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Efficacy and safety of a hyaluronic acid-containing cream in the treatment of chronic, venous, or mixed-origin leg ulcers: a prospective, multicenter, randomized, controlled trial

Submission date	**Recruitment status**	[_] Prospectively registered
23/11/2020	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
23/11/2020	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
02/12/2022	Circulatory System	

Plain English summary of protocol

Background and study aims
A cream containing 0.2% hyaluronic acid as an active ingredient has been developed and marketed for over 20 years for the topical treatment of non-infected, exuding or superinfected wounds, including leg ulcers. Ialuset® cream creates a moist environment around the wound that promotes healing. It is applied on a daily basis in addition to standard of care. The aim of this study is to confirm the effectiveness and safety of Ialuset cream compared with a neutral comparator cream.

Who can participate?
Patients aged 18 and over with a venous leg ulcer

What does the study involve?
Participants are randomly allocated to have ialuset® cream or a neutral comparator cream applied once daily for a maximum of 20 weeks or until complete ulcer healing, whichever occurs first. There are a total of eight visits for each participant, consisting of screening/inclusion (Visit 0), randomization and first treatment (Visit 1), Weeks 4, 8, 12, 16, and 20 of treatment (Visits 2–6), and a final evaluation (follow-up) visit (visit 7) at day 162 (week 23) or 3 weeks after complete healing if it occurs before week 20. The healing of the target ulcer is assessed and recorded at each study visit. The target ulcer is evaluated by the Investigator and documented by standardized digital photography.

What are the possible benefits and risks of participating?
The patients may benefit from effective treatment of their leg ulcer. The study does not involve any major risks as the treatment is very well known.

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

When is the study starting and how long is it expected to run for?
February 2017 to July 2020

Who is funding the study?
IBSA Institut Biochimique SA (Switzerland)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
16FPL- iacr09

Study information

Scientific Title

A confirmatory multicentre, multinational, prospective, parallel-group, randomized, double-blind clinical investigation of the performance and safety of Ialuset® cream versus neutral comparator cream in the treatment of chronic, venous or mixed origin leg ulcer

Study objectives
Efficiency (performance) of Ialuset® cream is superior to a neutral comparator in the treatment of chronic leg ulcers of venous or mixed origin. This hypothesis will be judged by comparing the proportion of subjects that achieved complete target ulcer healing (defined as 100% re-epithelialisation of the wound area) after 20 weeks of treatment and confirmed after 3 weeks from the treatment completion.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 05/04/2017, Bioethics committee at the medical district in Lodz, (ul, Czerwona 3, 93-005 Lodz, Poland; +48 (0)426 831 744; email: not provided), ref: K.B.-9/17
2. Approved 26/06/2017, Personal protection committee Ile-de-France IV, Pitié-Salpetriere Hospital (47 boulevard de l'hôpital, 75651 Paris Cedex 13, France; +33 (0)1 42 16 16 83; email: not provided), ref: 25-17 ID-RCB: 2017-A00892-51

Study design
Confirmatory multicentre multinational prospective parallel-group randomized double-blind clinical investigation

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied
Treatment of chronic, venous or mixed origin leg ulcer

Interventions
Eligible particpants are randomly allocated to Ialuset® cream or a neutral comparator in a ratio of 1:1 using a centralized randomisation system. Target ulcer size (target ulcer size ≤20 cm^2 or >20 cm^2) is applied as a stratification factor. Treatment assignment is determined by the unique randomisation number allocated to the participant by the central randomisation system. The randomisation number corresponds to an IMD labelled with an identical number.

Ialuset® cream or neutral comparator cream is applied once daily for maximum 20 weeks (active treatment period) or until complete ulcer healing, whichever occurred first. Ialuset® cream or neutral comparator cream is applied directly on the ulcer identified as target ulcer for the investigation.
The wound is cleansed with a physiological solution and debrided when necessary prior to cream application. The cream application is followed by a sterile gauze dressing application and appropriate compression bandaging.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Ialuset® cream

Primary outcome measure
The proportion (%) of subjects with completely healed target ulcer (defined as 100% reepithelialisation of the wound area based on standardised photographs of the target ulcer), as observed at Study Visit 6, or at any earliest study visit and further confirmed at a follow-up visit 3 weeks post last treatment, centrally assessed on standardized pictures

