster containing the painkiller diclofenac in comparison with the marketed diclofenac medicated plaster (Flector EP Tissugel®)

Submission date
09/12/2020

Recruitment status
No longer recruiting

Registration date
15/12/2020

Overall study status
Completed

Last Edited
07/12/2022

Condition category
Other

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

Plain English summary of protocol

Background and study aims
This is a preliminary study of tolerability and bioavailability.
'Bioavailability' is the amount of the active substance of 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 present study has been designed to assess the local tolerability after once daily (o.d.) application for 2 consecutive days of a new diclofenac medicated plaster formulation containing 360 mg/140 cm2 and of the same diclofenac medicated plaster formulation cut in half (180 mg /70 cm2 of diclofenac), in comparison with the marketed DHEP medicated plaster 182 mg/140 cm2 (Flector EP Tissugel®).
Moreover, the diclofenac pharmacokinetic (PK) profile after application of the three investigational products will also be comparatively investigated in a subset of the study population. These evaluations will allow to preliminary appreciate if the new plaster is suitable for further clinical development.
Diclofenac is a medicine that reduces inflammation and pain.

Who can participate?
Healthy male and female aged 18 - 45 years old, were able to participate. Participants had to comprehend the full nature and purpose of the study, including possible risks and side effects

and co-operate with the investigator to comply with the requirements of the entire study. Women of childbearing potential were required to use at least one reliable method of contraception.

What does the study involve?
One (1) diclofenac medicated plaster (T1: 360 mg; T2: 180 mg; R: 182 mg) will be applied to the study participants once a day (o.d.) for 2 consecutive days in 3 study periods. An interval of at least 5 days will separate the second application of the previous period and the first application of the following period.
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 local tolerability and vital parameters recorded at regular intervals. In addition, only a subset of the study participants will have blood samples taken at regular intervals.

What are the possible benefits and risks of participating?
Participating in this study is not expected to bring any direct benefit to participants, with the exception of the medical tests that will be performed during the study. No particular risks are expected at the dose foreseen in the present study, which will be administered o.d. for 2 consecutive days in 3 study periods to each volunteer. 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?
The study will be conducted at the CROSS Research S.A. Phase I Unit Clinical Centre, in Arzo, Switzerland.

When is the study starting and how long is it expected to run for?
July 2018 to February 2019.

Who is funding the study?
IBSA Institut Biochimique S.A. (Switzerland)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
18CH-Fpf03

Study information

Scientific Title
Pilot tolerability and bioavailability study of a new DHEP medicated plaster, administered at two doses, in comparison with the marketed DHEP medicated plaster (Flector EP Tissugel®)

Study objectives
This study is designed to evaluate the local tolerability of DHEP medicated plaster (Test 1, 360 mg or Test 2, 180 mg or Reference, 182 mg) after once a day (o. d.) application for 2 consecutive days to healthy male and female volunteers

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/10/2018, 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: 2018-01787/CE 3404

Primary study design
Interventional

Study design
Single centre multiple-dose randomized 3-way cross-over open-label pilot comparative tolerability and bioavailability study

Study type(s)
Other

Health condition(s) or problem(s) studied
Tolerability and bioavailability of a new DHEP medicated plaster versus a market reference formulation on healthy subjects

Interventions
The first screening visit takes place between Day -21 and Day -2.
One (1) DHEP medicated plaster (T1: 360mg/140cm²; T2: 180mg/140cm²; R: 182mg/140cm²) is applied once a day (o.d.) for 2 consecutive days in 3 study periods according to a 3-way cross-over randomised Williams design.
The sequence of Investigational Medical Products (IMPs) in the 3 study periods (T1/T2/R or T1/R /T2 or T2/T1/R or T2/R/T1 or R/T1/T2 or R/T2/T1) is assigned to each randomised subject

according to a computer generated randomisation list.
Before T2 application, the 140 cm2 (14 cm x 10 cm) Test plaster is cut in half (7 cm x 10 cm). One of the two pieces of the cut plaster, containing 180 mg of DHEP, is applied. The plasters are applied to the subjects' inner upper arm on study days 1 and 2 in the morning at 8:00±1 h and kept in place for 24 h using a loose fitting elastic net sleeve (the same supplied in the commercial package of the reference product Flector EP Tissugel® and approved for use both in Europe and USA) to avoid inadvertent detachment. The plasters is applied to the same application area of the same arm in the 3 study periods. The subjects take a shower on study Day -1 only. Afterwards, the plaster application area is checked by the investigator or his deputy and shaved if necessary. Day 1 plaster application of periods 2 and 3 is performed after a washout of at least 5 days following day 2 plaster applications of periods 1 and 2, respectively.

Local tolerability is assessed as adverse drug reactions (ADRs) that is evaluated as:
- application site erythema, dryness, swelling and exfoliation assessed by the investigator using a 4-grade scale
(0 = none; 1 = mild; 2 = moderate; 3 = severe) immediately before the first plaster application (Day 1) and after each plaster removal (Day 2 and Day 3);
- all other treatment-related AEs occurring at the application site, spontaneously reported by the subjects or observed by the investigator.
Relevant skin reactions/irritations is fixed with a photo.

Only participants of the pharmacokinetic (PK) population subset (that will include the first 12 enrolled subjects, meeting all required inclusion criteria) have blood samples taken at regular intervals.
Blood samples are taken on Day 1 at pre-dose (0) and on Days 2-3: Day 2 pre-dose (0) and 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h post-dose (12 samples in each study period).

