Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial

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Summary

Background Diabetic foot ulcers are serious and challenging wounds associated with high risk of infection and lower-limb amputation. Ulcers are deemed neuroischaemic if peripheral neuropathy and peripheral artery disease are both present. No satisfactory treatment for neuroischaemic ulcers currently exists, and no evidence supports one particular dressing. We aimed to assess the effect of a sucrose octasulfate dressing versus a control dressing on wound closure in patients with neuroischaemic diabetic foot ulcers.

Methods We did a randomised, double-blind clinical trial (Explorer) in 43 hospitals with specialised diabetic foot clinics in France, Spain, Italy, Germany, and the UK. Eligible participants were inpatients or outpatients aged 18 years or older with diabetes and a non-infected neuroischaemic diabetic foot ulcer greater than 1 cm² and of grade IC or IIC (as defined by the University of Texas Diabetic Wound Classification system). We excluded patients with a severe illness that might lead to them discontinuing the trial and those who had surgical revascularisation in the month before study entry. We randomly assigned participants (1:1) via a computer-generated randomisation procedure (concealed block size two); stratified by study centre and wound area (1–5 cm² and 5–30 cm²), to treatment with either a sucrose octasulfate wound dressing or a control dressing (the same dressing without sucrose octasulfate) for 20 weeks. Both groups otherwise received the same standard of care for a 2-week screening period before randomisation and throughout the 20-week trial. Dressings were applied by nursing staff (or by instructed relatives for some outpatients). Frequencies of dressing changes were decided by the investigator on the basis of the clinical condition of the wound. Patients were assessed 2 weeks after randomisation, then monthly until week 20 or occurrence of wound closure. The primary outcome, assessed by intention-to-treat, was proportion of patients with wound closure at week 20. This trial is registered with ClinicalTrials.gov, number NCT01717183.

Findings Between March 21, 2013, and March 31, 2016, we randomly assigned 240 individuals to treatment: 126 to the sucrose octasulfate dressing and 114 to the control dressing. After 20 weeks, wound closure occurred in 60 patients (48%) in the sucrose octasulfate dressing group and 34 patients (30%) in the control dressing group (18 percentage points difference, 95% CI 5–30; adjusted odds ratio 2·60, 95% CI 1·43–4·73; p=0·002). In both groups, the most frequent adverse events were infections of the target wound: 33 wound infections in 25 (20%) patients of 126 in the sucrose octasulfate dressing group and 36 in 32 (28%) patients of 114 in the control dressing group. Minor amputations not affecting the wound site were also reported in one (1%) patient in the sucrose octasulfate dressing group and two (2%) patients in the control dressing group. Three (2%) patients assigned to the sucrose octasulfate dressing and four (4%) assigned to the control dressing died, but none of the deaths were related to treatment, procedure, wound progression, or subsequent to amputation.

Interpretation A sucrose octasulfate dressing significantly improved wound closure of neuroischaemic diabetic foot ulcers without affecting safety after 20 weeks of treatment along with standard care. These findings support the use of sucrose octasulfate dressing as a local treatment for neuroischaemic diabetic foot ulcers.

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Introduction

Diabetic foot ulceration is a serious and common complication of type 1 and type 2 diabetes, affecting 9·1–26·1 million people annually worldwide and approximately 19–34% of people with diabetes at least once in their life.[1] Because the global prevalence of diabetes continues to increase substantially, with a prediction of 642 million people worldwide in 2040,[2] the complex and costly management of these disabling and recurrent wounds remains a therapeutic challenge.[1,3,4] The prognosis of patients with diabetic foot ulcers is deeply affected by the high prevalence of infection and amputation associated with these wounds. The risk of death at 5 years for a patient with a diabetic foot ulcer is 2·5 times higher than for a

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Research in context

Evidence before this study
Management of diabetic foot ulcers is a therapeutic challenge. We searched MEDLINE and Embase on July 20, 2017, without language or date exclusions, with the terms "wound healing" AND "diabetic foot ulcers'" AND ("neuro-ischaemic" or "peripheral artery disease") for reports of randomised controlled trials. We identified 33 papers, but no relevant study could be selected because no studies had so far assessed the superiority of any device in a cohort of patients who only had neuroischaemic ulcers. We expanded our search (again with no language or date exclusions) using the terms "wound healing" AND "diabetic foot ulcers" for meta-analyses and systematic reviews of randomised controlled trials, with a special interest in trials assessing dressing efficacy. Our search identified 146 papers from which we selected four that provided sufficient up-dated or recent evidence on wound closure and on the quality of analysed trials. Our search revealed that most trials assessing skin substitutes, growth factors, or dressings had included patients with only neuropathic ulcers or mixed populations of patients with neuropathic and neuroischaemic ulcers. According to most recent guidelines and systematic reviews, evidence to support the adoption of any particular intervention in the management of diabetic foot ulcers is poor. A strong need exists for robust evidence from studies using high-quality methods. To address this quality evidence gap, Jeffcoate and colleagues listed the key points that should ideally be included in the design and reporting of clinical studies in this field in a 2016 Personal View in *The Lancet Diabetes & Endocrinology*. Some positive clinical

evidence has also been reported with sucrose octasulfate dressing in the management of chronic wounds with vascular involvement and protease imbalance. The results of two randomised controlled trials in patients with leg ulcers of venous or mixed origin, and of a pooled data analysis of eight real-life surveys in a variety of chronic wounds including diabetic foot ulcers, indicated a potential use of sucrose octasulfate dressings in the management of neuroischaemic diabetic foot ulcers, but the evidence needed to be established through a randomised clinical trial containing patients with diabetic foot ulcers.

Added value of this study
Our study is, to our knowledge, the first randomised double-blind controlled trial to compare two types of dressings in patients with rigorously assessed neuroischaemic diabetic foot ulcers. Sucrose octasulfate dressing along with good standard of care was significantly more effective at achieving would closure after 20 weeks of treatment than a control dressing (the same dressing without sucrose octasulfate) with similar care.

