BMJ Open

Negative Pressure Wound Therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026345
Article Type:	Original research
Date Submitted by the Author:	28-Aug-2018
Complete List of Authors:	Seidel, Dörthe; Universitat Witten/Herdecke, Institut für Forschung in der Operativen Medizin (IFOM) Storck, Martin; Stadtisches Klinikum Karlsruhe gGmbH, Klinik für Gefäß- und Thoraxchirurgie Lawall, Holger; Praxis für Herzkreislauferkrankungen; Max-Grundig Klinik Wozniak, Gernold; Knappschaftskrankenhaus Bottrop GmbH, Gefäßchirurgische Klinik Mauckner, Peter; St. Remigius Krankenhaus Opladen, Innere Medizin Hochlenert, Dirk; Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Wetzel-Roth, Walter; Chirurgische Praxis Wetzel-Roth Sondern, Klemens; Marien Hospital Dortmund-Hombruch, Klinik für Innere Medizin/Diabetologie Hahn, Matthias; Helfenstein Klinik, Allgemein- und Viszeralchirurgie Rothenaicher, Gerhard; Chirurgische Praxis Rothenaicher Krönert, Thomas; Thüringen-Kliniken "Georgius Agricola" GmbH, Klinik für Gefäßchirurgie Zink, Karl; Diabetes Klinik Neugebauer, Edmund; Universitat Witten/Herdecke Department fur Humanmedizin; Medizinische Hochschule Brandenburg -Theodor Fontane
Keywords:	negative pressure wound therapy, standard moist wound care, wound healing, benefit assessment, wound treatment, health care research

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Negative Pressure Wound Therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT

Dörthe Seidel, Martin Storck, Holger Lawall, Gernold Wozniak, Peter Maukner, Dirk Hochlenert, Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert, Karl Zink, Edmund Neugebauer

Institut für Forschung in der Operativen Medizin (IFOM), University of Witten/Herdecke, Köln, Germany (D Seidel MD), Doerthe.Seidel@uni-wh.de

Klinik für Gefäß- und Thoraxchirurgie, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany (Prof M Storck MD), Martin.Storck@klinikum-karlsruhe.de

Praxis für Herzkreislauferkrankungen, Ettlingen und Max-Grundig Klinik Bühlerhöhe, Germany (Dr med H Lawall MD), holger.lawall@gmail.com

Gefäßchirurgische Klinik, Knappschaftskrankenhaus, Bottrop, Germany (Prof G Wozniak MD), gernold.wozniak@kk-bottrop.de

Innere Medizin, St. Remigius Krankenhaus Opladen, Leverkusen, Germany (Dr med P Maukner MD), peter-mauckner@live.de

Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock, Köln, Germany (Dr med D Hochlenert MD), dirk.hochlenert@web.de

Chirurgische Praxis Wetzel-Roth, Buchloe, Germany (Dr med W Wetzel-Roth MD), info@wetzel-roth.de

Klinik für Innere Medizin/Diabetologie, Marien Hospital Dortmund-Hombruch, Dortmund, Germany (Dr med Sondern MD), klemens.sondern@marien-hospital-dortmund.de

Allgemein- und Viszeralchirurgie, Helfenstein Klinik, Geisslingen, Germany (Dr med M Hahn, MD), matthias.hahn@af-k.de

Chirurgische Praxis Rothenaicher, München, Germany (G Rothenaicher MD), rothenaicher@arcor.de

Klinik für Gefäßchirurgie, Thüringen-Kliniken "Georgius Agricola" GmbH, Saalfeld, Germany (Dr med T Krönert MD), tkroenert@thueringen-kliniken.de

Diabetes Klinik, Bad Mergentheim, Germany (Dr med K Zink MD), zink@diabetes-zentrum.de

University of Witten/Herdecke, Köln, Germany (Prof E Neugebauer), Edmund.Neugebauer@uni-wh.de

Correspondence to:

Dörthe Seidel*

Institut für Forschung in der Operativen Medizin (IFOM)

University of Witten/Herdecke

Ostmerheimerstraße 200 Haus 38

Köln (Cologne)

51109 Germany

Doerthe.Seidel@uni-wh.de

Abstract

Objectives

The aim of the DiaFu-study was to evaluate effectiveness and safety of negative pressure wound therapy (NPWT) in clinical practice. The hypothesis was that NPWT leads to faster and more frequent closure of diabetic foot wounds than standard moist wound care (SMWC).

Design

In this observer-blinded, controlled trial patients were randomized in a 1:1 ratio stratified by study site and ulcer severity grade using a web-based tool.

Setting

This German cross-sectoral study was conducted in 40 surgical and internal medicine in- and outpatient facilities specialized in diabetes foot care.

Participants

368 patients were randomized and 345 participants were included in the ITT population. Consentable adult patients suffering from a diabetic foot ulcer at least for 4 weeks, suitable for study participation, and without contraindication for NPWT were allowed to be included.

Interventions

NPWT using the devices of KCI and Smith & Nephew was compared with SMWC according to local standards and guidelines.

Primary and secondary outcome measures

Primary endpoints were wound closure rate and healing time within 16 weeks. Secondary endpoints were wound and treatment related adverse events, amputations, recurrences, wound size and wound tissue development, pain, and quality of life.

Results

In the ITT population 25 patients in the NPWT-arm (14·6%) and 21 patients in the SMWC-arm (12·1%) achieved wound closure (p=0·53). Wound healing time was not significantly shorter in the NPWT-arm (p=0·244). 96 patients in the NPWT-arm compared with 72 patients in the SMWC-arm had at least one adverse event (p=0·007), but only 11 events have been possibly related to NPWT. Premature treatment cessation had a significant negative impact on wound closure.

Conclusions

NPWT is not superior to SMWC in real life. The overall wound closure rate is low. Deviations from treatment guidelines limit the treatment success. Adequate quality assurance is necessary.

Trial registration

Clinical Trials.gov: NCT01480362

Strengths and limitations of this study

- The DiaFu study evaluates the effectiveness and safety of NPWT compared to the current standard of care (SMWC) in clinical practice while applying methods against bias whenever possible.
- Due to the nature of the compared treatment methods, a direct blinding of patients and investigator was not possible.
- This study assesses patient-relevant endpoints and includes a high number of participants without selecting specific patient groups.
- Strength of the DiaFu-study is the high transferability of the results to the real medical care situation.
- This healthcare research study did not focus on a qualitative evaluation of the treatment of the underlying disease or other comorbidities, but selected study sites by means of a qualification checklist and referred to the binding nature of the existing evidence-based treatment guidelines in the study protocol.

Background

Wound therapy is a growing challenge for health care professionals as well as for the entire health system. Acute and chronic wounds affect at least 1% of the population worldwide [1]. The diabetic foot ulcer is one of the most important examples of chronic wounds which in case of severe complications can lead to leg amputation or death. The World Health Organization (WHO) and the International Diabetes Federation (IDF) estimate that more than 400 million people worldwide suffer from diabetes [2, 3]. Several authors estimate that about 15% of all patients suffering from diabetes will develop a diabetic foot ulcer during their lifetime [4, 5] and that approximately 50-70% of all lower limb amputations are due to diabetes [5]. Only a few of the available modern moist wound dressings and topical agents have been convincingly shown to achieve higher wound closure rates compared with traditional wet gauze dressings [6, 7]. Innovative medical devices are substantial for modern wound care. Negative pressure wound therapy (NPWT) is one of the most commonly used and well-established advanced therapies to facilitate wound healing [8]. The first use of vacuum sealing was described in 1993 by Fleischmann et al. [9] and the commercially available product was developed later in the 1990s [10, 11]. Positive effects of NPWT on wound healing have been demonstrated in various basic studies [11, 12].

The European marketing authorization for medical products using the treatment method NPWT only requires information on the functionality within the intended use of the respective device. Medical devices with CE marking (is no longer of literal significance, but a symbol of over-the-counter marketability in the European Union) can be immediately used in in-patient care and are subject to the European guidelines for the

implementation of adequate post marketing surveillance. However, in order to be able to answer the question about (added) patient benefit and reimbursability of the treatment method by the social health insurance, qualitatively adequate clinical studies are necessary. Social health insurance systems ensure health care for a large part of the population in many European countries. The patient relevant benefit of examination and treatment methods is always in focus. The German authorities are known to have the toughest evaluation methods in Europe, which are based exclusively on the rules of evidence-based medicine. German decisions often set an example in Europe.

In Germany the Federal Joint Committee (German: Gemeinsamer Bundesausschuss (G-BA)) is the legislative institution of the German healthcare self-administration system [13]. It issues directives for the benefit catalogue of the statutory health insurance funds and specifies measures for quality assurance in inpatient and outpatient areas of the health care system. In the inpatient sector, the Federal Joint Committee has the right to prohibit medical services for reimbursement, if the treatment method has no (added) benefit and no potential to be a valuable treatment alternative or is harmful for the patients. In the outpatient sector, a method can only be carried out at the expense of the statutory health insurance funds if the G-BA permits this. All decisions are based on the benefit assessment which is usually carried out by the independent scientific Institute for Quality and Efficiency in Health Care (German: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)) [14]. The benefit basically refers to the treatment method used, not to the medical device. Benefit assessment therefore considers all studies that include an adequate comparison of the treatment method with the currently accepted standard, a placebo or no therapy. Thus, it is also possible to carry out a study with more than one medical device.

In 2004, the G-BA commissioned a benefit assessment on NPWT for the IQWiG in order to support decision-making on reimbursement of NPWT by German statutory health insurance funds in outpatient care. The body of evidence available has been deemed insufficient to clearly prove an additional clinical benefit of NPWT. The large number of prematurely terminated and unpublished trials has also been a reason for concern [15-17]. Since the evidence situation was unchanged in a subsequent evaluation, the G-BA decided in August 2010 that NPWT would not be reimbursable in German outpatient care. In the following years several researchers performed updates or similar systematic literature reviews on the use of NPWT for chronic wounds. The reviews of Ubbink et al in 2008 [18, 19], Gregor et al in 2008 [17], Peinemann and Sauerland in 2011 [20], Dumville et al in 2013 [21], an assessment in the home setting [22] and a health technology assessment particularly issued for the evaluation of NPWT for managing diabetic foot ulcers [23] in 2014, as well as the most recent work of Liu et al in 2017 [24] all concluded that although NPWT may have a positive effect, the trials that have been performed

have methodological flaws and sufficient, unbiased evidence of whether wounds heal better or worse with NPWT than with conventional treatment is still missing. Two trials performed by Armstrong 2005 [25] and Blume 2008 [26] provided a solid basis for planning a RCT that meets national and international quality requirements [15, 20].

In 2007, the G-BA decided to suspend the method evaluation of NPWT for an initial period of 3 years in order to evaluate the treatment method within a so-called model project. This included the conduct of clinical studies. The G-BA defined basic requirements for the overall project. Further quality requirements were based on IQWiG's general methods [27]. This essentially concerned the formulation of a study hypothesis that supports G-BA's overall question if NPWT can be reimbursed in German outpatient care without any limitation; the selection of a comparator that represents the current treatment standard in Germany; and implementation of all measures to ensure a sufficient certainty of results.

Following the announcement of the G-BA, the German statutory health insurance funds initiated a project through a European tender in which a randomized controlled clinical trial was one part and the diabetic foot ulcer has been chosen to be representative for chronic wounds.

Methods

Aim of the study

The aim of our DiaFu-study was to evaluate whether the effectiveness and safety of NPWT is superior to standard moist wound care (SMWC) in real-life clinical practice. Unlike previous studies, in this health care research study with a pragmatic approach the question should be answered as to whether the treatment method is effective and safe when used under routine conditions.

Study Design

The DiaFu-study was a cross-sectoral, randomized controlled clinical superiority trial with blinded analysis of wound photographs. This German national study was conducted both in hospital departments and outpatient facilities with a special qualification for diabetic foot care. Study treatment was allowed to be started both in in- and outpatient care and should be continued outpatient whenever possible. Ethical approval of the Lead Ethical Committee of the University of Witten/Herdecke has been fully granted without any conditions. More detailed information on the study design can be found in the study protocol publication that is available open access [28].

Patient and Public Involvement

Patients were not involved in the design, recruitment or conduct of the study. The results of this study will not be disseminated directly to study participants.

Participants

In order to answer the overall question if NPWT is eligible to be reimbursed in clinical practice without any limitation, a patient population was included that largely corresponded to clinical routine. In- and exclusion criteria have been selected based on manufacturers' contraindications and FDA warnings, the necessity to excluded patients in need of protection and who are unable to give their consent, and the intention to avoid general study-related influences on the results.

Adult patients (age >18 years) with at least 4-week-old chronic diabetic foot ulcers corresponding to Wagner 2 to 4 were screened for study participation by the local investigators. The initially planned minimum ulcer age of 6 weeks was reduced to 4 weeks during the course of the study. The entry criteria of a minimum of 4 weeks ulcer history has been chosen in order to optimally represent the typical initial contact of patients with the physician. Written informed consent was obtained from every participant after being informed about all aspects of the trial and before randomization and any trial-related procedure. Patients estimated to be at risk of non-compliance with study requirements were excluded. Diabetic foot wounds after adequate wound pretreatment as well as amputation wounds below the upper ankle joint were eligible for inclusion. Patients with necrotic tissue that could not be removed by debridement or amputation were excluded. If a sufficient covering of exposed blood

vessels within or directly surrounding the wound was not possible or the vessels carried an increased risk of bleeding with hemodynamic consequences, the patient was excluded from participating in the study. Outpatients were excluded if receiving anticoagulation therapy or suffering from a high grade impaired clotting function with a heightened risk of bleeding with hemodynamic consequences. The use of NPWT devices on the study wound within six weeks prior to study start represented an exclusion criterion in order to demonstrate a clear therapeutic effect of each treatment arm. As the participating health insurance funds provided integrated care contracts for outpatient NPWT, it was only possible to include patients in the study who were members of a participating health insurance fund.

Basic data were collected for all patients considered for study participation during screening and have been updated during the randomization visit. No recording of the actual ulcer age was made, as experience has shown that this usually cannot be adequately stated by the patients. Within this healthcare research study, clinical diagnoses rather than surrogate parameters were recorded to describe the patient population. Respective available evidence-based guidelines were referred to in the study protocol. Study sites have been selected based on their qualifications and experience using a pre-study qualification checklist and annual quality reports of the respective institution (if available).

Randomization and masking

Patients were randomly allocated to the treatment arms in a 1:1 ratio using a computer generated list located on a centralized web-based tool. The randomization list consisted of permuted blocks of variable length (4, 6) which were randomly arranged. Patients were stratified by study site and by Wagner-Armstrong stage within each site (<Wagner-Armstrong stage 2C and ≥ Wagner-Armstrong stage 2C). Each registered investigator received individual access to the website, randomization tool and case report forms (CRF). The investigators were responsible for adequately implementing the assigned therapy. Due to the physical differences between the treatment regimens it was not possible to blind either participant or physician to the treatment assignment. Confirmation of wound closure was performed by independent, blinded assessment of wound photographs.

Procedures

All patients underwent an amputation, debridement or at least thorough wound cleansing no longer than six hours before randomization and start of study treatment. Wound bed preparation before study start has been performed according to patient's needs and study wound treatment has been applied according to randomization once the wound bed was ready for the definite treatment in order to achieve complete wound closure. Patients received an extensive examination of overall health status and specific diabetes associated disorders during screening with an update at the randomization visit including diagnostics for peripheral artery disease (PAD)

using Rutherford's chronic limb ischemia classification [29]. In the study protocol, factors influencing the patient-relevant therapeutic objective of complete wound healing were defined, which were examined with regard to their actual influence within the study. Therapeutic factors such as pressure relief were deliberately not selected, as optimal patient care is assumed, errors in treatment are not the focus of this evaluation, and this type of influencing factors should be evenly distributed to both arms of therapy by randomization. Study therapy could be started either in-hospital or as outpatient and was intended to be continued in outpatient care whenever possible.