Vital signs (blood pressure [mmHg], heart rate [bpm]) are measured by the investigator after 5 min at rest in sitting position at screening and in each study period on Day -1 and on Day 3, 24 h post-application. The Period 3, 24 h post-application assessment correspond to the final assessment. In case of early discontinuation the final assessment is performed at ETV.

A 12-Lead ECGs is performed in the supine position at screening only.

Subjects are weighed (kg) lightly clothed without shoes to record body weight at screening and final visit or the early termination visit (ETV). Height is measured at screening only. Body Mass Index (BMI) is calculated as weight [kg]/(height [m] x height [m]) at screening and final visit/ETV.

The following laboratory analysis are performed:
1. Haematology, blood chemistry, serum virology, and urine analysis at the screening visit
2. A urine drug test and a serum pregnancy test at the screening visit and at the entrance of each study period
3. Haematology, blood chemistry, and urine analysis at the final visit/ETV

Subjects are asked about the occurrence of adverse events (AEs) from the Informed Consent (IC) signature to the study end. Additionally, any clinically significant vital sign or laboratory value is reported as AE. AEs are coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA). AEs are classified as pre-treatment AEs (PTAEs) and Treatment-Emergent AEs (TEAEs), according to the period of occurrence, as follows:
1. PTAEs include all AEs occurring after IC signature by the enrolled subject but before the first dose of IMP
2. TEAEs include all AEs occurring or worsening after the administration of the first dose of IMP

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
diclofenac-N-(2-hydroxyethyl)-pyrrolidine (DHEP) medicated plaster, Flector EP Tissugel®

Primary outcome(s)
1. Local tolerability of diclofenac is evaluated as adverse drug reactions (ADRs) at the application site measured after application for 2 consecutive days, including:
1.1. Application site erythema, dryness, swelling and exfoliationass essed by the investigator using a 4-grade scale
1.2. All other treatment-related AEs occurring at the application site, spontaneously reported by the subjects or observed by the investigator

Key secondary outcome(s)
1. Pharmacokinetic (PK) profile of diclofenac in plasma after o.d. application for 2 consecutive days. PK profile will be evaluated using a fully validated method Liquid Chromatography with tandem mass spectrometry (LC-MS/MS) method, with a lower quantification limit of 1 ng/ml, on blood samples taken on Day 1: pre-dose (0) and Days 2-3: Day 2 at pre-dose (0) and 1, 2, 3, 4, 6, 8, 10, 12, 16 and Day 3 at 24 h post-dose (12 samples in each study period)
2. Collection of safety data of the study products assessed during the study by the number of adverse events (AEs) reported through the study duration and measured using:
2.1. Blood and urine samples for haematology, blood chemistry, and urine analysis at the screening visit and final visit/ETV
2.2. Body weight (kg) at the screening visit and final visit/ETV and height at the screening visit to calculate Body Mass Index (BMI) at the screening visit and final visit/ETV
2.3. Vital signs (blood pressure [mmHg], heart rate [bpm]) at the screening visit, in each study period on Day -1 and on Day 3, 24 h post-application and at ETV (ifv applicable)
2.4. ECG measured using 12-Lead electrocardiogram at the screening visit

Completion date
15/02/2019

Eligibility

Key inclusion criteria
1. Informed Consent: signed written Informed Consent before inclusion in the study
2. Sex and Age: males and females, 18-45 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
6. Contraception and fertility (women only): women of childbearing potential must be using at least one of the following reliable methods of contraception:
6.1. Hormonal oral, implantable, intrauterine device [IUD], transdermal or injectable

contraceptives for at least 2 months before the screening visit
6.2. A non-hormonal 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 screeningvisit;
6.3. A male sexual partner who agrees to use a male condom with spermicide
6.4. A sterile sexual partner
Women of non-childbearing potential or in post-menopausal status for at least 1 year will be admitted.
For all women, pregnancy test result must be negative at screening and Day -1 of each study period.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
45 Years

Sex
All

Total final enrolment
24

Key exclusion criteria
1. Electrocardiogram (12-lead ECG in supine position): clinically significant abnormalities
2. Physical findings: clinically significant abnormal physical findings which could interfere with the objectives of the study and which the investigator considers may affect the outcome of the study
3. Laboratory analyses: clinically significant abnormal laboratory values indicative of physical illness
4. Application site: diseased-skin, skin wounds, open injuries or tattoos at the application site
5. 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
6. Diseases: history of clinically significant renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study
7. Medications: medications, including over the counter medications and herbal remedies for 2 weeks before the start of the study. Hormonal contraceptives for females will be allowed
8. 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
9. Blood donation (Population subgroup for PK analysis only): blood donations for 3 months before this study
10. 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] or caffeine abuse (>5 cups
coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
11. Drug test: positive result at the drug test at screening or Day-1
12. Alcohol test: positive alcohol breath test at Day -1
13. Diet: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians
14. Pregnancy (women only): positive or missing pregnancy test at screening or Day -1, pregnant or lactating women

Date of first enrolment
11/01/2019

Date of final enrolment
17/01/2019

Locations

Countries of recruitment
Italy

Switzerland

Study participating centre
CROSS Research S.A., Phase I Unit
Via F.A. Giorgioli 14
Arzo
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Sponsor information

Organisation
IBSA Institut Biochimique (Switzerland)

ROR
https://ror.org/051tj3a26

Funder(s)

Funder type
Industry

Funder Name
IBSA Institut Biochimique S.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		09/09/2021	27/09/2021	No	No
Participant information sheet	version v2.0	18/10/2018	04/01/2021	No	Yes