Implications of all the available evidence
Sucrose octasulfate dressings could be used in current local treatment and management of neuroischaemic diabetic foot ulcers. In the context of multidisciplinary and complex management of this condition, efficient and safe treatments that are also easy to implement by all health-care professionals are needed. Sucrose octasulfate dressings could be considered as a new standard of care.

patient without, and up to 70% of patients could die within 5 years after amputation.[1,5] Thus, effective and safe treatments are needed that do not increase staff workload, are easy to provide, and are well received by patients.

Existing guidelines for the management of diabetic foot ulcers recommend appropriate local wound care with efficient debridement, use of wound dressings that maintain a moist environment, treatment of infection, vascular assessment and revascularisation if required, pressure relief, treatment of comorbidities, metabolic control, and patient education—however, outcomes with these management strategies are unsatisfactory.[4,6–8] Some emerging treatments have been proposed with varying degrees of success, but according to guidelines and systematic reviews, none of these interventions can be recommended over others owing to poor evidence. Only a few published studies of novel interventions were of high quality and most were susceptible to biases, including small study sizes, heterogeneous patient cohorts, and a high number of dropouts.[7,9–11]

Diabetic foot ulcers are usually categorised as neuropathic, ischaemic, or neuroischaemic ulcers, the latter being diagnosed if peripheral neuropathy and peripheral artery disease are both involved. Because more accurate and frequent vascular assessment can be done

today in current practice, peripheral artery disease is increasingly recognised when present and neuroischaemic ulcers are now estimated to be present in more than half the patients with diabetic foot ulcers in high-income countries.[8,12–15] Unfortunately, the situation has not changed since 2011, when Armstrong and colleagues[14] suggested that "peripheral artery disease in [diabetic foot ulcers] is also associated with the most severe adverse outcomes, including lower probability of healing, longer healing times, higher probability of ulcer recurrence, greater risk of amputations, and potentially higher mortality". To date, there are no devices or drugs with proven efficacy for this indication.[14]

Over the past few years, knowledge of the underlying metabolic and cellular changes involved in diabetic foot ulcers and peripheral artery disease has progressed.[16–20] Diabetic foot ulcers have a prolonged inflammatory phase with fibroblast dysfunction, impaired neovascularisation, and increased concentrations of matrix metalloproteinases.[18,19] These matrix metalloproteinases impede wound healing through degradation of growth factors and destruction of the extracellular matrix.[17,19] In neuroischaemic ulcers, this protease imbalance has been associated with poor outcomes.[16,17,21] The potassium salt of sucrose octasulfate acts at the tissue level and has been shown to

inhibit excess matrix metalloproteinases.[22] Additionally, the potassium salt of sucrose octasulfate has a unique structure that interacts with growth factors and thus restores their biological functions contributing to tissue formation.[22–24] Therefore, we hypothesised that a sucrose octasulfate dressing could be a potential treatment for neuroischaemic diabetic foot ulcers. Sucrose octasulfate dressings have been successfully used for the treatment of various chronic wounds.[25–27] Its favourable benefit–risk ratio has been established through randomised studies of patients with leg ulcers arising from venous or mixed origins, when compared with either a control dressing or a protease modulating dressing.[25,26] Additionally, a pooled-data analysis of real-life surveys in Europe has revealed that sucrose octasulfate dressings might shorten the time to closure of chronic wounds.[27] However, evidence for its usefulness in treating neuroischaemic diabetic foot ulcers is scarce. We therefore aimed to assess the efficacy of treatment with a sucrose octasulfate dressing to improve wound closure in patients with a neuroischaemic diabetic foot ulcer, compared with a control dressing without sucrose octasulfate.

Methods

Study design

The design and rationale for this study have been published.[28] We did a randomised, double-blind, controlled, clinical trial (Explorer) at 43 hospitals with specialised diabetic foot clinics using a multidisciplinary approach. These centres had diabetology, vascular medicine, vascular surgery, and rehabilitation units and were located in France, Spain, Italy, Germany, and the UK.

The study was done in compliance with the regulatory requirements of the five countries. Approval of the relevant competent authority and opinions delivered by national or local ethics committees are in the appendix.

Participants

Eligible participants were outpatients or inpatients older than 18 years presenting with diabetes and a non-infected neuroischaemic diabetic foot ulcer of grade IC (ischaemic, non-infected superficial wound) or IIC (ischaemic, non-infected wound penetrating to tendon or capsule), as defined by the University of Texas Diabetic Wound Classification system.[29] Glycaemic control was confirmed by an HbA$_{1c}$ of 10% (85·8 mmol/mol) or lower in the 3 months before enrolment or during screening. Neuropathy was verified by insensitivity to the 5·07 Semmes-Weinstein 10 g monofilament. Peripheral artery disease without critical limb ischaemia was confirmed by vascular assessment of the affected foot. To be eligible, a patient's Ankle Brachial Pressure Index (ABPI) score had to be 0·9 or less, and toe pressure of at least 50 mm Hg (or ankle pressure at least 70 mm Hg if toe pressure could not be measured). After the trial started, a protocol amendment made on May 22, 2014, specified that patients with an ABPI score of greater than 0·9 were also

eligible, providing they had a Toe Brachial Pressure Index score of 0·7 or less and toe pressure of at least 50 mm Hg. This amendment was made to account for falsely high ABPI values resulting from medial arterial calcification, a common diabetes complication that might misleadingly rule out the presence of peripheral artery disease. Additional key eligibility requirements were location of the target ulcer on the toe or lateral, dorsal, or plantar aspect of the foot; wound surface area between 1 and 30 cm² after clinical debridement; wound duration of between 1 and 24 months at inclusion; and no local infection of any wound on the lower limbs, as defined by criteria from the Infectious Diseases Society of America and International Working Group on the Diabetic Foot.[30] We excluded patients with a severe illness that might lead to them to prematurely discontinue the trial and those who had undergone surgery or surgical revascularisation (vascular reconstruction or angioplasty) in the month before trial entry. At the end of a screening period, patients were assessed to determine whether they continued to satisfy the eligibility criteria applied at enrolment and were excluded if they had a reduction in the wound area of more than 30%, a wound area of less than 1 cm², or a wound infection. A full list of inclusion and exclusion criteria is in the appendix. All participants provided written informed consent before taking part in the study.