In the intervention group commercially available CE-marked NPWT devices of the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew were used in the discretion of the clinical investigator according to clinical routine and manufacturer's instructions [28]. Recommendations for use can be found on the manufacturers' websites. Before study start, the participating study sites were allocated to the manufacturers. A direct comparison of the used products was explicitly not planned, since the therapy method and not the medical products are to be evaluated. NPWT as interim therapy needed to be discontinued once the condition of a wound was suitable for closing, either spontaneously by epithelialization or surgically. It was determined in the study protocol that the optimal preparation of the wound for subsequent therapy aiming to achieve complete wound closure requires a granulation area of at least 95 %. Control therapy was defined as any SMWC according to local clinical standards and guidelines [7, 30]. Healthcare providers were obligated to provide patients with best practice. In the control arm it was permitted to apply any local wound treatment standard used in the respective study site that did not have an experimental status or was NPWT. To ensure the best quality of local wound treatment, the study sites were trained for both the intervention arm by the manufacturers and the control arm by the German Society for Wound Healing and Wound Treatment which provided parts of its curriculum and experienced instructors.

The maximum study treatment time was 16 weeks after randomization. Study visits needed to be performed at week one, three, five, 12 and 16 and included a complete wound examination. Study participants were followed up until 6 months after randomization. The initially planned follow-up period of 12 months was reduced to 6 months in the course of the study. The amendment to the study protocol was endorsed by the Ethics Committee and immediately communicated to all participating trial sites.

Outcomes

Our primary outcome comprised the two primary effectiveness endpoints wound closure rate and the time until complete wound closure within a maximum study treatment period of 16 weeks. Complete wound closure was defined as 100% epithelialization of the wound, no drainage, no suture material and no need for wound dressing

or adjuvants. Wound closure needed to sustain a minimum of 14 days after the first diagnosis and to be confirmed by independent blinded observers using wound photographs. Wound closure could also be achieved by secondary intention or by surgical intervention at any time during the study treatment period.

During study planning, possible factors influencing the primary endpoints were identified. Presence and stage of a diabetic neuropathic osteoarthropathy, severity of the foot wound according to Wagner Armstrong (<stadium 2c and ≥ stadium 2c), diagnosis of a peripheral arterial occlusive disease (paVK) and the stadiums according to Fontaine and Rutherford classification, presence and stages of chronic venous insufficiency (CVI), presence of extreme foot deformities and malpositions, untreated or therapy-refractory inflammation in the wound area, chronic anemia, proven by a hemoglobin value <10 g/dl during screening and after 16 weeks, presence of a heel necrosis, presence of a lymphedema, infection, infection with resistant strains, glycated hemoglobin (HbA1c) level, dialysis, treatment with hyperbaric oxygen therapy (HBO) or normothermal therapy, application of recombinant or autologous growth factors to the study wound, and application of skin or dermal substitutes and with living cells that produce growth factors. These covariates were analyzed for their effect on the two primary endpoints. Covariates were excluded from the analysis if the number of missing values was too high or they did not occur at all.

Secondary outcomes were wound closure rate after six months; time until optimal preparation of the wound bed (a minimum of 95% granulation) within 16 weeks; recurrence within 6 months and amputation within 16 weeks. The initial planned secondary endpoint of time until wound closure within 6 months was abandoned during the course of the study. It was found that a time-to-event survey was not possible outside the active study treatment period. This was mostly due to the fact that after this 16-week period weekly study visits were no longer an obligation and further patient care was no longer bound to the study site. Only one follow-up visit was planned and carried out after 6 months, in which wound or healing status and recurrences were documented.

Minor and major amputations were considered separately, whereas the disarticulation at the midtarsal joint (Chopart's amputation) was considered still to be minor. Wound size and wound tissue composition (percentage of granulation tissue, fibrin and necrosis) were monitored at each study visit. Quality of life (QoL) was measured using the questionnaire Euro Quol 5D (EQ5D) at inclusion, end of the maximum treatment time or end of the therapy and at the six-month follow-up visit. At each study visit participants were asked to provide their assessment of wound-associated pain on a numerical rating scale (0 to 10). The incidence of serious adverse events (SAEs) within six months and the incidence of device-related and wound-related adverse events occurring within 16 weeks or until wound closure confirmation were safety endpoints of this trial.

Statistical analysis

Sample size calculation was performed using the expected difference between wound closure rates in both treatment arms based on information extracted from previously published studies. Armstrong and Lavery described a rate of complete wound closure in 56% of patients with NPWT and in 39% of patients in the corresponding control group [25]. Blume showed a rate of complete wound closure in 43% of patients treated with NPWT and 29% of patients in the control group [26]. We assumed a complete wound closure rate of 45% for NPWT and 30% in the SMWC group, resulting in a minimum difference of 15% after a treatment time of 16 weeks. Based on a type one error of $\alpha = 0.05$ and a type two error of $\beta = 0.2$ (corresponding to a power of 80%) a total sample size of 162 patients per group was calculated. The computer program of Dupont and Plummer was used for sample size calculation [31].

We performed all analyses based on the intention-to-treat (ITT) population that includes all randomized participants who have a valid baseline and at least one valid post baseline wound assessment. As a secondary approach a per-protocol (PP) analysis has been performed excluding patients with any serious protocol deviations, temporary changes from SMWC to NPWT, permanent wound treatment changes or without valid documentation until wound closure confirmation or end of maximum treatment time (EOMT). Safety data are presented on an 'as treated' basis. Subgroup analysis is presented for small vs big wound subpopulations. There was no interim analysis.

The superiority hypothesis was tested in parallel for wound closure rate and time to wound closure within16 weeks. Incidence of complete wound closure was analyzed using a chi-squared test (Fisher's exact test) comparing the two treatment arms. Time to complete wound closure was compared between the two treatment arms using a log-rank test. The method of Bonferroni-Holm was used for adjustment of the α-error for parallel confirmatory testing of both primary endpoints. Missing values have been incorporated as censored values. Safety and secondary endpoints were analyzed using conventional univariate testing.

Within a priori planned subgroup analysis the ITT population was divided into a group of small wounds and a group of big wounds based on the wound surface area documented during the randomization visit. Wounds smaller than or equal to the total median wound surface (483 mm^2) were assigned to the subgroup "small wounds". Patients with wound surface areas larger than the median value were assigned to the subgroup "large wounds". Since no citable scientific definition of a large wound was available at the time of study planning and the clinical experts involved could not make a decision, the median of all wounds was chosen as the criterion for the division into the two subgroups.

IBM SPSS Statistics (version 23) was used for all analyses.

This study is registered with ClinicalTrials.gov· number NCT01480362 and in the German Clinical Trial Registry, number DRKS00003347.

A data monitoring committee was formed to oversee overall study performance and safety.

Role of the funding source

Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds, which provided integrated care contracts for all study participants and for up to 7000 patients with acute and chronic wounds in Germany; defined basic rules for study design based on the requirements of the German authorities; and provided a critical review of the study protocol and the final report. The study was funded by the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary support and information about the used material. The manufacturers had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

Results

Between Dec 23, 2011 and August 12, 2014 386 patients were enrolled and randomly assigned to receive NPWT (181) or SMWC (187) in the DiaFu-study (**Error! Reference source not found.**) in overall 40 study sites (that recruited minimum 1 patient and maximum 76 patients. A full list of investigator can be found in the appendix. 13 investigators randomized more than 10 patients. 23 study sites enrolled only between 1 and 4 patients. Most of these study sites refused further study participation due lack of time and staff for adequately performing the documentation. In the further course of the trial research nurses have been hired by the independent scientific institute overseeing the trial in order to support the documentation in the study sites whenever needed. Baseline characteristics of the patients in the NPWT-and the SMWC-arm are similar both in the ITT and the PP population (**Error! Reference source not found.** and appendix).

Baseline parameters (ITT population)	**Total N=345 (100 %)**	**NPWT N=171 (49·6%)**	**SMWC N=174 (50·4%)**
Male	267 of 345 (77·4%)	133of 171 (77·8%)	134 of 174(77·0%)
Female	78 of 345 (22·6%)	38 of 171(22·2%)	40 of 174(23·0%)
Age (years) (N=345)	67·8 (11·9)	67·6 of 171(12·3)	68·1 (11·5)
Height (N=340) (in cm)	174·1 (12·4)	173·4 (14·6)	174·8 (9·9)
Weight (N=335) (in kg)	93·3 (22)	92·7 (21·5)	93·8 (22·6)
Alcohol	N=341	N=169	N=172
Occasionally	157 (46%)	83 (48·5%)	74 (42·3%)
Chronic	10 (2·9%)	3 (1·8%)	7 (4·0%)
No	174 (51%)	83 (48·5%)	91 (52%)
Nicotine	N=342	N=169	N=173
No	49 (14·3%)	25 (14·6%)	24 (13·7%)
Yes	293 (85·7%)	144 (84·3%)	149 (85·1%)
Number of years (Mean· SD)	34·8 (13·5)	36·5 (14·9)	33·1 (12·1)
Packs / day (Mean)	1·1	1·1	1·2
Drugs	N=341	N=169	N=172
Occasionally	1 (0·3%)	1 (0·6%)	0
Chronic	2 (0·6%)	0	2 (1·1%)
No	338 (97·7%)	168 (98·2%)	170 (97·1%)
Requiring dialysis	N=343	N=170	N=173
Yes	29 (8·4 %)	15 (8·8%)	14 (8·0%)

No	314 (90·8%)	155 (90·6%)	159 (90·9%)
Allergies	N=343	N=170	N=173
Yes	37 (10·7%)	16 (9·4%)	21 (12·0%)
No	306 (88·4%)	154 (90·1%)	152 (86·9%)
Subjective assessment of nutritional condition	N=342	N=169	N=173
Well-nourished	325 (94·2%)	162 (94·7%)	163 (93·7%)
Moderately malnourished or suspected malnutrition	11 (3·2%)	4 (2·3%)	7 (4%)
Malnourished	0 (0%)	0 (0%)	0 (0%)
Peripheral arterial occlusive disease (PAOD)	N=345 244 (70·7%)	N=171 121 (70·8%)	N=174 123 (70·7·0%)
Without critical limb ischemia	217 (89·3%)	106 (87·6%)	111 (91·0%)
With critical limb ischemia	26 (10·7%)	15 (12·4%)	11 (9·0%)
Rutherford classification for chronic limb ischemia (Grade/Category)	N=244	N=121	N=123
0/0 Asymptomatic—no hemodynamically significant occlusive disease	20 (8·2%)	8 (6·6%)	12 (9·8%)
I/1 Mild claudication	31 (12·7%)	16 (13·2%)	15 (12·2%)
I/2 Moderate claudication	20 (8·2%)	6 (5·0%)	14 (11·4%)
I/3 Severe claudication	5 (2·0%)	2 (1·7%)	3 (2·4%)
II/4 Ischemic rest pain	1 (0·4%)	1 (0·8%)	0 (0·0%)
III/5 Minor tissue loss—non-healing ulcer· focal gangrene with diffuse pedal ischemia	163 (66·8%)	87 (71·9%)	76 (61·8%)
III/6 Major tissue loss—extending above transmetatarsal level· functional foot no longer salvageable	4 (1·6%)	1 (0·8%)	3 (2·4%)
Revascularisation before study start	23 of 345 (6·7%)	9 of 171 (5·3%)	14 of 174 (8·0%)
Percutaneous transluminal angioplasty (PTA)	13 of 23 (57%)	6 of 9 (67%)	7 of 9 (50%)
PTA + Stent	1 of 23 (4%)	0 of 9 (0%)	1 of 9 (7%)
Veins-Bypass	5 of 23 (22%)	2 of 9 (22%)	3 of 9 (21%)
Polytetrafluoroethylene (PTFE) Bypass	1 of 23 (4%)	0 of 9 (0%)	1 of 9 (7%)
Thromboendarterectomy and patch plastic	2 of 23 (9%)	0 of 9 (0%)	2 of 9 (14%)
Revascularization with influence on the wound	22 of 23 (96%)	9 of 9 (100%)	13 of 14 (93·9%)
Sufficient revascularization result	20 of 23 (88%)	7 of 9 (78%)	13 of 14 (93%)

Insufficient revascularization result	2 of 23 (9%)	1 of 9 (11%)	1 of 14 (7%)
Revascularization result not assessable	1 of 23 (4%)	1 of 9 (11%)	0 of 14 (0%)

Table 1: The table shows patient demographics and baseline characteristics of the Per-Protocol (PP) population. Data are N (%) and Mean (SD). "N=" is stating the number of patients with actual available information. Findings, diagnoses and procedures documented by the investigators are presented.

Wound closure rate in the ITT population was higher in the NPWT arm but this was not significant (p 0·53) as the difference in healing rate between the two groups was only four patients (2·5%) (Table 2).

Time until optimal preparation of the wound bed (min 95 % granulation tissue)	**Total N=183**	**NPWT N=100**	**SMWC N=83**	**p**
Mean (SD)	42·7 (39·0)	35·6 (34·6)	51·4 (42·6)	**0·008**
Median (IQR)	31 (64)	22·0 (48·0)	49·0 (53·6)	
Min - Max	0 - 127	0 - 127	0 - 115	
Wound closure rate	**Total N=345**	**NPWT N=171**	**SMWC N=174**	**p**
Patients with wound closure within 16 weeks N (%)	46 (13·3 %)	25 (14·6%)	21 (12·1%)	0·53

Table 2: The table shows the wound closure rate for the ITT-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms. Wound closures within the maximum study treatment time of 16 weeks are shown with the number (N) and the percentage (%) of patients.

Wounds treated with NPWT had a slightly lower risk of remaining open than those of patients receiving SMWC (RR 0·97 [95% CI: 0·89-1·06)]).

Beginning in week five the number of study patients with open wounds in the NPWT-arm was lower than in the SMWC-arm (Figure 2). There is no significant difference in the wound healing time between the two treatment arms (p = 0.244, Log Rank Test). Since the cumulative number of patients with open wounds was more than 70% after 16 weeks, we were not able to calculate medians for time to wound closure.

Of the a priori defined factors potentially influencing wound closure nine factors needed to be excluded because the number of missing values was too high or they were never documented by the investigators. The covariate peripheral arterial occlusive disease had significant influence on the time until wound closure (p 0·026) and infection had a significant influence on the wound healing rate (p 0·012). However, both influencing factors were almost evenly distributed over both study arms by randomization. Thus the group comparison has not been influenced by these confounders.

After 6 months the wound closure rate was higher in the SMWC- than in the NPWT-arm (36 of 174 [20·7 %] vs 24 of 171 [14· 0 %]), but the difference was not significant (p 0·12).

The time until optimal preparation of the wound for further treatment to achieve a complete epithelization (min 95 % granulation tissue) was significantly shorter for patients treated with NPWT (p 0·021) (Table 2).

Time until optimal preparation of the wound bed (min 95 % granulation tissue)	**Total N=183**	**NPWT N=100**	**SMWC N=83**	**p**
Mean (SD)	42·7 (39·0)	35·6 (34·6)	51·4 (42·6)	**0·008**
Median (IQR)	31 (64)	22·0 (48·0)	49·0 (53·6)	
Min - Max	0 - 127	0 - 127	0 - 115	
Wound closure rate	**Total N=345**	**NPWT N=171**	**SMWC N=174**	**p**
Patients with wound closure within 16 weeks N (%)	46 (13·3 %)	25 (14·6%)	21 (12·1%)	0·53

Table 3: The table shows time until optimal preparation of the wound for further treatment (min 95 % granulation tissue for the ITT-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms. Time until optimal preparation of the wound is described with mean (SD); median (IQR); and minimum (min) and maximum (max).

