A Phase 3 Randomized, Placebo-Controlled, Blinded Study to Investigate the Safety and Efficacy of a Topical Gentamicin-Collagen Sponge in Combination with Systemic Antibiotic Therapy in Diabetic Patients with an Infected Foot Ulcer

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Primary Objective:To determine the effect of the Topical Gentamicin-Collagen Sponge (gentamicin-sponge) in combination with systemic antibiotic therapy compared to placebo-sponge and no-sponge, both in combination with systemic antibiotic therapy on...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON43839

Source
ToetsingOnline

Brief title
INN-TOP-005

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Diabetic complications

Synonym

Diabetic foot ulcer, Infected foot ulcers in diabetic patients

Research involving
Human

Sponsors and support

Primary sponsor: Innocoll Pharmaceuticals Ltd.
Source(s) of monetary or material Support: De sponsor;Innocoll Pharmaceutical Ltd.

Intervention

Keyword: Diabetes Mellitus, Infected foot ulcers

Outcome measures

Primary outcome

The primary efficacy variable is the percent of patients with a clinical

outcome of "clinical cure" at follow-up visist 1. (Clinical cure= Resolution of

all clinical signs and symptoms of infection).

Secondary outcome

* Percent of patients with both a clinical outcome of "clinical cure" and

"baseline pathogen eradication" at follow-up visit 1

* Percent of patients with re-infection

* Time (days) to a clinical outcome of "clinical cure"

* Percent of patients that have an amputation associated with the target ulcer

* Percent of patients with target ulcer closure at or before follow-up visit 2

* Time (days) to closure of the target ulcer

Study description

Background summary

Infected skin ulcerations in patients with diabetes mellitus can be

debilitating and may cause significant morbidity due to prolonged, more severe infection difficulty in healing. Diabetic ulcers are responsible for frequent health care visits, accounting for the largest number of diabetes-related hospital days. A diabetic ulcer on the foot or lower extremity is a major predictor of amputation. Coordinated patient management of the infected diabetic ulcer, as well as treatment of any underlying metabolic abnormalities, are required for successful healing of the ulcer.
A major predisposing factor for diabetic foot ulcers is foot sensory and motor neuropathy which can result in a patient's inability to sense pain or warmth. Another factor, peripheral vascular disease, causes diminished blood flow to the foot; this can result in a lack of erythema or induration, which are the visual cues of infection. These combined comorbidities make the diabetic foot prone to repeat ulceration and infection with subsequent negative consequences. Aggressive and early treatment is necessary to prevent the need for amputation.

Study objective

Primary Objective:

To determine the effect of the Topical Gentamicin-Collagen Sponge (gentamicin-sponge) in combination with systemic antibiotic therapy compared to placebo-sponge and no-sponge, both in combination with systemic antibiotic therapy on diabetic patients' clinical outcome in the treatment of infected foot ulcers.

Secondary Objectives:

To determine the effect of the genatmicin-sponge in combination with systemic antibiotic therapy compared to placebo-sponge and no-sponge, both in combination with systemic antibiotic therapy on microbiological outcome and eradication of baseline ulcer pathogens.

To assess the safety and tolerability of the gentamicin-sponge in combination with systemic antibiotic therapy.

Study design

This is a phase 3, randomized, controlled, blinded, multicenter study conducted in 3 parallel cohorts of diabetic patients with at least 1 infected foot ulcer. Patients will be randomized using an electronic randomization system to receive 1 of 3 study treatments; systemic antibiotic therapy and standard ulcer care with either (A) daily application of a gentamicin-sponge, (B) daily application of a placebo-sponge or (C) no-sponge, in the ratio 2:1:1. The investigator will be blinded to the patient's treatment group assignment and patients randomized to one of the 2 sponge groups will be blinded as to whether the sponge is active or placebo.

If a patient has multiple infected ulcers, the assigned treatment will be administered to all infected ulcers. The investigator will determine the highest severity ulcer to be used for all efficacy evaluations and will also determine the size and number of sponges (up to 4) that a patient will use in order to completely cover all infected ulcers. The investigator will prescribe an empiric systemic antibiotic therapy based on protocol instructions.

Patients will be treated for approximately 28 days and return to the clinic weekly for safety and efficacy assessments. The investigator will stop study treatment if a patient achieves clinical cure by or after the 3rd treatment visit (approximately study day 15). After completing treatment, patients will return to the clinic for scheduled follow-up visits or until ulcer closure. The final efficacy assessments used in the primary efficacy analyses will be obtained at the first follow-up visit approximately 10 days after treatment is stopped. The remaining follow-up visits will occur at approximately 30, 60 and 90 days after treatment is stopped when patients will be assessed for ulcer closure and any re-infection.

Intervention

Cohort A: The appropriate size and number of gentamicin-sponges to each infected ulcer on a daily basis, systemic antibiotic therapy as prescribed and standard ulcer care (= gentamicin-sponge group)

Cohort B: The appropriate size and number of placebo-sponges to each infected ulcer on a daily basis, systemic antibiotic therapy as prescribed and standard ulcer care (= placebo-sponge group)

Cohort C: Systemic antibiotic therapy as prescribed

Study burden and risks

Risks: possible side effects of the study medication

Burden:

* 9 visits at the study center
* at 6 of 9 visits: collection of urine and blood samples
* at 6 of 9 visits: assessment of the ulcer and (if deemed necessary) ulcer débridement
* at 3 of 9 visits: collection of a culture of the ulcer
* at 5 of 9 visits: a full physical examination will be performed

Patients need to fill out a patient worksheet/diary on a daily basis.

