A Phase III, Double-Blind, Placebo Controlled, Parallel Group, International, Multicenter Study of 12 Weeks Treatment with Trafermin 0.01% Spray in Patients with Diabetic Foot Ulcer of Neuropathic Origin.

Published: 25-02-2011
Last updated: 27-04-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON38005

Source
ToetsingOnline

Brief title
The Trans-North Study

Condition

- Diabetic complications

Synonym
diabetic foot ulcer

Research involving

Human

Sponsors and support

Primary sponsor: Olympus Biotech Europe SAS
Source(s) of monetary or material Support: Olympus Biotech Europe SAS

Intervention

Keyword: diabetic foot ulcer, trafermin

Outcome measures

Primary outcome

Wound closure is defined as observed 100% reepithelialization of the target DFU, without exudates, confirmed by a second medical evaluation after two weeks. The wound closure rate is the number of patients achieving wound closure at the specified timepoint during the 12-week double blind treatment period.

Secondary outcome

- Comparative evaluation of the trafermin 0.01% spray and placebo groups of the time to reach complete wound closure.

- Comparative evaluation of the trafermin 0.01% spray and placebo groups of absolute and relative wound area regression and of wound edge migration of target DFU (using Gilman's formula see Section 11.6.2) over 12 weeks and over 24 weeks, based on planimetry tracing.

- Comparative evaluation of the trafermin 0.01% spray and placebo groups of clinical infection occurrence on the target foot.

- Comparative evaluation of the trafermin 0.01% spray and placebo groups of amputation rate on the target foot.

- Comparative evaluation of the trafermin 0.01% spray and placebo groups of the

frequency of local surgical procedures

- Comparative evaluation of the trafermin 0.01% spray and placebo groups of reopening rates of closed wounds at 1, 2 and 3 months after confirmed reepithelialization.

- Maintenance of wound closure/time to re-opening up to 3 months after confirmed reepithelialization.

- Comparative evaluation of the trafermin 0.01% spray and placebo groups of new wound occurrence up to 6 months after randomization.

- Comparative evaluation of the trafermin 0.01% spray and placebo groups of new wound occurrence/wound recurrence up to 12 months after randomization.

- Comparative evaluation of variation in hs CRP levels between the trafermin 0.01% spray and placebo groups after the 12-week double blind treatment period.

Study description

Background summary

Diabetic foot ulcers (DFUs) have a complex pathophysiology and are, usually, a very difficult wound to heal. The most common cause of ulceration is repetitive mechanical forces of gait, which lead to callus, the most important pre-ulcerative lesion in the neuropathic foot. The lifetime risk of a person with diabetes developing foot ulceration is reported to be as high as 25%. More than a million people with diabetes require limb amputation each year and amputation is associated with significant morbidity and mortality. The strategy to improve healing rates is based on the management of peripheral arterial disease, relief of pressure (off-loading) areas, aggressive debridement, and infection control. However, apart from small, superficial and purely neuropathic DFU, wound closure within 20 to 24 weeks remains, in most cases, relatively poor and rarely exceeds 40 to 50%. Furthermore, the diabetic foot should be considered a lifelong condition, as having had one ulcer dramatically increases the risk of developing a new ulcer. For these reasons and because of the risk of severe complications, there is a strong need for efficient adjuvant treatments. Accordingly, numerous new treatments have