Randomisation and masking

Upon completion of a 2-week screening period, we randomly assigned eligible participants (1:1) to either a sucrose octasulfate wound dressing or a control dressing (the same dressing without sucrose octasulfate), for a 20-week treatment period. The study endpoint was the visit during the 20th week following randomisation or wound closure, whichever happened first. The randomisation list was prepared via a computer-generated block randomisation procedure (concealed block size of two) by an independent company (Vertical, Paris, France), which was also in charge of the data analysis for this study. Randomisation was stratified by study centre and wound area strata (1–5 cm² and 5–30 cm²).

Participants, caregivers, clinical investigators (outcome assessors), and individuals in charge of data collection were masked to group assignment for the duration of the study. Group assignments were not revealed to the individuals who did the statistical analyses before the clinical database had been cleaned and frozen and all planned analyses had been done. The appearance, shape, and packaging of the two study dressings were identical. Before the beginning of the trial, a likelihood jury of 16 testers who were not further involved in this clinical investigation assessed the dressings and established that none of the dressing features made it possible to distinguish the two batches. Treatment allocation was done centrally by the quality assurance department of the funder, which had no contact with study participants. The investigator received the allocated participant number by
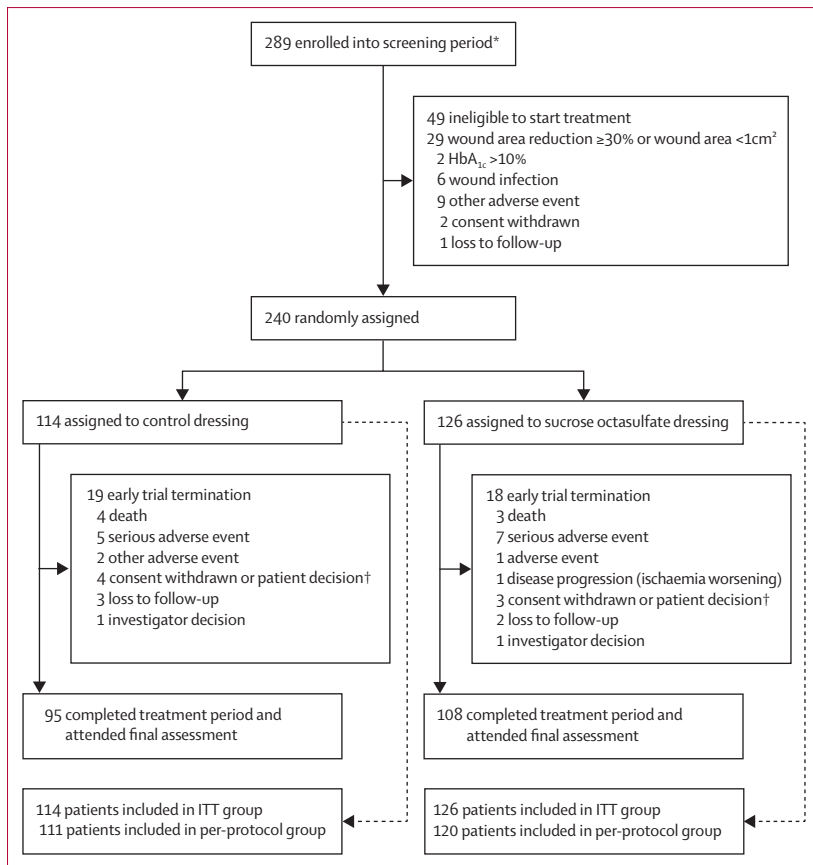
Figure: Trial profile

ITT=intention-to-treat. *Information about the number of patients screened for eligibility before entering the 2-week screening period was not available. †Patients classified as consent withdrawn or patient decision expressed their desire not to participate further in the study, whereas those lost to follow-up missed scheduled study visits and the investigator was unable to reach them for any explanation.

email and dressings were centrally labelled by participant number, so neither patient or investigator knew what each dressing contained.

Procedures

All the health-care professionals involved in the study (physicians, podiatrists, and nurses) were trained in the appropriate use of all the study materials (case report forms, the toe pressure device Systoe [Atys Medical, Soucieu en Jarrest, France], a microdoppler Huntleigh [Huntleigh Healthcare Ltd, Cardiff, UK], camera, and an approved offloading device list) before the start of the trial.

All eligible patients were managed with good standard of care and the control dressing for a 2-week screening period before randomisation. Demographic characteristics, medical history, current treatments, and wound characteristics were recorded at the screening visit (14 days before the randomisation visit). Diabetes complications and comorbidities were recorded in the case report form from the patient's medical file without additional examination. At the end of the screening period (baseline visit at day 0), patients who were still eligible

were randomly assigned to receive the same standard of care as previously delivered with either the control or the sucrose octasulfate dressing.

