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A study to assess the amount of drug that reaches the blood circulation of a new anti-inflammatory medicated plaster applied once a day in comparison with the similar medicated plaster (Flector®) applied twice a day in healthy volunteers

Submission date	Recruitment status	[_] Prospectively registered
30/03/2021	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
07/04/2021	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
06/12/2022	Other	

Plain English summary of protocol

Background and study aims

The Sponsor, IBSA Institut Biochimique S.A., has recently developed a new plaster formulation containing a higher concentration (2.6%) of diclofenac (DHEP), an anti-inflammatory pain killer, as compared to the already approved and marketed plaster known as Flector® (1.3% medicated plaster). At present, Flector® instructions recommend twice-daily applications of the medicated plaster. It is hoped that a plaster with a higher DHEP concentration will improve the pain relief and anti-inflammatory effectiveness of the plaster by increasing the amount of diclofenac at the site of the plaster while keeping a low amount of diclofenac throughout the whole bloodstream, to maintain the positive safety profile of the plaster form of the medication compared to diclofenac taken by mouth. It is hoped that a higher strength of the medication in the plaster would allow a reduction in the frequency of how often plasters would need to be applied to once per day, compared to twice per day with Flector®, thus improving the patient compliance.

The study aims to assess the amount of diclofenac in the bloodstream after the application of the DHEP 2.6% medicated plaster compared to Flector® and to evaluate if the new treatment tested is safe and well-tolerated.

Who can participate?

Healthy volunteers aged 18-55 years

What does the study involve?

Participants will be allocated to one of two groups, with an equal chance of being in either group (like tossing a coin) for the first half of the study. In the second half of the study, participants will receive the treatment/intervention that they did not receive in the first half of the study. There

will be a period of 5 days separating each half of the study. The two treatments are a plaster on the inner upper arm containing pain relief and anti-inflammatory medication known as diclofenac given once a day for 5 days and a plaster at the same site containing a lower dose of the diclofenac (Flector®) given twice a day for 5 days.

During the study, blood samples will be collected from participants for the measurement of diclofenac in the bloodstream. The subject heart rate and blood pressure will be measured, an electrocardiogram of the heart will be recorded and laboratory tests on blood and urine will be performed to test the safety of the plasters.

What are the possible benefits and risks of participating?
No potential benefits are foreseen for subjects participating in this study.

From the past experience with plasters containing diclofenac, skin reactions at the application site such as pruritus and erythema are the most common side effects.

Where is the study run from?
IBSA Institut Biochimique S.A. (Switzerland)

When is the study starting and how long is it expected to run for?
From October 2019 and July 2020

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

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CRO-PK-19-338 - Sponsor code 19CH-Fpf06

Study information

Scientific Title
Bioavailability study of a new 2.6% DHEP medicated plaster applied o.d. in comparison with the marketed 1.3% DHEP medicated plaster (Flector®) applied b.i.d.

Acronym
DHEP plaster 2.6%

Study objectives
To compare the bioavailability of diclofenac, safety, and tolerability of a DHEP-medicated plaster applied once daily at a concentration of 2.6% and a DHEP-medicated plaster applied twice daily at a concentration of 1.3% in healthy volunteers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/11/2019, Cantonal Ethics Committee Canton Ticino (c/o Health Office, Via Orico 5, 6501 Bellinzona, Switzerland; +41 (0)91 8143057; dss-ce@ti.ch), ref: 2019-01923 CE 3528

Study design
Single-centre open-label randomized 2-way cross-over, single and repeated applications, bioavailability study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
DHEP-medicated plaster for analgesia or anti-inflammatory effects

Interventions
Participants will be randomly allocated to receive either the test (T) or reference (R) medicated plaster for the first part of the study (period 1). In the second part of the study (period 2), participants will receive the treatment/intervention that they did not receive in the first part of the study. Regarding the randomisation process, subjects were assigned to a sequence of treatments (e.g. T/R or R/T) according to the computer-generated randomisation list supplied to the study site before study start. Subjects were randomly allocated to one of the 2 treatment sequences according to their randomisation number. The randomisation number was given to the subjects on study Day -1 of period 1, following a chronological order.