In the ITT-population wound surface area and wound volume decreased continuously during the study treatment time of 16 weeks in both treatment arms. The results of the blinded photo analysis using the Wound Healing Analyzing Tool (W.H.A.T.) were smaller than the values documented by the clinical investigators. In the NPWT-arm values for the wound surface area decreased faster during the beginning of the treatment time, but aligned with the values of the SMWC-arm after week five. Starting from a similar wound volume, values in the NPWT-arm decreased faster and remained consistently smaller until the end of the treatment period than those in the SMWC-arm. In the NPWT-arm granulation tissue increased faster at the beginning of the treatment period until week 8 and aligned with the measures in the SMWC-arm at the end of the treatment time. Values for fibrin were low and decreased slightly faster in the NPWT-arm than in the SMWC arm. The value for necrotic tissue was very low and did not differ relevantly between the treatment arms. The results of the W.H.A.T. evaluation deviate markedly form the values documented by the investigators and show the opposite course for granulation tissue and fibrin. In the PP-population wound surface area started at smaller baseline levels and decreased faster than in the ITT-population whereas the measures were smaller in the NPWT arm than in the SMWC arm. Wound volume started higher in the NPWT arm and ended at similar levels for the treatment arms after decreasing continuously during the treatment period. This effect was stronger in the SMWC arm. Wound volume

measures were lower in the PP-population than in the ITT-population. Wound tissues had a similar course over time like in the ITT population but showed higher values for granulation as well as lower values for fibrin and necrosis in the PP population. Detailed information about the course of wound surface area, volume and composition of tissues for both study populations can be found in the respective tables in the appendix.

No recurrences occurred during the study treatment time of 16 weeks. Patients treated with NPWT were more than twice as likely to get recurrences as patients treated with SMWC (RR 2·24 [95%CI: 0·80-6·31]), but the overall number of 17 recurrences in 16 patients was very low. 11 recurrences (6·4 %) occurred in the 171 patients in the NPWT arm. One patient had two recurrences. In the SMWC arm, five of 174 patients (2·9 %) had a recurrence. The difference is not significant (p 0·131).

A total of 102 amputations or resections were performed in 71 patients. There were 45 amputations in 35 (20·5%) patients in the NPWT group and 57 amputations in 36 (20·7 %) patients in the control group. There is no significant difference in the number of patients with amputation or resection (p 1·00) or the overall number of performed interventions (p 0· 89) between NPWT and SMWC arm. Patients treated with NPWT have a slightly lower risk of undergoing an amputation or resection than patients treated with SMWC (RR: 0·99 [95%CI: 0·65-1·50]). A total of 69 patients (20 %) underwent a minor amputation (NPWT 33 [19·3 %] SMWC 36 [20·7 %], p 0·79). Two patients in the NPWT arm and no patient of the SMWC arm underwent a major amputation (p 0·25).

Overall, pain levels were very low and decreased further during the study treatment time. The values hardly differ between the treatment arms at any observation time point. A table with pain levels can be found in the appendix.

At baseline Quality of life (EQ5D) had significant limitations in both treatment arms. Patients reaching the end of treatment within 16 weeks showed improved EQ5D levels in the NPWT arm and in the SMWC arm. Similar results have been found for patients who reached the end of the maximum treatment time without successful end of therapy. At the follow-up time after 6-months all patients still show increased EQ5D levels in both treatment arms and both study populations. A table with detailed results for the EQ5D is provided in the appendix.

269 adverse events (AE) (NPWT 167; SMWC 102) occurred during the active study treatment period of 112 days. For 96 (56· 1%) patients in the NPWT group and 72 patients (41· 4%) in the SMWC group at least one adverse event has been documented (p 0·007) but only 16 (10· 2%) of the AEs in the NPWT group were decided by the investigators to have a definite relation to the medical device. A total of 163 AEs occurring within the study observation period of 6 months were classified as serious adverse events (SAE) in the opinion of the investigators (NPWT 87, SMWC 76). In the NPWT arm, 63 patients (36·8 %) had at least one documented SAE. 45 patients had one and 18 patients had two or more SAEs. In the SMWC arm, 58 patients (33·3%) had a

minimum of one SAE (45 patients with one SAE; 13 patients with two or more SAEs). The difference between the treatment arms was not significant (p 0·50). None of the SAEs in the NWPT group were documented as definitely or possibly related to the medical device by investigators. In one case in the SMWC group the investigator documented a definite relationship between the SAE and SMWC. In one case the investigator documented a possible relationship to SMWC in the NPWT group. Table 3 gives a detailed overview on the AEs documented within the study treatment time of 112 days.

Adverse Events (AE) **N=269**	**NPWT** **N=167**	**SMWC** **N=102**
Day of occurrence (N) Mean (SD) Median (IQR)	167 37·5 (28,6) 30·0 (40·0)	102 42·7 (29·2) 38·0 (50·0)
Duration in days (N) Mean (SD) Median (IQR)	157 19·7 (29·0) 10·0 (20·0)	97 25·3 (38·6) 13·0 (22·0)
Severity (N) Mild Moderate Severe	161 64 (39·8%) 54 (33·5%) 43 (26·7%)	102 24 (23·5%) 38 (37·3%) 40 (39·2%)
AE expected / unexpected (N) Expected Unexpected	159 52 (32·7%) 107 (67·3%)	100 27 (27·0%) 73 (73·0%)
Relationship to the medical device (N) Yes Possible No Not assessable	157 16 (10· 2%) 11 (7·0%) 117 (74·5%) 13 (8·3%)	100 0 (0%) 2 (2·0%)* 94 (94·0%) 4 (4·0%)
* No treatment change to NPWT has been documented.		
Relationship to SMWC (N) Yes Possible No Not assessable	110 0 (0%) 5 (4·5%) 96 (87·3%) 9 (8·2%)	75 2 (2·7%) 0 (0%) 67 (89·3%) 6 (8·0%)
Relationship to treatment procedure (N) Yes Possible No Not assessable	148 6 (4·1%) 15 (10·1%) 111 (75·0%) 16 (10·8%)	96 4 (4·2%) 2 (2·1%) 80 (83·3%) 10 (10·4%)

Action taken (N)	146	94
No	23 (15·8%)	23 (24·5%)
Yes	123 (84·2%)	71 (75·5%)
Cessation of therapy	10 of 123 (8·1%)	0 of 71 (0%)
Temporary interruption of therapy	28 of 123 (22·8%)	2 of 71 (2·8%)
Adaptation of therapy / treatment	52 of 123 (42·3%)	48 of 71 (67·6%)
Other	33 of 123 (26·8%)	21 of 71 (29·6%)
Outcome (N)	148	96
Fixed without consequences	72 (48·6%)	43 (44·8%)
Condition improved	32 (21·6%)	26 (27·1%)
Fixed with consequences	22 (14·9%)	12 (12·5%)
Not fixed	4 (2·7%)	3 (3·1%)
Death	9 (6·1%)	6 (6·3%)
Unknown	9 (6·1%)	6 (6·3%)

Table 1: The table shows the adverse events in the active study treatment time of 112 days after randomization. Data are N (%), Mean (SD), and Median (IQR). "N=" is stating the number of patients with actual available information.

In the NPWT arm 48.5% (N=83) of patients have small wounds and 51.5% (N=88) of patients have large wounds. The SMWC arm has 51.7% (N=90) small wounds and 48.3% (N=84) big wounds. The differences between the treatment arms are not significant.

An overview of the measures for small and big wounds and detailed results for this subgroup analysis can be found in the appendix. In the subgroup of big wounds, wound closure rate was significantly higher in the NPWT arm within 16 weeks (p 0·08). Patients with big wounds have a lower risk of not achieving wound closure within 16 weeks when treated with NPWT (RR 0·91 [95%CI: 0·82-1·0]). In the subgroup of big wounds a significantly faster wound closure was achieved in the NPWT arm (p 0·027) (Figure 3). Time until complete, sustained and verified wound closure was not significantly different between the treatment arms in the subgroup of small wounds (Figure 4).

In the subgroup of small wounds the time to reach 95 % granulation tissue was significantly shorter for the patients treated with NPWT (p 0·005). Time until optimal wound bed preparation was shorter in the NPWT arm in the subgroup of big wounds, but did not significantly differ to the result of the SMWC arm (p 0·27). There are no relevant or significant differences in the overall number of patients with amputation or resection between the treatment arms in both subgroups. Both major amputations were performed in patients with big wounds treated with NPWT. Due to the low overall number of recurrences (N=16) we were not able to perform a subgroup analysis for this outcome parameter.

In the PP-population patients treated with NPWT showed a 14·5 % higher wound closure rate within 16 weeks than patients treated with SMWC (Appendix), but the difference was not significant (p 0·053). Wounds treated with NPWT had a lower risk of remaining open after 16 weeks (RR 0·82 [95%CI: 0·66-1·03]) than wounds treated with SMWC. Time to wound closure in the NPWT arm was significantly shorter (p=0·004) (Figure 5). After 6 months, wound closure rate in the SMWC-arm was higher than in the NPWT-arm, but the difference was not significant (p 0·84). As in the ITT population, optimal wound bed preparation was achieved significantly faster in patients receiving NPWT (p<0·001). Patients receiving NPWT had a higher risk of recurrence than those in the control group (RR 1·50 [95%CI: 0·37-6·01]), however there was no significant difference between the treatment arms regarding the total number of recurrences (p 0.38) or the number of patients with recurrences (p 0·69). 9 patients in the NPWT group and 21 (21·4%) patients in the SMWC group had an amputation or resection (NPWT RR 1·07 [95%CI: 0·53-2·15]). Neither the number of patients with amputations or resections (NPWT 9 (20·5%) SMWC 21 (21·4%) p 0·83) nor the number of amputations or resections performed (NPWT 11 SMWC 28 p 0·86) differ significantly between the treatment arms. No major amputations were performed in the PP population. Like in the ITT population, pain levels were very low, showing no relevant difference between the treatment arms, and further decreased during the study treatment period. In the PP-population EQ5D values are higher than in the ITT population during screening, but still show that all patients have significant problems. In the NPWT arm QoL measures are similar to those of the SMWC arm for patients reaching end of maximum treatment time before end of therapy. EQ5D shows higher values for patients reaching the end of therapy during the study treatment time of 16 weeks. Detailed results for the PP population can be found in the appendix.

29 (17·0%) patients in the NPWT group had a temporary therapy change to SMWC (mean duration 20·5 ± 21·6 days). In the SMWC group, 17 (9·8%) patients had a temporary therapy change to NPWT (mean duration 28·9 ± 21·6 days). For only 2 of the 29 NPWT patients (6·9%) with a temporary therapy change to SMWC the wound closure was achieved within 16 weeks, whereas 16·2% (23 von 142) of the wounds of the NPWT patients without therapy change were completely closed.

A total of 57·3% (98 of 171) of the patients randomized to NPWT completed treatment before achieving a granulation surface of the wound of at least 95%. Significantly fewer patients with this premature end of NPWT (4·7%, N=8) achieved a complete wound closure than patients with no premature end of therapy (9·9, N=17) (p 0· 008). Mean NPWT-duration until premature end of therapy was 28.5 days (SD 24·1), while a mean granulation area of 59.6% (SD 30· 5) was achieved.

For 131 patients (76· 6 %) in the NPWT arm less than the required three dressing changes per week were documented. 19 patients (14· 5 %) with this protocol violation achieved a complete wound closure. Six (15·4%) of the 39 NPWT patients who received at least 3 therapy changes per week achieved a complete wound closure.

In the electronic Case Report Forms (eCRF) a wound closure was documented for 96 patients (NPWT 56 of 171; SMWC 40 of 174), but only for 46 patients (NPWT 25; SMWC 21) all criteria for a complete, verified and sustained wound closure have been met. For the wound closure visit seven wound photographs (NPWT 7; SMWC 0) and for the wound closure confirmation visit four photographs (NPWT 3; SMWC 1) were missing. In addition, two of the existing wound photographs for the wound closure (NPWT 0; SMWC 2) and two photographs for the wound closure confirmation (NPWT 1, SMWC 3) were not assessable by the blinded observers due to serious quality issues. Furthermore 23 (NPWT 15; SMWC 8) existing and assessable wound photographs were not able to confirm the wound closure and 3 (NPWT 1; SMWC 2) photographs were not able to confirm the wound closure after 14 days.

Discussion

In the DiaFu-study wound closure rates were higher in the NPWT group but did not significantly differ from those in the SMWC group, although optimal preparation of the wound bed (95% granulation tissue) was achieved significantly earlier when using NPWT in both populations. Time to wound healing in the NPWT group is lower than in the SMWC group while the difference between the treatment groups becomes statistically significant only in the PP population. Thus, with this study we were not able to confirm our hypothesis that wound closure can be achieved more often and faster with NPWT than with SMWC when used in the complex treatment process for diabetic foot ulcers in clinical practice. Findings of previous RCTs that showed a significant superiority in healing when using NPWT on amputation and chronic wounds [25, 26] could not be confirmed by this trial. We were able to show that although significantly more adverse events have been documented in the NPWT group only a small number of these events were related to the medical device according to the investigator`s assessment. Mortality rates were very low in both groups and there was no significant difference between the treatment groups regarding amputations and resections performed during the study. Only two major amputations have been performed in patients with big wounds treated with NPWT. None of the two treatments resulted in an additional impairment of the patients' quality of life during study treatment time or follow up. Time until complete wound closure was significantly shorter with NPWT than with SMWC in the subgroup of big wounds, which indicates that NPWT has the potential to be valuable treatment method for this kind of wounds.

The DiaFu-study was designed to evaluate effectiveness and safety of NPWT for chronic diabetic foot wounds in real-life clinical practice while avoiding any bias that have been described by several systematic reviews [15-18, 20, 21, 24, 32]. Methods against bias have been implemented successfully, but within this study shortcomings in documentation quality negatively impact the results.

None of the previous studies examined the influence of therapy adherence and target-oriented therapy application on the clinical outcome. Our study is the first to show that unauthorized temporary therapy changes and premature therapy cessation have a strong or significant impact on reaching the patient relevant therapy outcome complete wound healing. Thus, an important finding of the DiaFu-study is that if NPWT is not used with a clear focus and applied consistently under consideration of all prescriptions of the authorities and the manufacturers, the desired treatment outcome will not be reached.

Not addressing and analyzing all factors influencing the overall treatment outcome like targeted pressure relief, infection control and adequate treatment of the underlying disease may be seen as a weakness of this health care research study. Study sites have been selected based on a self-disclosure by means of a qualification checklist

and cross checks using quality reports. This ensured that all prerequisites were met for guideline-compliant patient care. Nevertheless, even in the application of NPWT there were deviations from the standards. Anyway, questioning the quality of investigators' treatment was not the main focus of this health services research trial. Evaluating the individual treatment quality within a single RCT is neither feasible nor effective.

Other than previous studies the DiaFu-study evaluated the effectiveness of NPWT most closely to real-life using a patient population as diverse as in clinical practice. The DiaFu-study therefore included patients with chronic diabetic foot ulcers, regardless of whether a simple wound cleansing, tissue debridement or even amputation was necessary prior to application of wound therapy targeted to achieve complete wound closure. Thus, results can easier be generalized and applied in routine practice settings, but the problems of the clinical routine also affect data quality.

Some of the previous studies did choose granulation tissue formation for primary outcome. Wound bed preparation and granulation tissue formation are important prerequisites for wound healing, but the selection of a patient-relevant primary endpoint and the implementation of adequate measures against bias as required by the German authorities have been a priority during planning. Preparing the wound bed significantly faster with NPWT is an important result for the therapeutic approach, but is not a proof of effectiveness and cannot serve as a basis for the benefit assessment of NPWT. Thus, complete wound healing needed to be chosen to be the primary outcome rather than the evaluation of the functionality within in the purpose of the evaluated medical device, which is still part of a complex treatment process.