The sucrose octasulfate dressing (UrgoStart Contact, 10 × 10 cm, Laboratoires Urgo Medical, Chenôve, France) was a non-adherent, non-occlusive wound dressing with a flexible contact layer composed of a polyester mesh impregnated with a lipidocolloid matrix containing sucrose octasulfate potassium salt (nano-oligosaccharide factor). The control dressing (UrgoTul, Laboratoires Urgo Medical) had the same composition as the treatment dressing without the sucrose octasulfate potassium salt.[22]

Patient assessments took place 2 weeks after randomisation, then monthly until the end of the study. In this pragmatic study, variation in practice was allowed within limited options; during the screening and treatment periods, care and treatment was recorded in the study files. Offloading devices used were preapproved by the study coordinators and selected by the investigators at patient enrolment. Patients were taught that it was important to wear the offloading device at all times. More details on the offloading strategy are in the appendix. At each visit, wound debridement and removal of any hyperkeratosis were done at the investigator's discretion. The use of 0·9% sodium chloride was recommended for wound cleaning. Dressing changes were recommended on average every 2–4 days, but frequency was decided by the investigator at each visit on the basis of clinical condition of the wound and its level of exudate. The study dressings were dispensed by the investigating team at each clinical assessment. Between each assessment, dressings were applied to inpatients by the investigating nursing staff and to outpatients by community nurses or relatives who had been instructed by investigators. If during the course of the study an investigator thought that substitution of the allocated dressing for another dressing was more appropriate for the patient, this was allowed and did not lead to patient withdrawal from the study. Such patients continued to receive the same standard of care and the change in dressing was recorded in the case report form as discontinuation of the allocated dressing. The choice of the secondary dressing covering the trial dressings was left up to the investigators. No systemic treatments were contraindicated. Wound infections were treated at the investigator's discretion. Wound area tracing was done and photos were taken after debridement at each assessment, and if wound closure occurred.

Outcomes

The primary outcome was the proportion of participants with wound closure at the end of the treatment phase. Wound closure was assessed by local investigators and was defined as 100% epithelialisation without exudate, confirmed at least 10 days after closure was first assessed. Secondary outcomes included estimated time to reach wound closure (from randomisation visit to first 100% re-epithelialisation visit, in days), absolute (in cm²)

	Control dressing group (n=114)	Sucrose octasulfate dressing group (n=126)
Residential status at recruitment		
Outpatient	107 (94%)	117 (93%)
Inpatient	7 (6%)	9 (7%)
Sex		
Men	93 (82%)	108 (86%)
Women	21 (18%)	18 (14%)
Age (years)	64·9 (10·7)	64·2 (11·2)
Age ≥70 years	39 (34%)	44 (35%)
BMI (kg/m²)*	29·8 (5·9)	30·4 (5·7)
BMI ≥30 kg/m²	48 (42%)	59 (48%)
Diabetes type		
Type 1	8 (7%)	12 (10%)
Type 2	104 (91%)	114 (90%)
Other†	2 (2%)	0 (0%)
Diagnosed diabetes duration (years)‡	17·7 (10·6)	17·7 (10·3)
HbA$_{1c}$		
Mean (SD) (%)	7·3 (1·3)	7·4 (1·3)
Mean (SD) (mmol/mol)	57 (14)	58 (14)
Median (IQR) (%)	7·2% (6·3 – 8·4)	7·4 (6·5 – 8·2)
Median (IQR) mmol/mol	55 (45 – 68)	57 (48 – 66)
Diabetes treatment prescribed		
Any oral hypoglycaemic agent	67 (59%)	74 (59%)
Metformin§	58 (58%)	57 (53%)
Insulin	69 (61%)	92 (73%)
Diabetes complications		
Retinopathy‡	51 (46%)	72 (57%)
Non-proliferative	26/51 (51%)	35/72 (49%)
Proliferative	22/51 (43%)	31/72 (43%)
Others	3/51 (6%)	6/72 (8%)
Nephropathy¶	48 (42%)	50 (40%)
Microalbuminuria	17/46 (37%)	17/50 (34%)
Macroalbuminuria	3/46 (7%)	7/50 (14%)
Renal failure	26/46 (57%)	26/50 (52%)
(Table 1 continues on next column)		

	Control dressing group (n=114)	Sucrose octasulfate dressing group (n=126)
(Continued from previous column)		
Serum creatinine (mg/L)‖	10·2 (4·5)	10·4 (4·8)
Revascularisation history	52 (46%)	64 (51%)
Amputation history	63 (55%)	84 (67%)
Minor amputation	57/63 (90%)	78/84 (93%)
Major amputation	6/63 (10%)	6/84 (7%)
On one leg	47/63 (75%)	61/84 (73%)
On both legs	16/63 (25%)	23/84 (27%)
Comorbidities		
Hypertension	101 (89%)	109 (87%)
Cardiac history**	46 (40%)	56 (45%)
Current smokers	18 (16%)	23 (18%)
Other current treatments		
Antihypertensive	98 (86%)	108 (86%)
Lipid lowering	86 (75%)	98 (78%)
Antiplatelet	82 (72%)	96 (76%)

Data are mean (SD), n (%), or n/N (%) unless otherwise specified. Treatments listed could be combined with others. *n=124 in treatment group. †Other types of diabetes included one latent autoimmune diabetes of adulthood and one secondary diabetes resulting from alcohol-related chronic pancreatitis. ‡n=112 in control group. §n=100 in control group and n=107 in treatment group. ¶Two unspecified nephropathy types in control group. ‖n=74 in control group and n=92 in the treatment group. **n=125 in treatment group.

Table 1: **Baseline characteristics and medical history of the intention-to-treat population**

and relative (%) wound surface area regression, magnitude of the re-epithelialisation wave (Gilman's parameter in mm per week), proportion of patients with a wound area reduction of at least 50% at week 4 and at the last assessment, instantaneous healing rate (in cm² per week), and health-related quality of life (assessed by the EuroQol-5D-5L Quality of Life Questionnaire) during the treatment period. Safety outcomes included nature and incidence of any general or local adverse events. Adverse events of note included clinical infection of the target wound and minor or major amputation of the target limb.

Statistical analysis

A retrospective 2-year review[31] of all patients with diabetic foot ulcers and peripheral artery disease who presented at an interdisciplinary diabetic foot clinic from 2006–07 at Malmo University Hospital (Sweden) showed that no more than 25% of neuroischaemic diabetic foot ulcers were expected to close within 20 weeks with best local care. From this assumption, we considered that an increase of 18 percentage points in the number of participants with wound closure in the treatment group (ie, 43% in the treatment group *vs* 25% in the control group) would represent a substantial clinical improvement in wound management efficacy and would be considered clinically relevant. To detect such a difference with 80% power and an α risk of 5% (bilateral situation), we calculated that 108 patients per group (216 patients in total) was needed. Assuming a dropout rate of broadly 10%, we calculated that a sample size of 238 randomly assigned participants was required.