been explored such as growth
factors, bioengineered skin substitutes, extracellular matrix proteins, and various other products. Growth factors are involved throughout the healing process. They act by binding to specific receptors in the plasma membranes of target cells, thereby activating signal
transduction mechanisms. At the cellular level, growth factors mediate macrophage migration, neovascularization, collagen synthesis, fibroblast proliferation, as well as final reepithelialization. Importantly, each growth factor acts on several cell lines, and this interaction enhances healing. While the restoration of a normal healing cascade may be elusive, any improvement in healing rates obtained with growth factors would be useful. Fibroblast growth factors (FGF) have two types of protein with different iso-electric points on the basic and acidic sides: basic FGF (b-FGF) and acidic FGF. Human b-FGF is a singlestranded polypeptide without any sugar chain. Its molecular weight is about 17 kDa, and it has a high affinity for heparin. b-FGF has been reported to expedite the wound healing process in rats by promoting neovascularization, granulation and epithelialization. Trafermin is a recombinant human b-FGF; (original development code KCB-1), which is
manufactured by genetic engineering using Eschericia coli by Kaken Pharmaceutical Co., Ltd. in Japan. Trafermin 0.01% spray (OTD-101) is a spray formulation of a recombinant human b-FGF indicated for the treatment of pressure ulcers and other dermal ulcers. Trafermin 0.01% spray obtained marketing authorization in 2001 in Japan for the treatment of pressure ulcers and skin ulcers (burn wounds and leg ulcers). The product obtained marketing authorization in South Korea in 2008. The further development of trafermin spray for the European market is planned for diabetic ulcer, since this indication is the most serious and most difficult to treat of all wounds.

Study objective

Trafermin spray is a new treatment that is being studied in wound healing and particularly for the treatment of diabetic foot ulcers. When trafermin is sprayed onto a wound, it stimulates the skin and blood vessels to grow again and so speeds up the time it takes for the wound to close up. Trafermin has been studied in people with pressure ulcers and in people with different types of skin ulcers, for example burn wounds, leg ulcers, diabetic ulcers (wound on your foot as complication of diabetes), and ulcers that can form after an operation or an accident. The results have been encouraging and so the purpose of this study is find out if trafermin is a useful treatment for a particular type of diabetic foot ulcer. Trafermin has been marketed in Japan since 2001 and is used to treat different types of wound.

Primary Objective
To demonstrate a superior wound closure rate of diabetic foot ulcers (DFUs) of neuropathic origin after a maximum of 12 weeks topical daily application of trafermin 0.01% spray compared with placebo, in addition to best local care. Wound closure is defined as 100% reepithelialization of the target DFU, without

exudates.

Secondary Objectives
- To determine the time to reach complete wound closure.
- To determine absolute and relative wound area regression and wound edge migration based on planimetry tracing.
- To determine the occurrence rate of clinical infection on the target DFU.
- To evaluate the safety of trafermin 0.01% spray.
- To determine the rate of amputations on the target DFU.
- To determine the frequency of local surgical procedures.
- To determine the maintenance of wound closure/time to re-opening up to 3 monthsafter observed reepithelialization.
- To determine DFU new occurrence/recurrence up to 12 months.
- To explore biomarkers from target wound fluid (selected centers only).
- To assess high sensitivity C-Reactive Protein (hs CRP) level variations.
- To explore the correlation of absolute and relative wound area regression and wound

Study design

An international, double-blind, placebo-controlled multicenter trial with parallel groups

Intervention

Patients who give written informed consent will be screened for the study. Suitable patients will enter a 2-week placebo run-in period during which off-loading and best local care will be applied.

At the end of the run-in period, eligible patients will be randomized in equal numbers to double-blind treatment with trafermin 0.01% spray or placebo spray, in addition to off-loading and best local care. The double-blind treatment period will continue for maximum12 weeks, or until wound closure (100% reepithelialization of the target DFU, i.e the target wound only, without exudates) is achieved, whichever is sooner.

After the double-blind treatment period, patients will be followed up for a total of 9 months from last treatment application:
- Primary follow-up for efficacy and safety - for 3 months ±2 weeks starting after wound closure, or Week 12, whichever is sooner.
- Secondary follow-up for safety - for 6 months ±1 month starting after the primary follow-up period.

Patients will be assessed at intervals of 2 weeks during the double-blind treatment period, at intervals of 4 weeks during the primary follow-up period, and at intervals of 3 months during the secondary follow-up period.