In order to support the decision making process of the German G-BA on general reimbursement of NPWT in German outpatient care the DiaFu-study was conducted with a population according to the clinical routine without excluding certain patient groups; with therapy application in the discretion of the attending physician; and with evaluation of patient relevant outcome. Within this setting we were not able to show a significant superiority of NPWT for achieving wound closure, but despite all limitations NPWT showed a significant superiority in wound bed preparation. This indicates that NPWT works according to its intended use and has at least a potential to be a valuable treatment alternative. Anyway, in the complex treatment process of the diabetic wound a satisfactory rate of wound healing was reached with neither NPWT or with SMWC.

Conclusions

NPWT is not superior to SMWC when evaluated in German real-life clinical practice. Missing compliance with therapy guidelines and poor documentation quality lead to restrictions in achieving the patient-relevant endpoint complete wound closure and prevent a clear proof of effectiveness. The question if NPWT is superior to SMWC

for treating diabetic foot wounds remains unanswered due to the limitations of the DiaFu-study. An overall low number of wound closures indicate problems with the overall treatment quality. The results of the PP-population suggest that without the negative impact of premature treatment cessation, temporary changes of the randomized therapy and partly incomplete documentation, NPWT may be more effective for treating diabetic foot wounds than SMWC. NPWT should be evaluated again after implementation of a sufficient, well-considered and widely-accepted concept for quality control. The simple provision of information on existing standards and guidelines seems to be not sufficient. Control mechanisms must be implemented. An adequate quality assurance system must be established in Germany. In a future health care research study the treatment outcome before and after the implementation of these quality measures should be evaluated, for which the results of this trial may serve as a basis. Practitioners worldwide should review their processes with regard to the problems described here.

Ethics approval and consent to participate

Ethical approval of the main ethical committee (EC): Ethical Committee of the University of Witten-Herdecke, has been fully granted without any conditions. Due to performing the trial according to § 23b MPG (German Medical Device Act), participating study sites in Germany only received a consultation for the main clinical investigator according to professional law by the respective EC. All investigators have been fully approved by the respective ECs. An evaluation of the study's content by ECs of participating study sites in Germany was not applicable. All study participants gave written informed consent prior to randomization and any trial related procedure.

Data sharing

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Datasets are available in German language.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare:

The German statutory health insurance companies commissioned the Witten/Herdecke University (UW/H) to plan, conduct, analyze and publish the study. Dörthe Seidel is an employee of the UW/H. The study has been financed by the manufacturers KCI (Acelity) and Smith&Nephew. Dörthe Seidel received a consulting fee for the presentation of the study during an event organized by the manufacturer Hartmann. During study planning and conduct Edmund Neugebauer was an employee of the UW/H. He was the director of the IFOM.

The clinical investigators Martin Storck, Holger Lawall, Gernold Wozniak, Peter Maukner, Dirk Hochlenert, Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink received a case fee of 1000 € for each patient included in the DiaFu-study in order to compensate for the additional organizational and especially the documentation effort during trial conduct. Furthermore all investigators received compensation for travelling to the investigator meetings. The institutions of the investigators used integrated care contracts for NPWT during study conduct in order to provide best practice for the study participants during outpatient care.

Gernold Wozniak and Walter Wetzel-Roth are members of the scientific advisory board of the manufacturer Kinetic Concepts Incorporated (KCI) (now Acelity).

Funding

Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds, which provided integrated care contracts for all study participants and for up to 7000 patients with acute and chronic wounds in Germany; defined basic rules for study design based on the requirements of the German authorities; and provided a critical review of the study protocol and the final report. The study was funded by the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary support and information about the used material. The manufacturers had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

Authors' contributions

Dörthe Seidel was the principal coordinating investigator. She conceived the study, reviewed the scientific literature, and was responsible for study design, data analysis, data interpretation, writing and reviewing of the report. She is the lead author and takes overall responsibility for this report. She affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Martin Storck and Holger Lawall were study investigators and contributed to study design, data collection and interpretation, and reviewed the report.

Gernold Wozniak, Peter Maukner, Walter Wetzel-Roth and Dirk Hochlenert were study investigators and contributed to data collection and data interpretation and reviewed the report.

Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink were study investigators and contributed to data collection and reviewed the report.

Edmund Neugebauer contributed to study design and data interpretation and reviewed the report.

All authors approved the final version of the report.

Acknowledgements

The authors thank all investigators, nurses, patients and partners for supporting the study.

At least one patient was included in the following facilities: HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für Gefäßchirurgie Ludwig-Erhard-Straße 100 65199 Wiesbaden; Asklepios Westklinikum Hamburg Zentrum für

Gefäßmedizin Suurheid 20 22559 Hamburg; Knappschaftskrankenhaus Bottrop Gefäßchirurgische Klinik Osterfelderstraße 157 46242 Bottrop; Städtisches Klinikum Karlsruhe Klinik für Gefäß- und Thoraxchirurgie Moltkestraße 90 76133 Karlsruhe; Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Merheimer Straße 217 50733 Köln; Klinikum Döbeln Abt. für Gefäßchirurgie Sörmitzer Straße 10 04720 Döbeln; Klinikum Bielefeld Mitte Klinik für Allgemeine Innere Medizin Teutoburger Straße 50 33604 Bielefeld; Klinikum Frankfurt/Oder Klinik für Gefäßchirurgie Müllroser Chaussee 7 15236 Frankfurt/Oder; Weißeritztal-Kliniken GmbH Medizinische Klinik III Bürgerstraße 7 01705 Freital; Krankenhaus Porz am Rhein Klinik für Gefäßchirurgie Urbacher Weg 19 51149 Köln; St. Remigius Krankenhaus Opladen Innere Medizin An St. Remigius 26 51379 Leverkusen; Marien Hospital Dortmund-Hombruch Klinik für Innere Medizin/Diabetologie Gablonzstraße 9 44225 Dortmund; Zentrum für Chirurgie Klinik für Gefäß- und Endovascularchirurgie Theodor-Stern-Kai 7, Haus 23C/EG 60590 Frankfurt am Main; Facharzt für Chirurgie Thorax-Kardiovaskularchirurgie Hindenburgstraße 1 86807 Buchloe; Helfenstein Klinik Geisslingen Allgemein- und Viszeralchirurgie Eybstraße 16 73312 Geislingen/Steige; Paracelsus-Klinik am Silbersee Wundzentrum Hannover Oertzeweg 24 30851 Langenhagen; Klinikum Darmstadt Chirurgische Klinik III Grafenstraße 9 64283 Darmstadt; Ortenau Klinikum Offenburg-Ebertplatz Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ebertplatz 12 77654 Offenburg; Thüringen-Kliniken "Georgius Agricola" GmbH Klinik für Gefäßchirurgie Rainweg 68 07318 Saalfeld; Klinikum Dorothea Christiane Erxleben GmbH Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ditfurter Weg 24 06484 Quedlinburg; Franziskus-Krankenhaus Berlin Abt. für Innere Medizin Budapester Straße 15-19 10787 Berlin; Hegau-Bodensee Klinikum Radolfzell (HBK) Klinik für Innere Medizin Hausherrenstraße 12 78315 Radolfzell; Diabetologische Schwerpunktpraxis Dr. med. Hansjörg Mühlen & Partner Ruhrorter Straße 195 47119 Duisburg; Kliniken Maria Hilf Mönchengladbach Klinik für Gefäßchirurgie und Angiologie Sandradstraße 43 41061 Mönchengladbach; Städtisches Klinikum München/Bogenhausen Klinik für Endokrinologie, Diabetologie und Angiologie Englschalkingerstraße 77 81925 München; Gerhard Rothenaicher Facharzt für Chirurgie Cosimastraße 2 81927 München; Bürgerhospital Frankfurt am Main Interdisziplinäres Zentrum Diabetischer Fuß (DDG) Nibelungenallee 37- 41 60318 Frankfurt am Main; Gemeinschaftspraxis für Chirurgie und Gefäßmedizin Drs. Alter/Pourhassan/Heim Klosterstraße 12 46145 Oberhausen; Ev. KH Königin Elisabeth Herzberge gGmbH Abt. für Kardiologie, Angiologie und Diabetologie Herzbergstraße 79 10365 Berlin; Städtisches Klinikum Neunkirchen gGmbH Abt. für Gefäßchirurgie & Phlebologie Brunnenstraße 20 66538 Neunkirchen; Westküstenklinikum Heide Klinik für Viszeral- und Gefäßchirurgie Esmarchstraße 50 25746 Heide/Holstein; Chir. Praxisgemeinschaft am Bayenthalgürtel Praxis Dr. med. Gerald Engels Bayenthalgürtel 45 50968 Köln; Malteser Krankenhaus – St.

Franziskus-Hospital Medizinische Klinik I, Abt. für Diabetologie Waldstraße 17 24939 Flensburg; St. Marienkrankenhaus Siegen gGmbH Klinik für Gastroenterologie Kampenstraße 51 57072 Siegen; Krankenhaus Bietigheim Klinik für Innere Medizin, Kardiologie, Endokrinologie, Diabetologie und Internistische Intensivmedizin Riedstraße 12 74321 Bietigheim-Bissingen; Asklepios Kliniken Harburg Eißendorfer Pferdeweg 52 21075 Hamburg; Diabetologikum Ludwigshafen Diabetes-Schwerpunktpraxis Ludwigsplatz 9 67059 Ludwigshafen; Mariannen-Hospital Werl Abt. für Chirurgie Unnaer Straße 15 59457 Werl; Diabetes Klinik GmbH & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim; Institut für Diabetesforschung Münster GmbH Hohenzollernring 70 48145 Münster.

The study was initiated by a consortium of 19 statutory German health insurance funds represented by the AOK federal association (AOK-Bundesverband – AOK-BV), the association of alternative health insurance funds (Verband der Ersatzkrankenkassen – vdek) and the minors (Knappschaft). In order to guarantee outpatient care for all study participants without any restrictions, the contracting health insurance companies provided integrated care contracts for outpatient negative pressure wound therapy.

A project advisory board was implemented to coordinate all processes and project partners. The board comprised two representatives each from the statutory health insurance funds, the management company and the sponsor as well as one representative each from the participating medical device manufacturers (KCI and smith & nephew). Representing the contracting authority (statutory German health insurance funds) Dr. Gerhard Schillinger (AOK-BV) and Ute Leonhard (vdek) acted as contact persons for all aspects of the project.

The management company “Gesundheitsforen Leipzig” has been entirely responsible for the logistics of the study. Central tasks of the management company included the recruitment of study sites and patients, the development of the IT infrastructure including the documentation, communication and invoicing software as well as the processing of all payments.

The manufacturers Kinetic Concepts Incorporated (KCI) (Acelity) and smith & nephew provided the NPWT devices as well as support and training for the investigators and financed the study.

The Private University of Witten/Herdecke gGmbH acted as the Sponsor of the trial and the Institute for Research in Operative Medicine with its former director Prof. E.A.M. Neugebauer, the current interim head Prof. Rolf Lefering and the head of the division for clinical research Dörthe Seidel was responsible for the scientific conception, the evaluation as well as the reporting and publication of the study. Prof. Dr. Rolf Lefering was responsible for the statistical planning and analysis. PD Dr. Peter Krüger was responsible for the data management of the study. Special thanks are going to Stefan Bauer, who supported the data management as well as the statistical analysis and reporting.

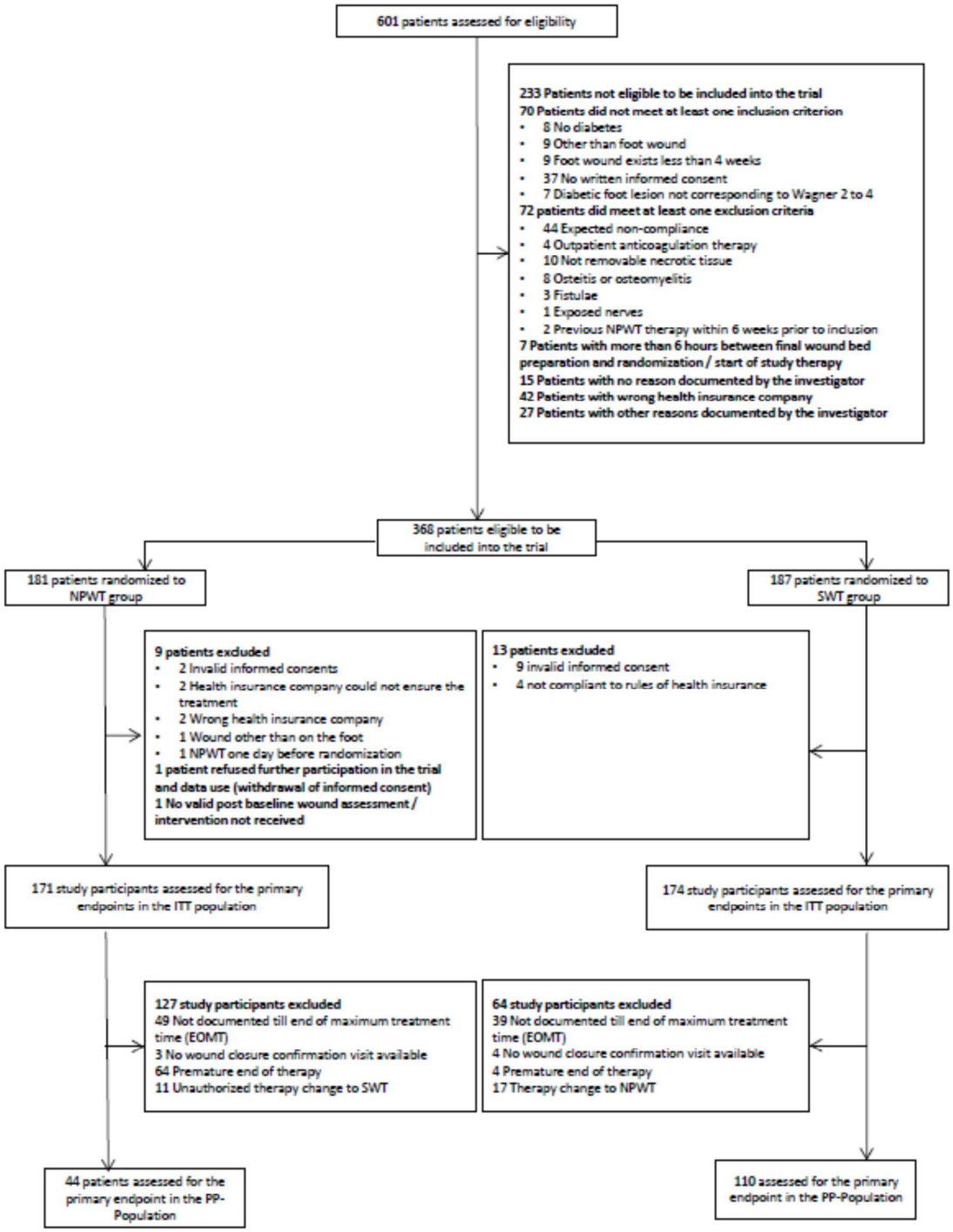
We would like to thank Sophie Thorn, who checked the article as a native English speaker with regard to spelling and grammar.