All primary analyses were done using a coded database (groups were identified as A and B). All analyses were done using the intention-to-treat (ITT) population, which included all randomly assigned patients with at least one post-treatment follow-up measurement. The per-protocol (PP) population, which included all ITT patients without deviation of major selection criteria, was used for sensitivity analyses.

The primary outcome was analysed with a binary logistic regression including group (treatment or control), country, wound area (1–5 cm² or 5–30 cm²), age (<70 years or

	Control dressing group	Sucrose octasulfate dressing group
Confirmed neuropathy	114 (100%)	126 (100%)
Confirmed peripheral artery disease	114 (100%)	126 (100%)
Ankle-Brachial Pressure Index (ABPI)*	0·88 (0·27) (n=111)	0·88 (0·24) (n=126)
Toe systolic pressure (mm Hg)	83·2 (24·8) (n=68)	81·2 (30·2) (n=75)
Ankle systolic pressure (mm Hg)	124·6 (42·2) (n=81)	125·9 (40·5) (n=88)
Toe-Brachial Pressure Index (TBPI)	0·58 (0·14) (n=45)	0·59 (0·16) (n=53)
Transcutaneous partial pressure of oxygen	38·7 (17·7) (n=27)	42·2 (18·0) (n=43)
Amputation history	57 (50%)	75 (60%)
Revascularisation history	42 (37%)	57 (45%)
Wound location		
Sole of the foot	57 (50%)	56 (44%)
Tip of the toe	10 (9%)	10 (8%)
Side of the foot	18 (16%)	26 (21%)
Dorsum of the foot	5 (4%)	11 (9%)
Other†	24 (21%)	23 (18%)
University of Texas Diabetic Wound grade classification		
IC: ischaemic not infected, superficial wound	99 (87%)	96 (76%)
IIC: ischaemic not infected wound penetrating to tendon or capsule	15 (13%)	30 (24%)
Wound duration (months)	7·1 (6·5)	7·3 (6·5)
Median (IQR) wound duration	4·0 (2·0–11·0)	5·0 (2·0–11·0)
Wound duration ≥6 months	46 (40%)	55 (44%)
Wound area (cm²)	4·2 (6·0)	5·3 (9·1)
Median (IQR) wound area	2·1 (1·2–3·9)	2·9 (1·4–5·2)
Wound area >5 cm²	18 (16%)	25 (20%)
Clinical status of the wound bed tissue		
Granulation tissue (%)	80 (40–100)	80 (50–100)
Sloughy tissue (%)	20 (0–60)	20 (0–50)
Black necrosis (%)	0 (0–0)	0 (0–0)
Periwound skin condition		
Healthy periwound skin	20 (18%)	23 (18%)
Hyperkeratosis	76 (67%)	78 (62%)

Data are mean (SD), n (%), or median (IQR). *Three patients in the control group were included in the study who did not have ABPI values (two patients had non-compressible foot arteries with TBPI values of 0·43 and 0·48 and Systolic Toe Blood Pressure values of 56 and 67 mm Hg; one patient had palpable pulses but also several minor amputations of both feet, including one of the big toe of the target limb, and a revascularisation history [percutaneous transluminal angioplasty], but presence of peripheral artery disease was diagnosed by the vascular specialist who recruited this patient). †Other wound locations mostly included toe amputation sites.

Table 2: Baseline characteristics of wound and periwound skin of the target limb or foot

≥70 years), wound duration (<6 months or ≥6 months), and limb amputation history as covariates. Country was selected as a covariate rather than centre, because according to our experience, patients' profiles and local care strategies differ more between countries than between specialised centres in a particular country, and we considered that a country effect might be more important than a centre effect to detect possible variance in the magnitude of effect. BMI was also planned to be entered in the model, but because BMI data were missing for two patients at baseline, we decided not to include this parameter in the main analysis, but did include it in a sensitivity analysis. The estimated effect size is given as an odds ratio (OR)

with 95% CIs. We assessed time to reach confirmed closure using a Kaplan-Meier procedure including wound area stratum followed by a log-rank test. We compared wound area regressions and Gilman's parameter values between groups using non-parametric Mann-Whitney U test, quality-of-life scores and indexes using Fisher's exact test, and incidence of adverse events using χ^2 test. All p values were two-tailed and p values less than 0·05 were considered significant. Values are reported as mean (SD) or median (IQR), and count (percentage), unless stated otherwise.

Sensitivity analyses were done using the same regression model and included analyses of possible wound closure, defined as confirmed or not by the investigator; centrally assessed wound closure, done through a blind assessment by two experienced clinicians not involved in this study on the basis of photos of wounds with an area reduction of 90% or more at the end of the treatment period; confirmed wound closure in the PP cohort; and wound closure with BMI included as an additional covariate in the model. To assess homogeneity of closure rate differences between groups, we did a post-hoc descriptive analysis in which we categorised the population according to wound duration. Statistical analyses were done with SPSS 18.0 software. There was no data monitoring board. The study was registered with ClinicalTrials.gov, number NCT01717183.