The DHEP medicated plaster will be applied to the inner upper arm of each participant for 5 consecutive days. A wash-out interval of at least 5 days will separate the last application of period 1 and the first application of period 2. The T medicated plaster will be applied once daily in the morning at 08:00 ±1 h each day, and will be kept in place for 24 h each day from day 1 to day 5. The R medicated plaster will be applied twice daily at 8:00 ±1 h and 20:00 ±1 h, and will be kept in place for 12 h each day from day 1 to day 5. T and R plasters will be kept in place using a loose fitting elastic net sleeve (the same supplied in the commercial package of the reference product Flector ® and approved for use both in Europe and USA) to avoid inadvertent detachment. The plasters will be applied to the same application area of the same arm in the 2 study periods.

The following assessments were performed during the interventional phase:
1. Vital signs measurement on Days 1 and 5 at pre-application; and on Days 2 and 6 at 24 h after Day 1 and Day 5 application (first-day application for the Reference plaster).
2. Blood sample collection for PK analysis on:
2.1. Days 1-2: pre-application (0) and 0.5, 1, 2, 3, 4, 6, 9, 12, 12.5, 13, 14, 15, 16, 18, 21 and 24 h post-application (after the first application for the Reference plaster)
2.2. Day 3: pre-application (0) (before first plaster application for Reference plaster)
2.3. Days 5-6: pre-application (0) and 1, 2, 4, 6, 9, 12, 13, 14, 16, 18, 21 and 24 h post-application (after the first application for the Reference plaster)
3. Clinical laboratory assays at final visit (study Day 6 of Period 2)

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Diclofenac-N-(2-hydroxyethyl)-pyrrolidine (DHEP)

Primary outcome(s)
Bioavailability and pharmacokinetic parameters measured using the diclofenac plasma concentrations in blood samples collected at 0 (pre-application), 0.5, 1, 2, 3, 4, 6, 9, 12, 12.5, 13,

14, 15, 16, 18, 21, and 24 h post-application (or after the first application for the Reference plaster) on day 1 of both study periods; at 0 h on day 3 of both study periods; and at 0 (pre-application), 1, 2, 4, 6, 9, 12, 13, 14, 16, 18, 21, and 24 h post-application (or after the first application for the Reference plaster) on day 5 of both study periods

Key secondary outcome(s))
Safety and tolerability measured using the following:
1. Incidence of treatment-emergent adverse events (TEAEs) throughout the study period
2. Vital signs (blood pressure and heart rate) at 0 and 24 h on day 1 and day 5 of both study periods
3. Clinical laboratory assays of blood and urine samples at 6 days during period 2

Completion date
06/07/2020

Eligibility

Key inclusion criteria
1. Signed written informed consent
2. Aged between 18 and 55 years, inclusive
3. Body Mass Index (BMI) between 18.5 and 30 kg/m² inclusive
4. Systolic blood pressure between 100 and 139 mmHg, diastolic blood pressure between 50 and 89 mmHg, and heart rate between 50 and 90 bpm, measured after 5 min at rest in the sitting position
5. The ability to comprehend the full nature and purpose of the study, including possible risks and side effects, and the ability to co-operate with the Investigator and to comply with the requirements of the entire study
6. 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
7. Female participants of non-child-bearing potential or in post-menopausal status for ≥1 year
8. Negative pregnancy test result 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
24

Key exclusion criteria
1. Clinically significant abnormalities on electrocardiogram (12-leads, supine position)
2. Clinically significant abnormal physical findings which could interfere with the objectives of the study
3. Clinically significant abnormal laboratory values indicative of physical illness
4. Diseased-skin, skin wounds, open injuries, tattoos, or the use of makeup, creams, lotions, powders, or other topical products at the application site
5. Ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients or history of anaphylaxis to drugs or allergic reactions in general, which in the opinion of the Investigator could affect the outcome of the study
6. History of significant renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that could interfere with the aim of the study
7. Medications including over the counter medications and herbal remedies, for 2 weeks before the start of the study, with the exception of hormonal contraceptives for women
8. Participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval was calculated as the time between the first calendar day of the month that followed the last visit of the previous study and the first day of the present study.
9. Blood donations for 3 months before this study
10. 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)
11. Positive result at the drug test at screening or day -1
12. Positive alcohol breath test at day -1
13. Abnormal diets (<1600 or >3500 kcal/day), substantial changes in eating habits in the 4 weeks before this study, or a vegetarian diet
14. Pregnant or lactating

Date of first enrolment
22/01/2020

Date of final enrolment
27/02/2020

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
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 data sharing plans for the current study are unknown and will be made 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		08/09/2021	08/09/2021	No	No