List of figures:

676 **Figures:**

677

678 Figure 1:



679

Figure 2:

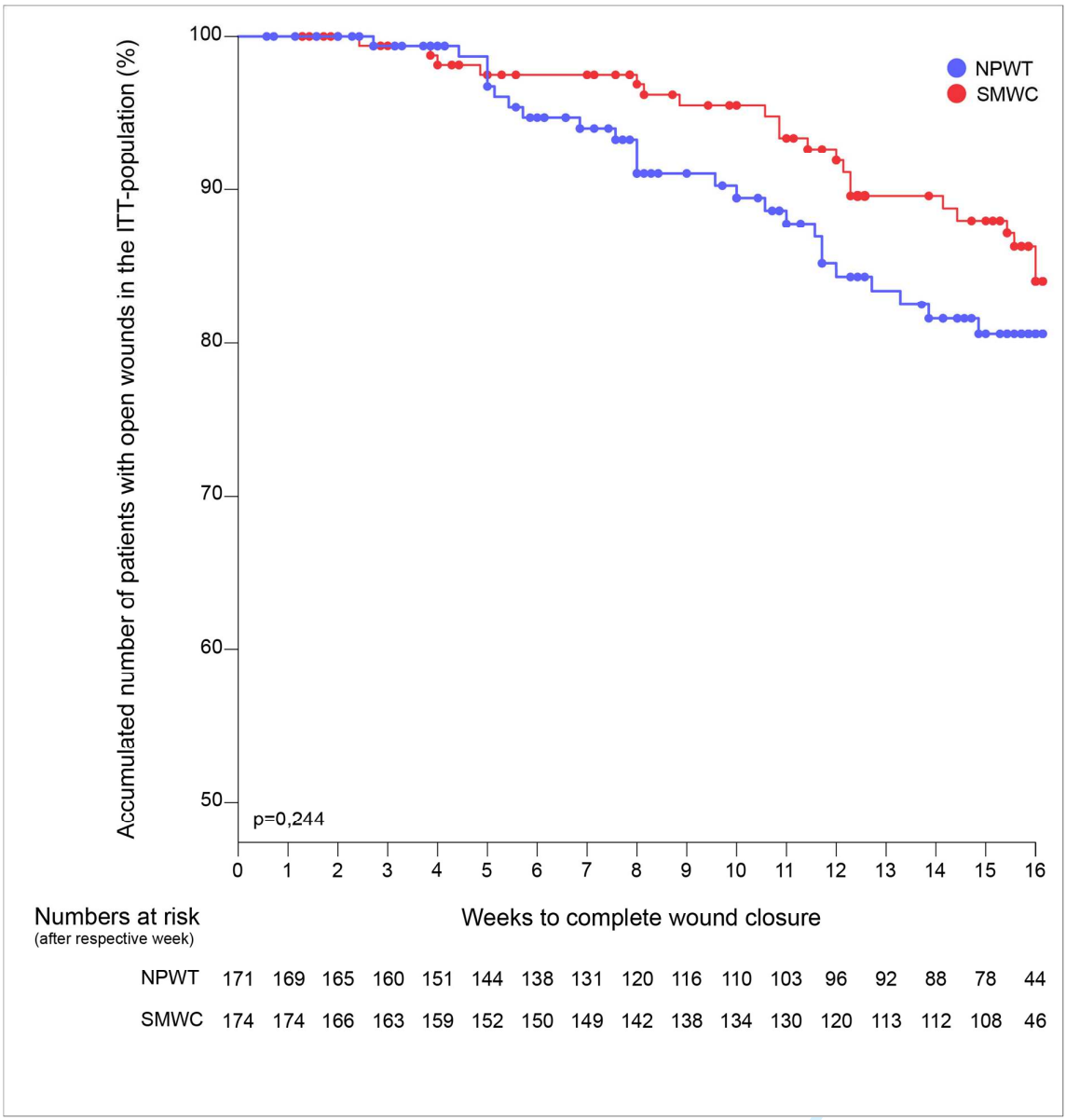


Figure 3:

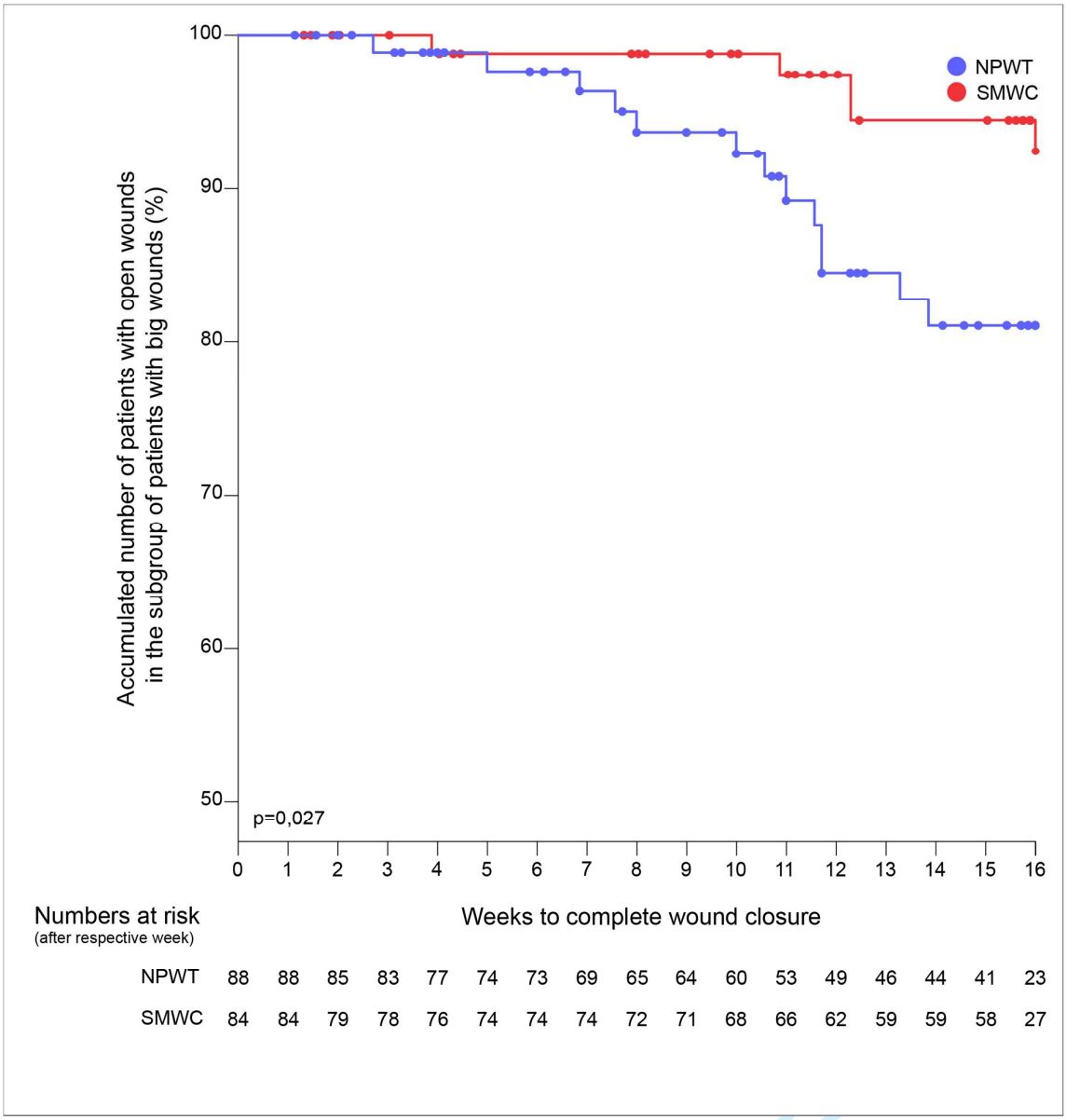


Figure 4:

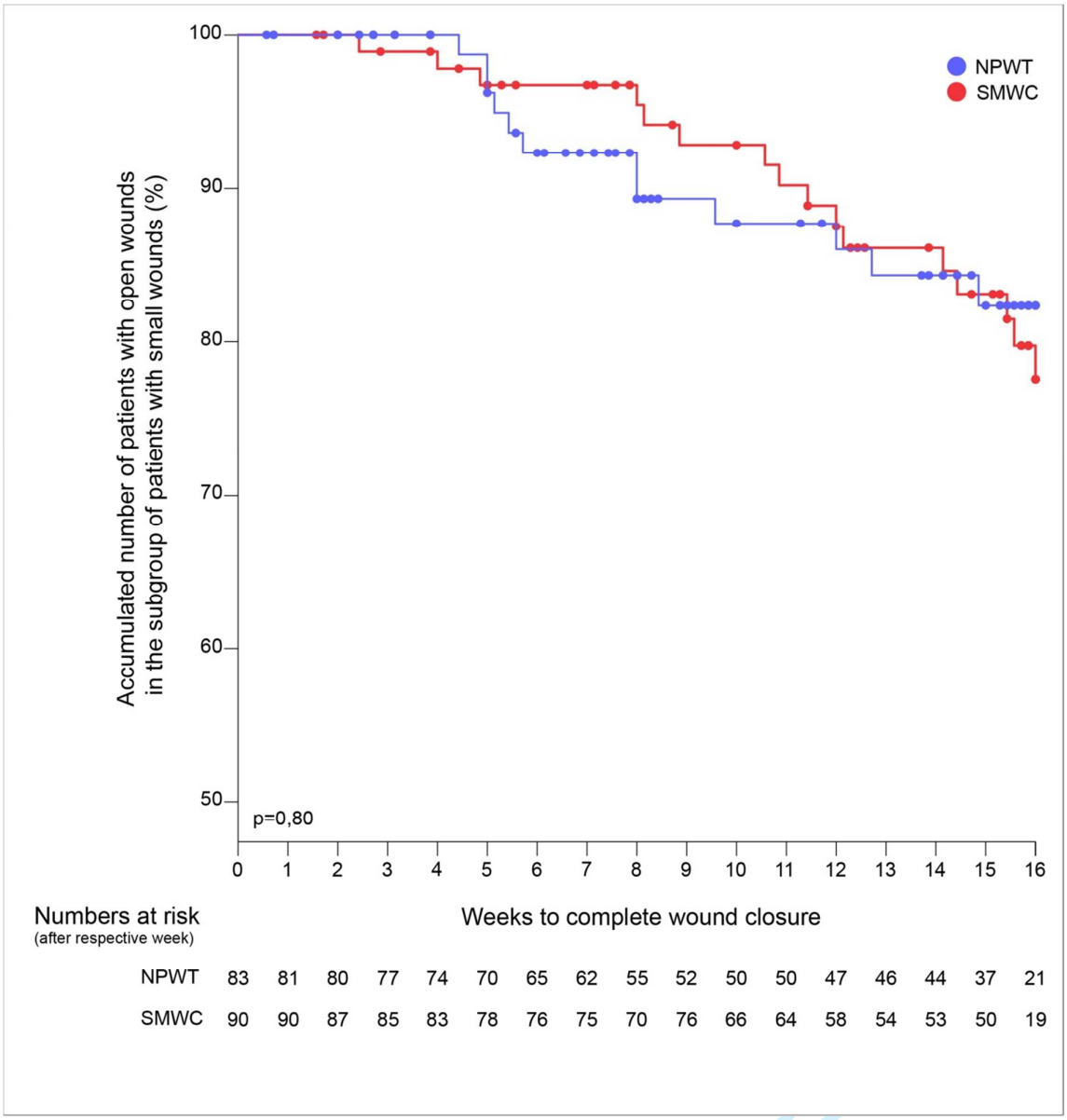
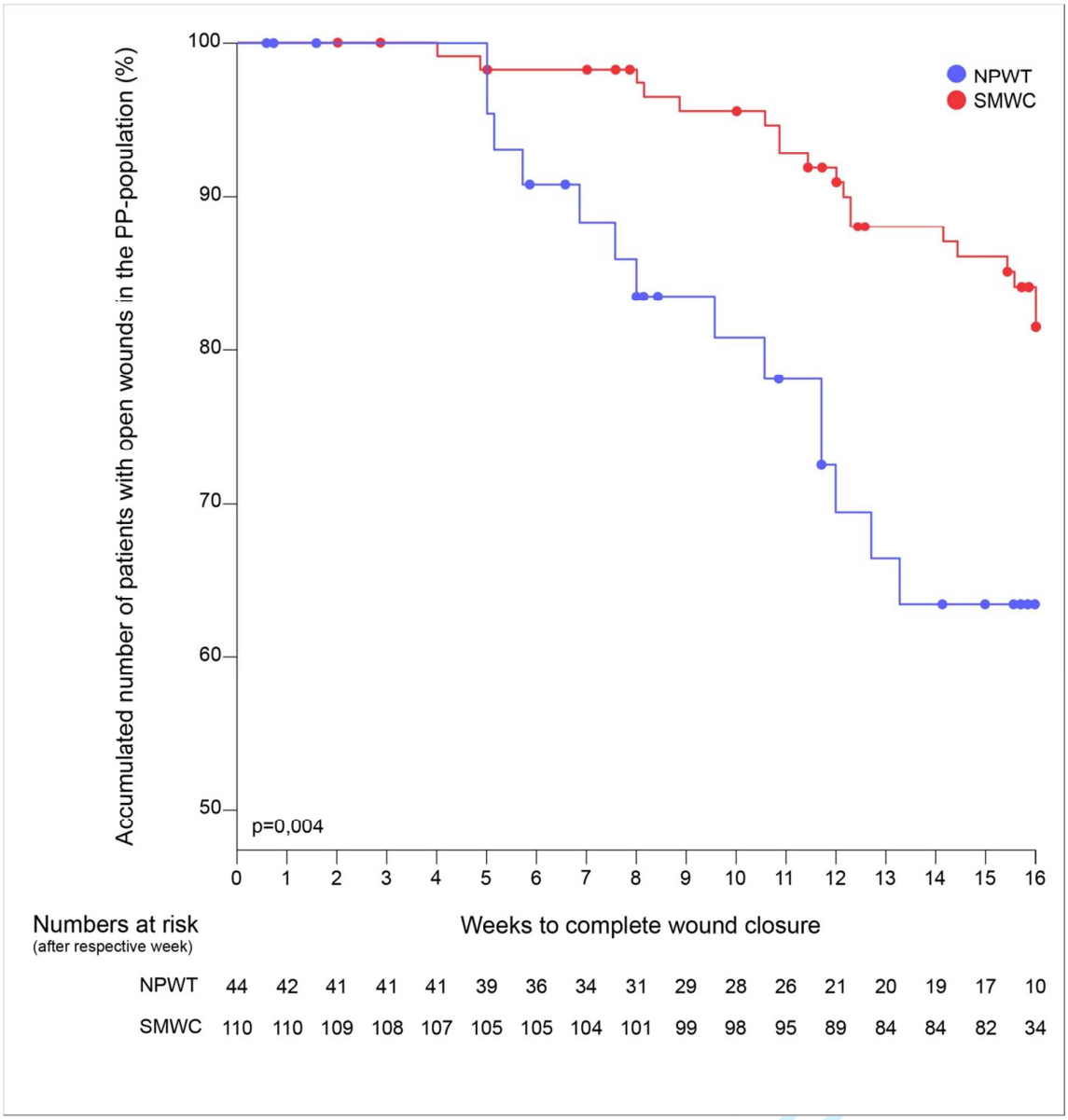


Figure5:



692

References

1. Graham, I.D., et al., *Prevalence of lower-limb ulceration: a systematic review of prevalence studies.* Adv Skin Wound Care, 2003. **16**(6): p. 305-16.
2. World Health Organization, *Global report on diabetes.* 2016, WHO: http://www.who.int/diabetes/global-report/en/.
3. International Diabetes Federation, *IDF Diabetes Atlas*. 2015, IDF: www.diabetesatlas.org.
4. Yazdanpanah, L., M. Nasiri, and S. Adarvishi, *Literature review on the management of diabetic foot ulcer.* World J Diabetes, 2015. **6**(1): p. 37-53.
5. Leone, S., et al., *[Epidemiology of diabetic foot]*. Infez Med, 2012. **20 Suppl 1**: p. 8-13.
6. Vermeulen, H., et al., *Systematic review of dressings and topical agents for surgical wounds healing by secondary intention.* Br J Surg, 2005. **92**(6): p. 665-72.
7. Ruttermann, M., et al., *Local treatment of chronic wounds: in patients with peripheral vascular disease, chronic venous insufficiency, and diabetes.* Dtsch Arztebl Int, 2013. **110**(3): p. 25-31.
8. Wu, S.C., W. Marston, and D.G. Armstrong, *Wound care: the role of advanced wound-healing technologies.* J Am Podiatr Med Assoc, 2010. **100**(5): p. 385-94.
9. Fleischmann, W., et al., *[Vacuum sealing as treatment of soft tissue damage in open fractures]*. Unfallchirurg, 1993. **96**(9): p. 488-92.
10. Argenta, L.C. and M.J. Morykwas, *Vacuum-assisted closure: a new method for wound control and treatment: clinical experience.* Ann Plast Surg, 1997. **38**(6): p. 563-76; discussion 577.
11. Morykwas, M.J., et al., *Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation.* Ann Plast Surg, 1997. **38**(6): p. 553-62.
12. Morykwas, M.J., et al., *Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine.* Ann Plast Surg, 2001. **47**(5): p. 547-51.
13. *German Federal Joint Committee*. 2018 [cited 2018 August 18]; The Federal Joint Committee is a legal entity in public law. Authorised representative: Prof. Josef Hecken Competent supervisory authority: Federal Ministry of Health]. Available from: http://www.english.g-ba.de/.
14. *Institute for Quality and Efficiency in Health Care (IQWiG)*. 2018 [cited 2018 August 16]; As an independent scientific institute, IQWiG examines the benefits and harms of medical interventions for patients. We provide information about the advantages and disadvantages of examination and treatment methods in the form of scientific reports and easily understandable health information.]. Available from: https://www.iqwig.de/en/home.2724.html.
15. IQWiG, *Vakuumversiegelungstherapie von Wunden. Abschlussbericht N04-03*. 2006, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG): Cologne.
16. IQWiG, *Vakuumversiegelungstherapie von Wunden -Rapid Report- N06-02*. 2007, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG): Cologne.
17. Gregor, S., et al., *Negative pressure wound therapy: a vacuum of evidence?* Arch Surg, 2008. **143**(2): p. 189-96.
18. Ubbink Dirk, T., et al. *Topical negative pressure for treating chronic wounds*. Cochrane Database of Systematic Reviews, 2008. DOI: 10.1002/14651858.CD001898.pub2.
19. Ubbink, D.T., et al., *A systematic review of topical negative pressure therapy for acute and chronic wounds.* Br J Surg, 2008. **95**(6): p. 685-92.
20. Peinemann, F. and S. Sauerland, *Negative-pressure wound therapy: systematic review of randomized controlled trials.* Dtsch Arztebl Int, 2011. **108**(22): p. 381-9.
21. Dumville, J.C., et al., *Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus.* Cochrane Database Syst Rev, 2013(10): p. CD010318.
22. Rhee, S.M., et al., *Negative Pressure Wound Therapy Technologies for Chronic Wound Care in the Home Setting*. 2014, Johns Hopkins University Evidence-based Practice Center: Rockville (MD).
23. Canadian Agency for Drugs and Technologies in Health, *Negative Pressure Wound Therapy for Managing Diabetic Foot Ulcers: A Review of the Clinical Effectiveness, Cost-effectiveness, and Guidelines*. 2014: Ottawa (ON).

24. Liu, S., et al., *Evaluation of negative-pressure wound therapy for patients with diabetic foot ulcers: systematic review and meta-analysis.* Ther Clin Risk Manag, 2017. **13**: p. 533-544.
25. Armstrong, D.G. and L.A. Lavery, *Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial.* Lancet, 2005. **366**(9498): p. 1704-10.
26. Blume, P.A., et al., *Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial.* Diabetes Care, 2008. **31**(4): p. 631-6.
27. IQWiG. *General Methods*. 2018; Available from: https://www.iqwig.de/en/methods/methods-paper.3020.html.
28. Seidel, D., et al., *Negative pressure wound therapy versus standard wound care in chronic diabetic foot wounds: study protocol for a randomized controlled trial.* Trials, 2014. **15**: p. 334.
29. Hardman, R.L., et al., *Overview of classification systems in peripheral artery disease.* Semin Intervent Radiol, 2014. **31**(4): p. 378-88.
30. Bauer, H., et al. *Typ-2-Diabetes: Präventions- und Behandlungsstrategien für Fußkomplikationen*. Nationale Versorgungs Leitlinien, 2010.
31. Dupont, W.D. and W.D. Plummer, Jr., *Power and sample size calculations. A review and computer program.* Control Clin Trials, 1990. **11**(2): p. 116-28.
32. Rhee, S.M., et al., in *Negative Pressure Wound Therapy Technologies for Chronic Wound Care in the Home Setting*. 2014: Rockville (MD).

Supplementary Appendix

Table of contents:

- List of investigators
- Supplementary discussion
- Supplementary tables

List of investigators:

At least one patient was included in the following facilities:

1. PD Dr. med. Achim Neufang	HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für Gefäßchirurgie Ludwig-Erhard-Straße 100 65199 Wiesbaden
2. Dr. med. Holger Lawall	Asklepios Westklinikum Hamburg Zentrum für Gefäßmedizin Suurheid 20 22559 Hamburg
3. Prof. Dr. med. Gernold Wozniak	Knappschaftskrankenhaus Bottrop Gefäßchirurgische Klinik Osterfelderstraße 157 46242 Bottrop
4. Prof. Dr. med. Martin Storck	Städtisches Klinikum Karlsruhe Klinik für Gefäß- und Thoraxchirurgie Moltkestraße 90 76133 Karlsruhe
5. Dr. med. Dirk Hochlenert	Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Merheimer Straße 217 50733 Köln
6. Dr. med. Gudrun Hetzel	Klinikum Döbeln Abt. für Gefäßchirurgie Sörmitzer Straße 10 04720 Döbeln
7. Dr. med. Karsten Jungheim	Klinikum Bielefeld Mitte Klinik für Allgemeine Innere Medizin Teutoburger Straße 50 33604 Bielefeld
8. Dr. med. Michael Petzold	Klinikum Frankfurt/Oder Klinik für Gefäßchirurgie Müllroser Chaussee 7 15236 Frankfurt/Oder

9. PD Dr. med. Matthias Weck	Weißeritztal-Kliniken GmbH Medizinische Klinik III Bürgerstraße 7 1705 tal
10. Dr. med. Alexandra Zidek	Krankenhaus Porz am Rhein Klinik für Gefäßchirurgie Urbacher Weg 19 51149 Köln
11. Dr. med. Peter Mauckner	St. Remigius Krankenhaus Opladen Innere Medizin An St. Remigius 26 51379 Leverkusen
12. Dr. med. Klemens M. Sondern	Marien Hospital Dortmund-Hombruch Klinik für Innere Medizin/Diabetologie Gablonzstraße 9 44225 Dortmund
13. Prof. Dr. med. Thomas Schmitz-Rixen	Universitätsklinikum Frankfurt Zentrum für Chirurgie Klinik für Gefäß- und Endovascularchirurgie Theodor-Stern-Kai 7, Haus 23C/EG 60590 Frankfurt am Main
14. Dr. med. Walter Wetzel-Roth	Facharztpraxis für Chirurgie Hindenburgstraße 1 86807 Buchloe
15. Dr. med. Matthias Hahn	Helfenstein Klinik Geisslingen Allgemein- und Viszeralchirurgie Eybstraße 16 73312 Geislingen/Steige
16. Dr. med. Karsten Glockemann	Paracelsus-Klinik am Silbersee Wundzentrum Hannover Oertzeweg 24 30851 Langenhagen
17. PD Dr. med. Farzin Adili	Klinikum Darmstadt Chirurgische Klinik III Grafenstraße 9 64283 Darmstadt
18. Dr. med. Andreas Riemer	Ortenau Klinikum Offenburg-Ebertplatz Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ebertplatz 12 77654 Offenburg

19. Dr. med. Thomas Krönert	Thüringen-Kliniken "Georgius Agricola" GmbH Klinik für Gefäßchirurgie Rainweg 68 7318 feld
20. Dr. med. Matthias Holfeld	Klinikum Dorothea Christiane Erxleben GmbH Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ditfurter Weg 24 6484 linburg
21. Prof. Dr. med. Jan Andre´ Schmidt-Lucke	Franziskus-Krankenhaus Berlin Abt. für Innere Medizin Budapester Straße 15-19 10787 Berlin
22. Dr. med. Wolf-Rüdiger Klare	Hegau-Bodensee Klinikum Radolfzell (HBK) Klinik für Innere Medizin Hausherrenstraße 12 78315 Radolfzell
23. Dr. med. Hansjörg Mühlen	Diabetologische Schwerpunktpraxis Dr. med. Hansjörg Mühlen & Partner Ruhrorter Straße 195 47119 Duisburg
24. Dr. med. Christian Reinhold	Kliniken Maria Hilf Mönchengladbach Klinik für Gefäßchirurgie und Angiologie Sandradstraße 43 41061 Mönchengladbach
25. Dr. med. Makarios Paschalidis	Städtisches Klinikum München/Bogenhausen Klinik für Endokrinologie, Diabetologie und Angiologie Englschalkingerstraße 77 81925 München
26. Gerhard Rothenaicher	Facharztpraxis für Chirurgie Cosimastraße 2 81927 München
27. Dr. med. Elke Anne Klug	Bürgerhospital Frankfurt am Main Interdisziplinäres Zentrum Diabetischer Fuß (DDG) Nibelungenallee 37- 41 60318 Frankfurt am Main
28. Dr. med. Siamak Pourhassan	Gemeinschaftspraxis für Chirurgie und Gefäßmedizin Drs. Alter / Pourhassan / Heim Klosterstraße 12 46145 Oberhausen
29. Dr. med. Jan Theil	Evangelisches Krankenhaus Königin Elisabeth Herzberge gGmbH Abt. für Kardiologie, Angiologie und Diabetologie

	Herzbergstraße 79 10365 Berlin
30. Dr. med. Martin Adolph	Städtisches Klinikum Neunkirchen gGmbH Abt. für Gefäßchirurgie & Phlebologie Brunnenstraße 20 66538 Neunkirchen
31. Dr. med. Frank von Feldmann	Westküstenklinikum Heide Klinik für Viszeral- und Gefäßchirurgie Esmarchstraße 50 25746 Heide/Holstein
32. Dr. med. Gerald Engels	Chir. Praxisgemeinschaft am Bayenthalgürtel Praxis Dr. med. Gerald Engels Bayenthalgürtel 45 50968 Köln
33. Dr. med. Joachim Oldenburg	Malteser Krankenhaus – St. Franziskus-Hospital Medizinische Klinik I Abt. für Diabetologie Waldstraße 17 24939 Flensburg
34. Dr. med. Philipp Kneppe	St. Marienkrankenhaus Siegen gGmbH Klinik für Gastroenterologie Kampenstraße 51 57072 Siegen
35. Dr. med. Steffen Hering	Krankenhaus Bietigheim Klinik für Innere Medizin, Kardiologie, Endokrinologie, Diabetologie und Internistische Intensivmedizin Riedstraße 12 74321 Bietigheim-Bissingen
36. Dr. med. Harald Daum	Asklepios Kliniken Harburg Eißendorfer Pferdeweg 52 21075 Hamburg
37. Dr. med. Lutz Stemler	Diabetologikum Ludwigshafen Diabetes-Schwerpunktpraxis Ludwigsplatz 9 67059 Ludwigshafen
38. Dr. med. Thomas Müller	Mariannen-Hospital Werl Abt. für Chirurgie Unnaer Straße 15 59457 Werl
39. Dr. med. Karl Zink	Diabetes Klinik GmbH & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim

40. Dr. med. Dirk Lammers	Institut für Diabetesforschung Münster GmbH Hohenzollernring 70 48145 Münster

Supplementary Discussion

As direct blinding of patients and investigators was not possible due to the nature of the applied treatment methods, issues of blinding have been addressed using independent blinded outcome assessors and the W.H.A.T. for evaluating the wound photographs. For wound size and wound tissue the values documented by the investigators reflect the expected course much better than the W.H.A.T. results. During study planning the W.H.A.T. (http://www.what-world.com/) was the only available validated instrument that was able to measure both wound size and wound tissue composition (granulation, fibrin, and necrosis). For the wound surface area, the difference between the clinical measurements and the W.H.A.T. results may have been caused by the different evaluation methods. An elliptical wound surface area was calculated by the investigators using length and width, but most wounds are not elliptical. The independent blinded assessors marked the wound margin on the photograph and the W.H.A.T. calculates the wound surface area automatically afterwards, thus if the wound photo is of good quality the W.H.A.T. is more precise. In addition, the depth of the wound cannot be assessed using a wound photo, thus wound volume has only been evaluated using the clinical measurements provided by the investigators. The values for granulation tissue and fibrin differ significantly between the clinical estimations and the W.H.A.T. results. This may be caused by the quality of the wound photography, the reliability and precision of both the clinical investigator and the W.H.A.T. system and the wound itself. Wounds with invisible, deeper areas cannot be detected without manipulation. Both circumstances possibly affect the results.

Supplementary tables

Demographic and baseline parameters (PP-Population)	**Total** **N=154 (100%)**	**NPWT** **N=44** **(28·6%)**	**SMWC** **N=110** **(71·4%)**
Sex	N=154	N=44	N=110
Male	113 (73·4%)	29 (65·9%)	84 (76·4%)
Female	41 (26·6%)	15 (34·1%)	26 (23·6%)
Age in years Mean (SD)	N=154 67·4 (10·6)	N=44 66·5 (11·0)	N=110 67·8 (10·4)
Height in cm Mean (SD)	N=153 173·8 (12·9)	N=43 173·5 (17·4)	N=110 174·0 (10·7)
Weight in kg Mean (SD)	N=150 95·4 (23·3)	N=42 96·2 (21·6)	N=108 95·1 (24·0)
Alcohol	N=153	N=44	N=109
Occasionally	71 (46·4%)	22 (50·0%)	49 (45·0%)

Chronic	3 (2·0%)	1 (2·3%)	2 (1·8%)
No	79 (51·6%)	21 (47·7%)	58 (53·2%)
Nicotine	N=154	N=44	N=110
No	16 (10·4%)	2 (4·5%)	14 (12·7%)
Yes	138 (89·6%)	42 (95·5%)	96 (87·3%)
Number of years (Mean (SD))	37·0 (9·2)	42·0 (2·8)	36·3 (9·7)
Packs / day (Mean)	1·0	1·0	1·0
Drugs	N=153	N=44	N=109
Occasionally	0 (0%)	0 (0%)	0 (0%)
Chronic	1 (0·7%)	0 (0%)	1 (0·9%)
No	152 (99·3%)	44 (100%)	108 (99·1%)
Requiring dialysis	N=154	N=44	N=110
Yes	11 (7·1 %)	2 (4·5%)	9 (8·2%)
No	143 (92·9%)	42 (95·5%)	101 (91·8%)
Allergies	N=154	N=44	N=110
Yes	16 (10·4%)	6 (13·6%)	10 (9·1%)
No	138 (89·6%)	38 (86·4%)	100 (90·9%)
Subjective assessment of nutritional condition	N=150	N=43	N=107
Well-nourished	147 (98·0%)	42 (97·7%)	105 (98·1%)
Moderately malnourished or suspected malnutrition	3 (2·0%)	1 (2·3%)	2 (1·9%)
Malnourished	0 (0%)	0 (0%)	0 (0%)
Peripheral arterial occlusive disease (PAOD)	N=109 (70·8%)	N=29 (65·9%)	N=80 (72·7%)
without critical limb ischemia	103 (94·5%)	28 (96·6%)	75 (93·8%)
with critical limb ischemia	6 (5·5%)	1 (3·4%)	5 (6·3%)
Rutherford classification for chronic limb ischemia (Grade/Category)	N=109	N=29	N=80
0/0 Asymptomatic—no hemodynamically significant occlusive disease	13 (11·9%)	4 (13·8%)	9 (11·3%)
I/1 Mild claudication	13 (11·9%)	2 (6·9%)	11 (13·8%)
I/2 Moderate claudication	8 (7·3%)	0 (0·0%)	8 (10·0%)
I/3 Severe claudication	4 (3·7%)	1 (3·4%)	3 (3·8%)
II/4 Ischemic rest pain	1 (0·9%)	1 (3·4%)	0 (0%)
III/5 Minor tissue loss—non healing ulcer, focal gangrene with	67 (61·5%)	21 (72·4%)	46 (57·5%)

diffuse pedal ischemia			
III/6 Major tissue loss—extending above transmetatarsal level, functional foot no longer salvageable	3 (2·8%)	0 (0·0%)	3 (3·8%)
Revascularisation before study start	N=9 (5·8%)	N=1 (2·3%)	N=8 (7·3%)
Percutaneous transluminal angioplasty (PTA)	5 (55·6%)	0 (0·0%)	5 (62·5%)
PTA + Stent	0 (0%)	0 (0%)	0 (0%)
Veins-Bypass	1 (11·1%)	1 (100·0%)	0 (11·1%)
Polytetrafluoroethylene (PTFE) Bypass	1 (11·1%)	0 (0%)	1 (12·5%)
Thromboendarterectomy and patch plastic	2 (22·2%)	0 (0%)	2 (25·0%)
Revascularization with influence on the wound	9 of 9 (100%)	1 of 1 (100%)	0 of 8 (100%)
Sufficient revascularization result	9 of 9 (100%)	1 of 1 (100%)	8 of 8 (100%)
Insufficient revascularization result	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)
Revascularization result not assessable	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)

Table S1: Patient demographics and baseline characteristics of the Per-Protocol (PP) population. Data are N (%) and Mean (SD). "N=" is stating the number of patients with actual available information. Findings, diagnoses and procedures documented by the investigators are presented.