Role of the funding source

SB (medical director of the study funder) participated in formulation of the study protocol. AS (senior clinical project manager of the study funder) was in charge of the coordination of the external contract research organisations in control of device delivery, data monitoring, data collection, data extraction, and data analysis. SB and AS had access to the raw data but did not undertake data extraction or data analysis. The funder of the study had no role in data extraction, data analyses, and data interpretation, but did have a role in the writing of the report. The corresponding author had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

Between March 21, 2013, and March 31, 2016, we enrolled 289 patients. Among them, 69 patients were recruited before and 220 after the vascular assessment protocol amendment. 240 eligible individuals were randomly assigned to treatment: 114 to the control dressing and 126 to the sucrose octasulfate dressing (figure). Among them, 59 patients were recruited before the protocol amendment (24 were assigned to the control dressing and 35 to the sucrose octasulfate dressing). The median number of patients recruited by each centre was three (IQR 2–7; 54 patients in France, 20 in Germany 56 in Italy; 72 in Spain, and 38 in the UK). 37 (15%) patients of 240 withdrew during the treatment period. There was no difference between the control dressing and sucrose

octasulfate dressing groups in terms of rate of trial early discontinuations or stated reason (figure). Patients in the control dressing group were more likely to discontinue the allocated dressing (seven [6%] of 114: three adverse events, three investigator deemed dressing inappropriate, one patient deemed dressing inappropriate) than those in the sucrose octasulfate dressing group (one [1%] of 126: adverse event). For the per-protocol sensitivity analysis, three (3%) patients in the control group and six (5%) patients in the treatment group were excluded because of deviations of major selection criteria.

Baseline demographic characteristics and medical history of the randomly assigned patients were well balanced between the two groups (table 1). The nature and frequency of the reported complications was consistent with the degree of disease severity in the cohort. Wound and periwound skin characteristics were also similar in the two groups (table 2). Hyperkeratosis was the most frequent periwound skin issue documented.

The median duration of the treatment period was 135 days (IQR 56–141) for the control dressing group and 115 days (56–141) for the sucrose octasulfate dressing group. 1381 medical visits were documented: 665 in the control dressing group and 716 in the sucrose octasulfate dressing group; mean number of visits per patient was 5·8 (SD 1·9) in the control dressing group and 5·7 (1·7) in the sucrose octasulfate dressing group. The same type and frequency of wound debridement and of hyperkeratosis removal were done in the two groups. Dressing change frequency was similar in the two groups, with the same type of secondary dressings applied (table 3). All patients received an offloading device. The types of offloading devices provided were similar between groups, and a high level of patient adherence to offloading was reported throughout the study (table 3). 216 (90%) of 240 patients received offloading devices that matched the prespecified approved list (same brand name, or same characteristics with a different brand name). 24 (10%) of 240 patients (12 patients in each group) were supplied with devices that did not match the prespecified approved list; these alternative devices were customised shoes with an adapted sole or insole.

The primary outcome, wound closure, was achieved in 34 (30%) of 114 patients in the control dressing group and in 60 (48%) of 126 patients in the sucrose octasulfate dressing group (18 percentage points difference, 95% CI 5–230). The adjusted OR was 2·60 (95% CI 1·43–4·73, p=0·002) for wound closure with the sucrose octasulfate dressing compared with the control dressing. Besides treatment effect, the only other significant variable in the regression model was wound duration (OR 0·27 95% CI 0·15–0·51; p<0·0001 for closure of wounds of ≥6 months duration vs <6 months duration). The results of primary and secondary outcomes are in table 4 and the appendix.

The estimated mean time to closure was 60 days (95% CI 47–75) longer in the control dressing group than in the sucrose octasulfate dressing group (table 4). Furthermore,

	Control dressing group	Sucrose octasulfate dressing group
Offloading devices prescribed	n=114	n=126
Total contact cast which can be opened	4 (4%)	2 (2%)
Removable devices which could be rendered non-removable†	33 (29%)	40 (32%)
Removable devices that immobilised the ankle joint	14 (12%)	17 (13%)
Removable devices that did not immobilise the ankle joint	45 (39%)	50 (40%)
Customised shoes with adapted sole or adapted insole	12 (11%)	12 (10%)
Wheelchair or confined to bed	6 (5%)	5 (4%)
Investigator-reported patient adherence to offloading devices	n=510	n=534
Every day	426/510 (84%)	444/534 (83%)
As often as possible	78/510 (15%)	79/534 (15%)
From time to time	4/510 (1%)	10/534 (2%)
Rarely or never	2/510 (<1%)	1/534 (<1%)
Wound debridement	n=623	n=650
Mechanical	325/623 (52%)	333/650 (51%)
Surgical	210/623 (34%)	199/650 (31%)
Other	11/623 (2%)	21/650 (3%)
None	77/623 (12%)	97/650 (15%)
Hyperkeratosis removal	n=624	n=650
Mechanical	314/624 (50%)	306/650 (47%)
Others	141/624 (23%)	126/650 (19%)
None	169/624 (27%)	218/650 (34%)
Frequency of study dressing changes per week	3·0 (1·8) (n=111)	3·2 (1·8) (n=119)
In those with total contact cast devices which can be opened	1·6 (0·1) (n=4)	2·3 (1·1) (n=2)
In those with removable devices that could be rendered non-removable†	2·0 (0·8) (n=33)	2·1 (0·7) (n=37)
In those with other removable devices, confined to bed, or in a wheelchair	3·6 (2·0) (n=74)	3·8 (1·9) (n=80)
Secondary dressing applied	n=623	n=651
Gauze	283/623 (45%)	276/651 (42%)
Foam	83/623 (13%)	122/651 (19%)
Other	236/623 (38%)	226/651 (35%)
Unspecified	21/623 (3%)	27/651 (4%)

Data are n (%), n/N (% of visit reports), or mean (SD). *The adherence report for the screening period taken at day 0 is not included (good adherence was reported for 100% of patients at day 0). †Removable devices which immobilised the ankle and could be rendered non-removable through an inviolability bond. The non-removability of the devices was not tracked throughout the study.