Contacts

Public
Innocoll Pharmaceuticals Ltd.

Block D Monksland Business park, Monksland Unit 9
Athlone Co. Roscommon
IE
Scientific
Innocoll Pharmaceuticals Ltd.

Block D Monksland Business park, Monksland Unit 9
Athlone Co. Roscommon
IE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Is aged >= 18 and <= 85 years.
2. Has diabetes mellitus, according to the American Diabetes Association (ADA) criteria.
3. Has at least 1 skin ulcer located on or below the malleolus that presents with the following clinical manifestations of a moderate or severe infection based on the Infectious Disease Society of America guidelines for the *Diagnosis and Treatment of Diabetic Foot Infections* (CID 2012; 54:132-173) (IDSA guidelines):
• has >= 2 manifestations of inflammation (local swelling or induration, erythema, local tenderness or pain, local warmth, purulent discharge (thick, opaque to white or sanguineous secretion)
• has >= 1 of the following characteristics: erythema > 2cm, or involving structures deeper than skin and subcutaneous tissues (e.g. abscess, osteomyelitis, septic arthritis, fasciitis)
For patients with multiple infected ulcers, the ulcer with the highest Diabetic Foot Infection

Wound score (DFI score) must be on or below the malleolus and all infected ulcers must be completely coverable using no more than 4 sponges (sponges cannot be cut).
4. Has documented adequate arterial perfusion in the affected limb(s) (either palpable dorsalis pedis and posterior tibial pulses, or normal Doppler wave forms, a toe blood pressure >= 45 mm Hg or participation is approved by a vascular surgeon);
5. Has received appropriate surgical intervention to remove all necrotic and infected bone if diagnosed with osteomyelitis. [Note: The investigator is referred to Diabetes Metab Res Rev 2008; 24(Suppl 1): S145-S161 for recommendations for the diagnosis of diabetic foot osteomyelitis.]
6. Has received appropriate surgical debridement to remove all gangrenous tissue.
7. If female, is nonpregnant (negative pregnancy test results at the baseline/randomization visit) and nonlactating.
8. If female, is either not of childbearing potential (defined as postmenopausal for >= 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy or hysterectomy]) or practicing 1 of the following medically acceptable methods of birth control and agrees to continue with the regimen throughout the duration of the study:
• Oral, implantable or injectable contraceptives for 3 consecutive months before the baseline/randomization visit.
• Total abstinence from sexual intercourse (>= 1 complete menstrual cycle before the baseline/randomization visit).
• Intrauterine device (IUD).
• Double barrier method (condoms, sponge, diaphragm or vaginal ring with spermicidal jellies or cream).
9. Is willing and able to return to the study facility for all follow-up visits.
10. Is able to fluently speak and understand the local language and is able to provide meaningful written informed consent for the study.
Once baseline clinical laboratory results become available, a patient will continue to be eligible for study participation after enrollment if he or she meets the following criteria:
11. Has the following laboratory values
• white blood cells (WBC) >= 4000 cells/mm3 and/or absolute neutrophil count (ANC) >= 1500 cells/mm3
• hematocrit > 25%,
• hemoglobin > 8 g/L,
• platelet count >75 000/mm3
• coagulation test results less than 1.5 times the upper limit of normal (unless on anticoagulant therapy).
Any subject whose baseline laboratory results fall outside of these parameters will be withdrawn from the study.

Exclusion criteria

1. Has a known history of hypersensitivity to gentamicin (or other aminoglycosides).
2. Has a known or suspected hypersensitivity to bovine collagen.
3. Has an ulcer infection which, based upon the patient*s known history of hypersensitivity and/or as otherwise in the opinion of the investigator, cannot be adequately treated with at

least one of the empiric systemic antibiotic regimens allowed by this protocol.
4. Has an ulcer associated with prosthetic material or an implanted device.
5. Has received any systemic or topical antibiotic therapy for any reason within 7 days of randomization unless it was administered to specifically treat the infected ulcer(s) and only within 36 hours of randomization.
6. Requires or is likely to require treatment with any concomitant topical product or wound therapy before the first follow-up study visit.
7. Is severely immunocompromised, or likely to become severely immunocompromised during the study, in the opinion of the investigator.
8. Has a history of myasthenia gravis or other neurological condition where gentamicin use is contraindicated as determined by the investigator.
9. Has a history of epilepsy.
10. Has a history of alcohol or substance abuse in the past 12 months.
11. Has an uncontrolled illness that, in the opinion of the investigator, is likely to cause the patient to be withdrawn from the trial or would otherwise interfere with interpreting the results of the study.
12. Has a known history of severe renal impairment or has a creatinine clearance <= 30 mL/min at
Visit 1/Day 1.

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:	Recruitment stopped
Start date (anticipated):	04-03-2016
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Topical Gentamicin-Collagen Sponge
Generic name:	Gentamicin sponge
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-06-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-11-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-02-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2016
Application type:	Amendment

Review commission: CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2015-000934-31-NL
CCMO	NL53797.091.15

Study results

Date completed: 27-09-2016

Actual enrolment: 8

Summary results
Trial is onging in other countries