	Wound surface NPWT		**Wound surface SMWC**	
Observation time point	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**
Randomization	1060 (1536) 550 (1236) N=171 (2)	687 (879) 321 (760) N=118 (10)	1141 (3247) 471 (1007) N=174 (0)	664 (1050) 316 (658) N=129 (13)
Week 1	847 (1489) 397 (801) N=171 (15)	643 (820) 329 (750) N=118 (32)	1085 (3234) 395 (867) N=174 (25)	713 (1065) 307 (749) N=129 (36)
Week 3	810 (1472) 314 (860) N=171 (24)	590 (742) 273 (633) N=118 (28)	1025 (3242) 390 (913) N=174 (22)	701 (1212) 266 (768) N=129 (35)
Week 5	717 (1379) 275 (769) N=171 (37)	607 (828) 231 (843) N=118 (42)	759 (1466) 267 (824) N=174 (41)	610 (1119) 219 (635) N=129 (38)
Week 8	636 (1322) 220 (712)	495 (770) 182 (561)	674 (1410) 186 (783)	501 (937) 165 (481)

	N=171 (52)	N=118 (48)	N=174 (42)	N=129 (42)
Week 12	549 (858) 165 (964) N=171 (110)	457 (742) 134 (494) N=118 (88)	570 (940) 169 (632) N=174 (124)	493 (950) 133 (498) N=129 (104)
Week 16	440 (810) 79 (471) N=171 (80)	334 (649) 114 (363) N=118 (66)	493 (1095) 69 (415) N=174 (63)	351 (750) 77 (320) N=129 (56)

Table S2: Change of wound surface area in the course of the study treatment time of maximum 16 weeks in the ITT-population. Change of wound surface area in the course of the study treatment time of maximum 16 weeks separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis. An elliptical wound surface area has been calculated from the documented width and length (eCRF) [(pi / 4) x length x width = area]. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	**Wound volume NPWT (mm^3)**	**Wound volume SMWC (mm^3)**
Randomization	22498 (58930) 4710 (15048) N=171 (2)	21740 (74181) 4759 (12888) N=174 (0)
Week 1	13203 (28709) 2487 (6908) N=171 (15)	19979 (73143) 3533 (11407) N=174 (26)
Week 3	10708 (28521) 1884 (6857) N=171 (24)	16217 (67494) 2293 (8831) N=174 (23)
Week 5	7700 (19719) 1166 (5338) N=171 (37)	11286 (32566) 1365 (7539) N=174 (42)
Week 8	5592 (11535) 785 (4604) N=171 (78)	8772 (27674) 812 (5258) N=174 (67)
Week 12	5333 (12422) 565 (3913) N=171 (119)	6639 (16454) 625 (4083) N=174 (133)
Week 16	3880 (10534) 141 (1890) N=171 (83)	5465 (14874) 200 (1587) N=174 (64)

Table S3: Change of wound volume in the course of the study treatment time of maximum 16 weeks in the ITT-population. Change of wound volume (length x width x depth) in the course of the study treatment time of maximum 16 weeks calculated from width, length and depth as documented in the eCRF. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	NPWT Granulation		NPWT Fibrin		NPWT Necrosis		SMWC Granulation		SMWC Fibrin		SMWC Necrosis	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.
Rando	34 (36) 20 (70) 171 (2)	22 (25) 12 (37) 118 (8)	21 (28) 10 (30) 170 (4)	71 (27) 79 (46) 118 (8)	3 (10) 0 (0) 169 (5)	7 (15) 0 (5) 118 (8)	34 (37) 20 (71) 174 (3)	24 (26) 14 (39) 129 (12)	22 (29) 10 (40) 174 (1)	69 (28) 79 (44) 129 (12)	2 (9) 0 (0) 172 (2)	7 (14) 0 (8) 129 (12)
Week 1	58 (35) 70 (70) 171 (16)	21 (25) 10 (36) 118 (32)	19 (22) 10 (30) 71 (19)	73 (27) 81 (47) 118 (32)	5 (13) 0 (2) 169 (23)	6 (12) 0 (5) 118 (32)	49 (35) 50 (70) 174 (28)	21 (25) 10 (36) 129 (36)	24 (27) 15 (31) 174 (27)	74 (26) 85 (40) 129 (36)	6 (15) 0 (5) 172 (30)	5 (9) 0 (5) 129 (36)
Week 3	67 (31) 80 (55) 171 (26)	16 (23) 5 (25) 118 (27)	18 (22) 10 (30) 171 (30)	80 (25) 91 (30) 118 (27)	5 (13) 0 (0) 169 (28)	4 (11) 0 (1) 118 (27)	57 (32) 60 (60) 174 (24)	21 (25) 10 (36) 129 (35)	25 (26) 20 (35) 174 (25)	77 (25) 85 (36) 129 (35)	5 (13) 0 (3) 172 (30)	3 (7) 0 (1) 129 (35)
Week 5	70 (30) 80 (45) 171 (36)	15 (22) 6 (21) 118 (43)	18 (24) 10 (25) 171 (38)	83 (22) 91 (26) 118 (43)	4 (13) 0 (0) 169 (42)	2 (8) 0 (1) 118 (43)	62 (31) 63 (50) 174 (44)	18 (26) 4 (32) 129 (36)	23 (25) 10 (39) 174 (47)	80 (26) 93 834) 129 (36)	4 (12) 0 (0) 172 (46)	3 (10) 0 (0) 129 (36)
Week 8	74 (30) 90 (40) 171 (53)	16 (23) 4 (27) 118 (48)	17 (24) 10 (20) 171 (56)	82 (24) 93 (33) 118 (48)	4 (13) 0 (0) 171 (59)	2 (6) 0 (0) 118 (48)	70 (29) 80 (40) 174 (44)	17 (24) 3 (33) 129 (43)	17 (21) 10 (20) 174 (49)	80 (25) 92 (36) 129 (43)	5 (13) 0 (0) 174 (52)	3 (11) 0 (0) 129 (43)
Week 12	75 (30) 90 (40) 171(115)	15 (23) 4 (22) 118 (89)	17 (25) 5 (20) 171(118)	83 (24) 96 (23) 118 (89)	4 (13) 0 (0) 171(119)	1 (5) 0 (0) 118 (89)	73 (29) 80 (38) 174(124)	16 (23) 3 (29) 129(102)	16 (20) 10 (20) 174(125)	82 (23) 93 (32) 129(102)	5 (13) 0 (0) 172(126)	2 (6) 0 (0) 129(102)
Week 16	77 (30) 90 (40) 171 (78)	13 (22) 1 (17) 118 (66)	14 (22) 2 (20) 171 (79)	86 (24) 98 (19) 118 (66)	3 (10) 0 (0) 171 (82)	1 (6) 0 (0) 118 (66)	76 (30) 90 (40) 174 (62)	17 (24) 4 (31) 129 (576	15 (24) 5 (20) 174 (65)	81 (24) 93 (35) 129 (56)	3 (13) 0 (0) 174 (66)	2 (6) 0 (0) 129 (56)

Table S1: Change of wound tissue composition in the course of the study treatment time of maximum 16 week in the ITT-population. Change of wound tissue (granulation, fibrin, and necrosis) in the course of the study treatment time of maximum 16 weeks separately shown for the data documented in the eCRF and for the data derived from the photo analysis using the Wound Healing Analyzing Tool (W.H.A.T.). Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Pain Total N=344	Pain NPWT N=171	Pain SMWC N=173
Screening	2·1 (2·4) 1 (4) N=344 (0)	2·1 (2·3) 1 (4) N=171 (0)	2·1 (2·4) 1 (4) N=173 (0)
Week 1	1·7 (2·2) 1 (3) N=344 (6)	1·6 (2·2) 0 (2) N=171 (1)	1·8 (2·2) 1 (3) N=173 (5)
Week 3	1·5 (2·0) 1 (2) N=344 (27)	1·3 (1·9) 0 (2) N=171 (11)	1·7 (2·1) 1 (3) N=173 (16)
Week 5	1·3 (1·9) 0 (2) N=344 (45)	1·2 (1·9) 0 (2) N=171 (21)	1·4 (2·0) 0 (2) N=173 (24)
Week 8	1·3 (1·9) 0 (2) N=344 (70)	1·2 (1·9) 0 (2) N=171 (38)	1·3 (1·9) 0 (2) N=173 (32)
Week 12	1·1 (1·8) 0 (2) N=344 (115)	1·2 (1·9) 0 (2) N=171 (64)	1·1 (1·8) 0 (2) N=173 (51)
Week 16	1·0 (1·7) 0 (1) N=344 (129)	1·0 (1·7) 0 (2) N=171 (76)	0·9 (1·7) 0 (1) N=173 (53)

Table S2: Pain in the course of the study treatment time of maximum 16 weeks in the ITT-population. Pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	EQ5D NPWT	EQ5D SMWC
Screening	0,53 (0,27) 0,53 (0,2) N=156 (2)	0,53 (0,24) 0,53 (0,18) N=159 (3)
End of therapy	0,67 (0,24) 0,77 (0,29) N=62 (2)	0,72 (0,17) 0,66 (0,35) N=13 (0)

End of maximum study treatment time	0,66 (0,22) 0,66 (0,28) N=63 (2)	0,61 (0,25) 0,63 (0,24) N=95 (2)
Follow up after 6 months	0,69 (0,26) 0,77 (0,35) N=93 (3)	0,67 (0,23) 0,63 (0,39) N=97 (2)

Table S3: Quality of life (EQ5D) in the course of the study treatment time of 16 week in the ITT-population. Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT-population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Wound surface area	**Small wounds**				**Big wounds**			
mm^2	**Total N=173**	**NPWT N=83**	**SMWC N=90**	**p**	**Total N=172**	**NPWT N=88**	**SMWC N=84**	**p**
N (LOCF)	2	2	0	0·232	0	0	0	0·193
Mean (SD)	213 (136)	212 (138)	213 (135)		1995 (3377)	1860 (1805)	2135 (4474)	
Median (IQR)	188 (220)	176 (220)	196 (222)		1276 (1482)	1364 (1242)	1242 (1708)	
Min - Max	12-484	20-484	12-471		491-40773	520-13188	491-40773	

Table S4: Wound surface area for small and big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms, the number (N) of values substituted by the last observation carried forward (LOCF) method; mean (SD), median (IQR); and minimum (min) and maximum (max).

Wound closure rate **Small wounds**	**NPWT (N=171)** **N=83**	**SMWC (N=174)** **N=90**	**p**
Within 16 weeks maximum study treatment time	12 (14·5 %)	16 (17·8 %)	0·6
At follow up after 6 months	13 (15·7 %)	24 (26·7 %)	0·10

Table S5: Wound closure rates within the maximum study treatment time of 16 weeks and within the study observation time of 6 months for small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number of patients with wound closure (N) within 16 weeks and after 6 months as well the percentage (%) of patients achieving the endpoints within both treatment arms.

Wound closure rate **Big wounds**	**NPWT (N=171)** **N=88**	**SMWC (N=174)** **N=84**	**P**
Within 16 weeks maximum study treatment time	13 (14·8 %)	5 (6·0 %)	0·08
At follow up after 6 months	11 (12·5 %)	12 (14·3 %)	0·82

Table S6: Wound closure rates within the maximum study treatment time of 16 weeks and within the study observation time of 6 months for big wounds. Data show the number (N) of participants available for the analysis in total and for both

treatment arms and the number of patients with wound closure (N) within 16 weeks and after 6 months as well the percentage (%) of patients achieving the endpoints within both treatment arms.

Time until min. 95 % granulation tissue for small wounds	**Total (N=100)**	**NPWT (N=52)**	**SMWC (N=48)**	**p**
Mean (SD)	38·6 (37·4)	28·5 (30·0)	49·5 (41·6)	0·005
Median (IQR)	26·5 (50·0)	20·0 (28·0)	48·0 (79·0)	
Min-Max	0-114	0-113	0-114	

Table S7: Time until optimal preparation of the wound bed (min. 95 % granulation tissue) for the subgroup of small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Time until min 95 % granulation tissue for big wounds	**Total (N=80)**	**NPWT (N=47)**	**SMWC (N=33)**	**p**
Mean (SD)	47·8 (40·8)	43·4 (37·9)	54·0 (44·6)	0·27
Median (IQR)	36·5 (70·0)	35·0 (61·0)	56·0 (105·0)	
Min-Max	0-127	0-127	0-115	

Table S 8: Time until optimal preparation of the wound bed (min 95 % granulation tissue) for the subgroup of big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Amputations & Resections **Small wounds**	**Total** **N=173**	**NPWT** **N=83**	**SMWC** **N=90**	**p**
No. of patients with amputations or resections [N (%)]	35 (20·2%)	19 (22·9%)	16 (17·8%)	0·45 (F)
No. of performed amputations and resections [N]	50	22	28	0·51 (U)
No. of patients with minor amputations [N (%)]	35 (20·2%)	19 (22·9%)	16 (17·8%)	0·45 (F)
No. of patients with major amputations [N (%)]	0 (0%)	0 (0%)	0 (0%)	-

Table S9: Amputations and resections in the subgroup of small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

Amputations & Resections **Big wounds**	**Total** **N=172**	**NPWT** **N=88**	**SMWC** **N=84**	**p**

No. of patients with amputations or resections [N (%)]	36 (20·9%)	16 (18·2%)	20 (23·8%)	0·45 (F)
No. of performed amputations and resections [N]	52	45	57	0·41 (U)
No. of patients with minor amputations [N (%)]	34 (19·8%)	14 (15·9%)	20 (23·8%)	0·25 (F)
No. of patients with major amputations [N (%)]	2 (1·2%)	2 (2·3%)	0 (0%)	0·50 (F)

Table S10: Amputations and resections in the subgroup of big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

Wound closure rate	**Total N=154**	**NPWT N=44**	**SMWC N=110**	**p**
Wound closures [N (%)] within 16 weeks	33 (21·4 %)	14 (31·8%)	19 (17·3%)	0·053
Wound closures [N (%)] after 6 months	41 (26·6 %)	11 (25·0%)	30 (27·3%)	0·84

Table S11: Wound closure rate after 6 months and in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with wound closures within 16 weeks and after 6 months.