Secondary outcome measures
1. Percentage of patients with complete ulcer healing at 20 weeks and confirmed 3 weeks later, assessed by PI
2. Percentage of patients with complete ulcer healing at 4, 8, 12, 16, 20 and 23 weeks, centrally assessed
3. Target ulcer residual area (% relative) to baseline, centrally assessed at 4, 8, 12, 16, 20 and 23 weeks
4. Condition of the peri-ulcerous skin assessed by PI at 4, 8, 12, 16, 20 and 23 weeks
5. Total amount (doses) of analgesics consumed collected by the PI at 4, 8, 12, 16, 20 and 23 weeks
6. Percentage of subjects with infection of the target ulcer recorded by the PI after the start of IMD application
7. Compliance to the treatment assessed as the % IMD daily application counted from the returned IMD
8. Time to complete healing as centrally assessed calculated using percentage of complete healing over time
9. Pain measured using VAS score at 4, 8, 12, 16, 20 and 23 weeks
10. Safety outcomes measured using AEs, SAEs described by MeDRA system organ classes, frequency of AEs/SAEs and percentage of patients experiencing AEs/SAEs at 4, 8, 12, 16, 20 and 23 weeks

Overall study start date
24/02/2017

Completion date
18/07/2020

Eligibility

Key inclusion criteria
1. Adult male and female (aged ≥18 years)
2. Subject diagnosed with a leg ulcer >2 months and <4 years duration
3. Subject diagnosed with one or several leg ulcers of mere venous (varicose or post-thrombotic) origin, or of mixed venous and arterial origin with predominance of venous aetiology
4. Presence of an ulcer that was intended to be treated with a surface area ≥5 cm² and ≤40 cm²
5. Subject having undergone an arterial-venous Doppler examination within 6 months prior to inclusion, showing a superficial or profound reflux in the venous system, and/or a well-documented past history of deep venous thrombosis of the lower limbs, and/or clinical evidence of post-thrombotic syndrome with chronic oedema and lipodermatosclerosis
Ankle/brachial Doppler systolic pressure index ≥0.8 and ≤1.2 within 6 months prior to inclusion
6. Patient whose leg ulcer compression system was adapted and worn during the study
7. Subject having an albuminemia ≥25 g/l (measured ≤2 weeks prior to inclusion)
8. Female subjects of childbearing potential having a negative urine pregnancy test result at screening and at the randomisation visit, and practising two reliable methods of contraception throughout the study
9. Subject having a satisfactorily general condition and a life expectancy longer than the duration of the study, according to the Investigator
10. Having signed a written informed consent to participate in the study, according to GCP
11. For France: subjects covered by a health insurance system/policy

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
168

Total final enrolment
170

Key exclusion criteria
1. Subject with an ulcer of non-venous origin (e.g., phagedenic pyodermatitis, pyoderma gangrenosum, neoplastic or infectious origin) or related to a general cause (e.g., haematological cause).
2. Presence of necrotic tissue ≥50% of the target ulcer surface area
3. Subject with clinical evidence of a significant arterial insufficiency (claudication, pain of decubitus ulcers), and/or Ankle-Brachial Pressure Index (ABPI) <0.8 or >1.2
4. Subject with any type of diabetes mellitus, as per medical records (i.e. glycated haemoglobin – HbA1c <6.5%) or investigator judgment. (Note: HbA1c <6.5% was a typographical error and the investigators were told to interpret that as HbA1c >6.5%. This error was present in CIP v1.0, 24Feb2017, CRF v3.0, 11Aug2017)

5. Subject suffering from severe hepatic disorders (with serum activity of ALT/AST ≥2.5 UNL) or severe renal disorders (creatinine clearance <30 ml/min) identified within 3 months prior to inclusion
6. Subject with a clinical suspicion of wound infection (e.g., erysipelas, phlegmon) based on the presence of at least one of the following symptoms: peri-ulcerous inflammation, odorous and purulent flow, adenopathy, lymphangitis, fever, unexpected healing interruption, or abscess.
7. Ulcer with exposed tendon or bone
8. Ulcer due to local or extended malignancy
9. An episode of acute deep vein thrombosis (DVT) within 3 months prior to inclusion
10. Subject under treatment with drugs known to adversely affect the healing process: i.e., systemic corticosteroids, cytostatic drugs, immunosuppressive agents

Date of first enrolment
13/06/2017

Date of final enrolment
17/04/2019

Locations

Countries of recruitment
France

Poland

Study participating centre
CHU Dijon
14 Rue Paul Gaffarel
Dijon
France
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Study participating centre
NZOD MIKOMED
Ul. Plugowa 51
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Sponsor type
Industry

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ROR
https://ror.org/051tj3a26

Funder(s)

Funder type
Industry

Funder Name
IBSA Institut Biochimique SA (Switzerland)

Results and Publications

Publication and dissemination plan
1. For the time being, neither the clinical study protocol nor any other study document is expected to be made available
2. Planned publication in a peer-reviewed journal

Intention to publish date
18/07/2021

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?
Results article		01/11/2021	14/03/2022	Yes	No