Table 3: Interventions during the 20-week treatment period

a greater reduction in absolute wound surface area and in relative wound surface area, and a faster wound re-epithelialisation wave were recorded in the sucrose octasulfate dressing group than in the control group by week 20 (table 4). The difference between the two groups

	Control dressing group	Sucrose octasulfate dressing group	Adjusted odds ratio (95% CI; p value) or p value
Primary efficacy outcome (ITT cohort)			
Wound closure, confirmed by the investigator	34/114 (30%)	60/126 (48%)	2·60 (1·43–4·73; p=0·002)
Secondary efficacy outcomes (ITT cohort)			
Kaplan-Meier-estimated time to closure (days); mean (95% CI)	180 (163–198)	120 (110–129)	p=0·029
Extrapolated instantaneous Gilman parameter at week 20 (mm per week)	..	..	
Mean (SD)	0·3 (1·1)	0·5 (0·8)	NA
Median (IQR)	0·2 (0·0–0·5)	0·4 (0·0–0·8)	p=0·021 for median comparison
Absolute wound area reduction from day 0 to week 20 (cm²)	..	..	NA
Mean (SD)	2·3 (5·5)	3·2 (5·2)	NA
Median (IQR)	1·2 (0·6–2·4)	1·8 (0·9–3·8)	p=0·022 for median comparison
Relative wound area reduction from day 0 to week 20 (%)	..	..	
Mean (SD)	42 (115)	72 (47)	NA
Median (IQR)	90 (29–100)	98 (58–100)	p=0·024 for median comparison
Safety analysis (ITT cohort)			
Adverse events* (number of events)	66	64	NA
Adverse events (number of patients)	47 (41%)	40 (32%)	NA
Adverse event possibly or probably related to the procedure or dressing (number of events)†	6	2	NA
Serious adverse events			
Death‡	4 (4%)	3 (2%)	NA
Admission to hospital for >24 h (number of events)	19	22	NA
Admission to hospital for >24 h (number of patients)	16 (14%)	19 (15%)	NA
Local infection of the target wound	..	..	NA
Number of events	36	33	NA
Number of patients	32 (28%)	25 (20%)	..
Amputation of the target limb			
Number of events	2	1	NA
Number of patients	2 (2%)	1 (1%)	NA
Sensitivity analysis§			
Possible wound closure, confirmed or not by the investigator¶ (ITT cohort)	38/114 (33%)	61/126 (48%)	2·27 (1·26–4·07; p=0·006)
Centrally assessed wound closure (final blind review based on wound photos; ITT cohort)	32/114 (28%)	51/126 (40%)	1·89 (1·06–3·38; p=0·031)
Wound closure, confirmed by the investigator (PP cohort)	33/111 (30%)	57/120 (47%)	2·54 (1·38–4·69; p=0·003)
Wound closure, confirmed by the investigator‖ (ITT cohort)	34/114 (30%)	60/126 (48%)	2·73 (1·49–4·99; p=0·001)
Post-hoc analysis			
Wound closure, confirmed by the investigator (cohort with wound duration <6 months)	27/68 (40%)	46/71 (65%)	2·79 (1·33–5·89)
Wound closure, confirmed by the investigator (cohort with wound duration ≥6 months)	7/46 (15%)	14/55 (25%)	1·90 (0·63–6·16)

Data are n (%), mean (95% CI), mean (SD), or median (IQR) at week 20. ITT=intention-to-treat. PP=per protocol. NA=not applicable. *Includes all types of adverse events. †One adverse event with unspecified relationship in the control group. ‡No death was deemed related to treatment or procedure. §The binary logistic regression for the adjusted odds ratio included group (treatment, control), country, wound area strata (1–5 cm², 5–30 cm²), age class (<70 years, ≥70 years), wound duration strata (<6 months, ≥6 months), and limb amputation history (yes/no) as covariates. ¶Included 34 closures later confirmed and four not confirmed in the control group and 60 closures later confirmed and one not confirmed in the treatment group. ‖Included BMI as an additional covariate in the logistic regression model.

Table 4: **Primary and secondary outcome, safety, sensitivity, and post-hoc analyses**

in the proportion of patients with a wound area reduction of at least 50% was not significant at week 4 (p=0·076) but the proportion was higher in the octasulfate sucrose dressing group at the last assessment at 20 weeks (p=0·029; appendix). At the end of the treatment period, quality of life was similar between groups and remained poor overall (mean EuroQol-5D-5L Index of 0·69 [SD 0·32] in the control dressing group and 0·63 [0·30] in the

sucrose octasulfate dressing group [p=0·245]). Low indexes of quality-of-life (poor quality of life) were driven by restrictions on mobility and activity—of the five dimensions of the quality of life questionnaire, the Mobility and Usual Activities dimensions were the most impaired (appendix).

The types of adverse events reported during the treatment period were similar between the two groups (table 4). In both groups, the most frequent adverse events were infection of the target wound. By the end of the treatment period, two minor amputations of the target foot had been reported in the control dressing group (2%) and one in the sucrose octasulfate dressing group (1%). None of these amputations led to study withdrawal because the wound sites were not directly affected. These three patients had previously had minor amputations in their target limb. Three (2%) patients assigned to the sucrose octasulfate dressing group and four (4%) assigned to the control dressing group died, but none of the deaths were related to treatment, procedure, worsening of the wound or an amputation.

The results of sensitivity analyses done on the wound closure outcome were consistent with those of the primary analysis (table 4). Patients using the sucrose octasulfate dressing were more likely to have wound closure than those using the control dressing regardless of how closure was evaluated (confirmed or not by investigator, and assessed centrally or not), the population considered (ITT or PP), and BMI strata (table 4).

Discussion
In this multicentre, double blind, 20-week randomised trial, we showed that significantly more patients with a non-infected neuroischaemic diabetic foot ulcer greater than 1 cm² who were treated with a sucrose octasulfate dressing achieved wound closure than did those who received a control dressing, while patients in both groups received the same standard of care. Estimated time to reach wound closure was lower in those who received the sucrose octasulfate dressing and the safety profile was similar between groups.