Study burden and risks

See protocol section 6.3.7 Summary of the Schedule of Assessments p25-26

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provide written informed consent to participate.;2. Male or female patients age 18 years or older.;3. Type 1 or 2 diabetes.;4. A single full-thickness DFU that has been present for at least 2 weeks.;5. DFU surface area >= 0.9 cm2 and <=20 cm2 confirmed by the investigator*s measurement, and its surface area not decreased by more than 40% compared to the selection value. ;6. No exposure of bone in the target DFU.;7. Neuropathy confirmed by loss of protective sensation to monofilament test. ;8. Non-infected target foot DFU of confirmed

neuropathic origin with: ;- ABPI on the target leg (>0.9; <=1.3) or if ABPI is > 1.3 or is not assessable, TBPI on target foot >=0.7,;OR;- ABPI on target leg (>=0.7 - <=0.9) or if ABPI is > 1.3 or is not assessable, TBPI on target foot <0.7, AND a toe blood pressure of >40 mmHg.;9. Completed the 2-week placebo run-in period during which they were compliant to off-loading and to daily application of placebo spray, without major protocol violation. Compliance with the placebo run-in treatment regimen must be *excellent* or *acceptable*.;10. Glycosylated hemoglobin (HbA1c) <=10% (from a blood sample taken during the placebo run-in period).;11. Target DFU appropriately debrided (<10% black and at least 50% of red/pink on a colorimetric scale).;12. Target DFU of grade A1 or A2 on the University of Texas Wound Classification System or of Grade 1 or 2 of the Wagner classification.

Exclusion criteria

1. Active Charcot foot, or inactive Charcot foot, if the target DFU cannot be properly offloaded.;2. Ulcers of non-neuropathic origin (e.g., rheumatoid, radiation-related, vasculitis-related ulcers).;3. Presence of any foot ulcer (whether or not on the target foot) for which local or systemic antibiotic treatment is required.;4. Evidence of skin cancer within or adjacent to the target ulcer.;5. Any infected ulcers, defined as any problem such as (but not limited to) cellulitis, osteomyelitis, gangrene, or deep tissue infection requiring local or systemic antibiotic therapy. ;6. Another wound on the same foot as the target DFU (i.e. patients with another wound on the same limb as the target DFU are eligible for the study provided the concomitant wound is not infected and is above the ankle of the target foot).;7. Any known active malignancy that requires general, local, surgical or radiation therapy either ongoing or within the previous 6 months; or patients whose treatment has been suspended for compassionate reasons, or who are not considered as cured from any malignancy.;8. Morbid obesity, with body mass index (BMI) >=45 kg/m2.;9. Clinically significant medical conditions, in the investigator*s opinion, that could impair wound healing (e.g. hepatic impairment, immunocompromised patients).;10. Severe renal failure, defined as requirement for hemodialysis or peritoneal dialysis.;11. Females who are pregnant or breastfeeding, or who are of childbearing potential and not practicing a medically approved method of contraception.;12. Concomitant treatment with high dose oral or parenteral corticosteroids, defined as a daily dose of at least 7.5 mg prednisone or equivalent.;13. Participation in another clinical study within the previous 3 months.;14. Current participation in another clinical study with any drug or device.;15. History of drug or alcohol abuse within the previous year. ;16. Concurrent severe psychiatric disease (including severe depressive disorder).;17. Known intolerance to the IMP or to any of its excipients.;18. Known to be uncooperative or noncompliant.;19. Outpatients who are unable to comply with the requirement for daily spray application at home (either application by a family member or by a visiting nurse).;20. Any other condition which, in the opinion of the investigator, would render the patient unsuitable for the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-08-2011
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Trafermin
Generic name:	Trafermin

Ethics review

Approved WMO Date:	25-02-2011
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	04-04-2011
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	03-05-2011

Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	11-05-2011
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	31-05-2011
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	01-07-2011
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	19-07-2011
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	20-07-2011
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	04-05-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	13-06-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)

Approved WMO Date:	14-06-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	30-07-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	26-11-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	27-11-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-021015-16-NL
ClinicalTrials.gov	NCT01217476

Register	ID
CCMO	NL35738.072.11