To our knowledge, our study was the first to assess the efficacy of a dressing in individuals with diabetes and confirmed neuropathy and peripheral artery disease. Despite an increasing prevalence of neuroischaemic ulcers, comparison with results from other studies is difficult; an extensive review of the published scientific literature in management of diabetic foot ulcers showed that most data in this area were from people with neuropathic diabetic foot ulcers without peripheral artery disease. Peripheral artery disease is estimated to be present in more than half of patients with diabetes in developed countries and is a strong predictor of poor outcomes, but its contribution to the pathogenesis of diabetic foot ulcers has not previously been fully appreciated.[8,12–15] The trial steering committee decided to enrol only patients with non-infected neuroischaemic

diabetic foot ulcers greater than 1 cm² to ensure a homogeneous cohort of patients at baseline and facilitate interpretation of the results. We cannot be sure that the significant difference of outcomes reported in this trial can be extrapolated to patients with neuroischaemic diabetic foot ulcers of less than 1 cm².

Delayed wound healing in neuroischaemic diabetic foot ulcers has been related to excess matrix metalloprotease concentrations; these proteins destroy components of the extracellular matrix and damage growth factors and their receptors that are essential for healing.[16–21] Sulfated oligosaccharides are known to have many biological activities; in particular, the potassium salt of sucrose octasulfate has been shown to inhibit matrix metalloproteases[22] and to interact with growth factors and restore their biological functions because it has high charge density.[23,24] Two randomised controlled trials have reported favourable results with sucrose octasulfate dressing compared with a control dressing[25] or a protease-modulating dressing[26] in patients with leg ulcers of venous or mixed origin. Safety and acceptability of the sucrose octasulfate dressing have been documented in cohort surveys when used in the treatment of several chronic wounds, including more than 1000 diabetic foot ulcers.[22,27]

Previous evidence has shown that ulcers treated at an earlier stage close quicker, have less infection, occurrence of amputation is lower, and economic burden is less.[32,33] In our study, better outcomes were reached in wounds with duration of less than 6 months. Although we did not do an analysis of significance because of the small size of the subgroups, it seems reasonable to recommend treating wounds as soon as possible.

A strength of our study is that we followed proposed guidelines for the design and reporting of studies in this area.[34,35] In particular, systematic reviews and guidelines[9–11,36] about diabetic foot ulcers have highlighted the need for well powered randomised controlled trials with high-quality methods. Baseline characteristics of enrolled patients were well balanced between groups with regard to all prognostic factors. The risks of allocation, treatment, and assessment bias were avoided by the masking of care providers, patients, and outcome evaluators. Wound closure and time to reach closure, our primary and secondary outcomes, were analysed by ITT, and potential confounding factors were included as covariates in the treatment effect assessment. Additionally, the results of the sensitivity analyses were in agreement with those of the primary analysis. Good standard of care, as still recommended in the most recent guidelines,[4,6–8] was provided in both groups. Our study was carried out in diabetic foot clinics with extensive experience in treating diabetic foot ulcers, and standard care was carried out by expert clinicians. The good healing rate, and low infection and amputation rates reported in the control group despite the severe condition of the enrolled patients with neuroischaemic diabetic foot ulcers is attributable to this good standard

of care and the close collaboration established between specialised centres, community nurses, and patients.

The use of several offloading devices was a limitation of our study. We decided to use several devices rather than one unique device so as to undertake an international clinical trial across five European countries, each with different experience with and access to specific devices, and to assess diabetic foot ulcers in a variety of wound locations, which required different types of offloading. Devices were to be selected from a list of models preapproved by the trial steering committee; only 10% of the patients were supplied with an offloading device which did not conform to the features of the devices endorsed by the steering committee. When other devices were used, these were considered appropriate for these patients by the local investigator and affected patients were equally distributed between the two groups. In this report, the cost-effectiveness of the treatment was not reported. This assessment, which has to take into account the specificities of the different health-care authorities involved, is ongoing. However, our opinion is that treatment with a sucrose octasulfate dressing could be provided by all health-care professionals involved in hospital and community settings without additional training and without expending more time than for current dressings.

In conclusion, use of a sucrose octasulfate dressing improved rate of wound closure over 20 weeks in patients with neuroischaemic diabetic foot ulcers in comparison with use of a control dressing. Together with supportive safety and acceptability from this and other studies, our results support the use of this dressing in the treatment of neuroischaemic diabetic foot ulcers in addition to good standard of care. A sucrose octasulfate dressing is effective and safe, and its use is easy to implement by all health-care professionals. This dressing could form an important part of modern multidisciplinary management of neuro-ischaemic diabetic foot ulcers.

Contributors
The study protocol was written and approved by ME, JLL-M, JM, RL, SB, and AP. ME, JLL-M, JM, RL, and AP were the five national coordinating investigators of the study and formed the trial steering committee with SB. JMA-G, J-MP, GR, and LU were study investigators and had a substantial input in data collection. AS coordinated the work done by the external Contract Research Organisations. J-CK did the statistical analysis. ME, JLL-M, J-CK, AS, SB, and AP had full access to all the data in the study. ME, JLL-M, J-CK, RL, and AP interpreted the data with JM. The report was written by ME, JLL-M, and AP. The article was reviewed by the trial steering committee, who took responsibility for the conduct of the trial and integrity of the data, the overall content of the report, and the decision to submit it for publication. All authors approved the final submitted version of the report.

Declaration of interests
ME, JLL-M, JM, RL, AP and JMP, GR, and LU reported non-financial support from Laboratoires Urgo Medical (study materials) during the study. JMA-G reported personal fees from Laboratoires Urgo during the study. ME reports personal fees from Edixomed, Knox technologies, and Crawford. JLL and J-MP report personal fees from Laboratoires Urgo Medical. RL reports personal fees from Laboratoires Urgo Medical, Medac, and Biotec along with non-financial support from Biotec. AP reports other funding from Genetech. GR reports funding to attend the Diabetic Foot Conference in The Hague, 2016. ME, JLL-M, JM, RL,

and AP received honoraria from Laboratoires Urgo Medical for being part of the trial steering committee and coordinating investigator tasks. J-CK received honoraria from Laboratoires Urgo Medical for statistical analyses and interpretation of the data. AS and SB are employees of Laboratoires Urgo Medical.

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