Time until min. 95 % granulation tissue	**Total (N=100)**	**NPWT (N=38)**	**SMWC (N=62)**	**p**
Mean (SD)	43·8 (42·3)	23·8 (31·7)	56·0 (43·5)	<0·001
Median (IQR)	30·0 (76)	8·5 (28·0)	56·0 (96·0)	
Min - Max	0 - 127	0 - 127	0 - 115	

Table S12: Time until optimal preparation of the wound for further treatment (min 95 % granulation tissue) in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Recurrences	**Total (N=154)**	**NPWT (N=44)**	**SMWC (N=110)**	**p**
No. of patients with recurrences [N (%)]	8 (5·2 %)	3 (8·1 %)	5 (5·3%)	0·69
No. of recurrences [N]	9	4	5	0·38

Table S13: Recurrences in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with recurrences.

Amputations & Resections	**Total (N=154)**	**NPWT (N=44)**	**SMWC (N=110)**	**p**
No. of patients with amputation or resection [N (%)]	30 (19·5%)	9 (20·5%)	21 (21·4%)	0·83

No. of amputations or resections [N]	39	11	28	0·86
No. of patients with Minor-Amputations [N (%)]	30 (18·9%)	9 (12·8%)	21 (21·4%)	0·83
No. of patients with Major-Amputations [N (%)]	0 (0%)	0 (0%)	0 (0%)	-

Table S14: Amputations and resections in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

	Wound surface NPWT		**Wound surface SMWC**	
Observation time point	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**	**Observation time point**	**Calculated from width and length (according to eCRF entry)**
Randomization	964 (1392) 345 (1426) N= 44 (1)	633 (795) 299 (705) N=41 (3)	878 (1266) 373 (889) N= 110 (0)	669 (1143) 294 (692) N=102 (9)
Week 1	525 (696) 224 (408) N= 44 (5)	524 (614) 318 (561) N=41 (8)	827 (1238) 306 (863) N= 110 (16)	706 (1138) 289 (775) N=102 (27)
Week 3	428 (635) 176 (378) N= 44 (6)	477 (737) 165 (424) N=41 (9)	803 (1306) 238 (867) N= 110 (7)	714 (1316) 259 (656) N=102 (26)
Week 5	355 (590) 100 (291) N= 44 (8)	418 (602) 165 (435) N=41 (15)	650 (1157) 161 (670) N= 110 (18)	607 (1212) 167 (545) N=102 (29)
Week 8	284 (528) 53 (217) N= 44 (8)	320 (530) 83 (264) N=41 (16)	569 (1072) 106 (443) N= 110 (17)	479 (990) 123 (397) N=102 (29)
Week 12	283 (580) 14 (130) N= 44 (24)	289 (537) 62 (175) N=41 (32)	528 (1024) 79 (419) N= 110 (71)	474 (1006) 111 (407) N=102 (80)
Week 16	190 (416) 0 (95) N= 44 (14)	179 (333) 30 (204) N=41 (25)	386 (1124) 31 (159) N= 110 (19)	319 (724) 65 (256) N=102 (42)

Table S18: Change of wound surface area during the study treatment time of maximum 16 weeks separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Wound volume NPWT (mm^3)	Wound volume SMWC (mm^3)
Randomization	33359 (95749) 5746 (17330) N=44 (1)	14742 (36523) 3905 (11189) N=110 (0)
Week 1	11606 (26991) 1824 (6113) N=44 (5)	13525 (34844) 2470 (9479) N=110 (16)
Week 3	8636 (24698) 777 (3199) N=44 (6)	11907 (32047) 1864 (8039) N=110 (7)
Week 5	5480 (13967) 271 (1790) N=44 (7)	8981 (25570) 1027 (4745) N=110 (18)
Week 8	3955 (9056) 192 (809) N=44 (16)	6899 (18607) 506 (3915) N=110 (29)
Week 12	6052 (16114) 71 (681) N=44 (25)	5964 (15930) 361 (1890) N=110 (77)
Week 16	3246 (11245) 0 (319) N=44 (15)	3396 (10783) 57 (609) N=110 (19)

Table S15: Change of wound volume (length x width x depth) in the course of the study treatment time of maximum 16 weeks calculated from width· length and depth as documented in the eCRF. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	NPWT Granulation		NPWT Fibrin		NPWT Necrosis		SMWC Granulation		SMWC Fibrin		SMWC Necrosis	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.		eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF
Rando	32 (37)	23 (26)	18 (27)	68 (27)	2 (7)	9 (15)	38 (38)	26 (27)	21 (29)	67 (29)	1 (7)	7 (15)
	10 (68)	13 (37)	3 (28)	69 (45)	0 (0)	0 (15)	25 (80)	16 (42)	10 (33)	77 (56)	0 (0)	0 (8)
	44 (1)	41 (2)	44 (1)	41 (2)	44 (1)	41 (2)	110 (0)	102 (9)	110 (0)	102 (9)	108 (2)	102 (9)
Week 1	72 (37)	22 (26)	7 (13)	70 (28)	2 (7)	9 (15)	54 (35)	24 (27)	22 (24)	72 (27)	5 (14)	5 (9)
	90 (50)	9 (41)	0 (10)	75 (50)	0 (0)	0 (11)	63 (70)	13 (42)	13 (28)	78 (42)	0 (1)	0 (6)
	44 (5)	41 (8)	44 (6)	41 (8)	44 (7)	41 (8)	110 (16)	102 (27)	110 (16)	102 (27)	108 (19)	102 (27)
Week 3	77 (32)	16 (24)	11 (19)	79 (26)	1 (4)	6 (14)	61 (31)	24 (27)	25 (25)	75 (26)	4 (11)	3 (7)
	93 (34)	2 (29)	0 (20)	91 (37)	0 (0)	0 (1)	70 (50)	15 (42)	20 (35)	83 (41)	0 (0)	0 (1)
	44 (6)	41 (9)	44 (7)	41 (9)	44 (7)	41 (9)	110 (9)	102 (26)	110 (10)	102 (26)	108 (13)	102 (26)
Week 5	82 (29)	10 (16)	9 (19)	87 (17)	1 (4)	3 (9)	65 (29)	19 (27)	24 (24)	78 (27)	3 (9)	3 (11)
	95 (20)	4 (11)	2 (10)	93 (21)	0 (0)	0 (1)	73 (46)	4 (34)	13 (37)	93 (35)	0 (0)	0 (0)
	44 (7)	41 (16)	44 (8)	41 (16)	44 (9)	41 (16)	110 (19)	102 (27)	110 (22)	102 (27)	108 (22)	102 (27)
Week 8	85 (27)	15 (25)	6 (13)	82 (26)	2 (6)	3 (8)	74 (27)	20 (26)	18(21)	77 (27)	3 (10)	3 (12)
	100 (20)	1 (16)	0 (5)	96 (35)	0 (0)	0 (0)	80 (31)	3 (38)	10 (18)	91 (43)	0 (0)	0 (0)
	44 (9)	41 (16)	44 (10)	41 (16)	44 (9)	41 (16)	110 (18)	102 (30)	110 (21)	102 (30)	108 (25)	102 (30)
Week 12	86 (26)	13 (24)	6 (14)	85 (26)	2 (9)	2 (6)	77 (27)	18 (25)	16 (20)	80 (25)	3 (11)	2 (6)
	100 (18)	1 (13)	0 (4)	99 (20)	0 (0)	0 (0)	85 (29)	3 (36)	10 (20)	92 (36)	0 (0)	0 (0)
	44 (26)	41 (34)	44 (26)	41 (32)	44 (28)	41 (32)	110 (72)	101 (78)	110 (73)	102 (79)	108 (73)	102 (80)
Week 16	87 (25)	12 (22)	6 (14)	86 (24)	0·1 (1)	1 (6)	80 (30)	19 (25)	14 (24)	80 (26)	2 (11)	1 (5)
	100 (15)	0 (14)	0 (1)	100 (20)	0 (0)	0 (0)	95 (20)	5 (36)	0 (20)	92 (36)	0 (0)	0 (0)
	44 (14)	41 (25)	44 (16)	41 (25)	44 (15)	41 (25)	110 (18)	102 (42)	110 (21)	102 (42)	108 (24)	102 (42)

Table S20: Change of tissue (granulation, fibrin, necrosis) during the study treatment time of maximum 16 weeks separately shown for the data documented in the eCRF and for the data derived from the photo analysis using the wound healing analyzing too (W.H.A.T.). Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Pain Total N=344	Pain NPWT N=171
Screening	1·3 (2·1) 0 (2) N=44 (0)	1·8 (2·3) 1 (3) N=110 (0)
Week 1	0·7 (1·5) 0 (1) N=44 (0)	1·4 (2·1) 0 (3) N=110 (5)
Week 3	0·4 (0·7) 0 (1) N=44 (4)	1·3 (1·8) 0 (2) N=110 (3)
Week 5	0·3 (0·8) 0 (0) N=44 (2)	1·0 (1·6) 0 (2) N=110 (5)
Week 8	0·4 (1·1) 0 (0) N=44 (4)	0·9 (1·5) 0 (2) N=110 (9)
Week 12	0·3 (1·0) 0 (0) N=44 (11)	0·7 (1·3) 0 (1) N=110 (18)
Week 16	0·2 (0·7) 0 (0) N=44 (14)	0·5 (1·2) 0 (0) N=110 (13)

Table S16: Pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	EQ5D NPWT	EQ5D SMWC
Screening	0·61 (0·23) 0·63 (0·24) N=42 (1)	0·60 (0·20) 0·59 (0·25) N=100 (3)
End of therapy	0·65 (0·20) 0·78 (0·20) N=26 (2)	0·81 (0·14) 0·87 (0·26) N=8 (0)
End of maximum study treatment time	0·65 (0·25)	0·66 (0·21)

	0·66 (0·43) N=19 (0)	0·63 (0·28) N=73 (2)
Follow up after 6 months	0·75 (0·22) 0·78 (0·30) N=26 (0)	0·70 (0·23) 0·77 (0·34) N=73 (2)

Table S17: Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6,8,9
Participants	4a	Eligibility criteria for participants	6,7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7,8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8,9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	9,10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12 Fig. 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig. 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12,13,14Tab. 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig. 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14-20
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	14-20
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	18-19
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	19-20
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3,21-22
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	21
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10-11

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Negative Pressure Wound Therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026345.R1
Article Type:	Original research
Date Submitted by the Author:	14-Jun-2019
Complete List of Authors:	Seidel, Dörthe; Universitat Witten/Herdecke, Institut für Forschung in der Operativen Medizin (IFOM) Storck, Martin; Stadtisches Klinikum Karlsruhe gGmbH, Klinik für Gefäß- und Thoraxchirurgie Lawall, Holger; Praxis für Herzkreislauferkrankungen; Max-Grundig Klinik Wozniak, Gernold; Knappschaftskrankenhaus Bottrop GmbH, Gefäßchirurgische Klinik Mauckner, Peter; St. Remigius Krankenhaus Opladen, Innere Medizin Hochlenert, Dirk; Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Wetzel-Roth, Walter; Chirurgische Praxis Wetzel-Roth Sondern, Klemens; Marien Hospital Dortmund-Hombruch, Klinik für Innere Medizin/Diabetologie Hahn, Matthias; Helfenstein Klinik, Allgemein- und Viszeralchirurgie Rothenaicher, Gerhard; Chirurgische Praxis Rothenaicher Krönert, Thomas; Thüringen-Kliniken "Georgius Agricola" GmbH, Klinik für Gefäßchirurgie Zink, Karl; Diabetes Klinik Neugebauer, Edmund; Universitat Witten/Herdecke Department fur Humanmedizin; Medizinische Hochschule Brandenburg -Theodor Fontane
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Surgery, Evidence based practice, Dermatology
Keywords:	negative pressure wound therapy, wound healing, benefit assessment, wound treatment, Diabetic foot < DIABETES & ENDOCRINOLOGY, wound care

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Negative Pressure Wound Therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT

Dörthe Seidel, Martin Storck, Holger Lawall, Gernold Wozniak, Peter Mauckner, Dirk Hochlenert, Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert, Karl Zink, Edmund Neugebauer

Institut für Forschung in der Operativen Medizin (IFOM), University of Witten/Herdecke, Köln, Germany (D Seidel MD), Doerthe.Seidel@uni-wh.de

Klinik für Gefäß- und Thoraxchirurgie, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany (Prof M Storck MD), Martin.Storck@klinikum-karlsruhe.de

Praxis für Herzkreislauferkrankungen, Ettlingen und Max-Grundig Klinik Bühlerhöhe, Germany (Dr med H Lawall MD), holger.lawall@gmail.com

Gefäßchirurgische Klinik, Knappschaftskrankenhaus, Bottrop, Germany (Prof G Wozniak MD), gernold.wozniak@kk-bottrop.de

Innere Medizin, St. Remigius Krankenhaus Opladen, Leverkusen, Germany (Dr med P Mauckner MD), peter-mauckner@live.de

Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock, Köln, Germany (Dr med D Hochlenert MD), dirk.hochlenert@web.de

Chirurgische Praxis Wetzel-Roth, Buchloe, Germany (Dr med W Wetzel-Roth MD), info@wetzel-roth.de

Klinik für Innere Medizin/Diabetologie, Marien Hospital Dortmund-Hombruch, Dortmund, Germany (Dr med Sondern MD), klemens.sondern@marien-hospital-dortmund.de

Allgemein- und Viszeralchirurgie, Helfenstein Klinik, Geisslingen, Germany (Dr med M Hahn, MD), matthias.hahn@af-k.de

Chirurgische Praxis Rothenaicher, München, Germany (G Rothenaicher MD), rothenaicher@arcor.de

Klinik für Gefäßchirurgie, Thüringen-Kliniken "Georgius Agricola" GmbH, Saalfeld, Germany (Dr med T Krönert MD), tkroenert@thueringen-kliniken.de

Diabetes Klinik, Bad Mergentheim, Germany (Dr med K Zink MD), zink@diabetes-zentrum.de

University of Witten/Herdecke, Köln, Germany (Prof E Neugebauer), Edmund.Neugebauer@uni-wh.de

Correspondence to:

Dörthe Seidel*

Institut für Forschung in der Operativen Medizin (IFOM)

University of Witten/Herdecke

Ostmerheimerstraße 200 Haus 38

Köln (Cologne)

51109 Germany

Doerthe.Seidel@uni-wh.de

Abstract

Objectives

The aim of the DiaFu-study was to evaluate effectiveness and safety of negative pressure wound therapy (NPWT) in patients with diabetic foot wounds in clinical practice.

Design

In this controlled clinical superiority trial with blinded outcome assessment patients were randomized in a 1:1 ratio stratified by study site and ulcer severity grade using a web-based-tool.

Setting

This German-national study was conducted in 40 surgical and internal medicine in- and outpatient facilities specialized in diabetes foot care.

Participants

368 patients were randomized and 345 participants were included in the modified ITT-population. Consentable, compliant adult patients suffering from a diabetic foot ulcer at least for 4 weeks and without contraindication for NPWT were allowed to be included.

Interventions

NPWT was compared with SMWC according to local standards and guidelines.

Primary and secondary outcome measures

Primary endpoints were wound closure rate and time to closure within 16 weeks. Secondary endpoints were wound and treatment related adverse events, amputations, time until optimal wound bed preparation, wound size and wound tissue composition, pain, and quality of life within 16 weeks, and recurrences and wound closure rate within 6 months.

Results

In the ITT-population 25 patients in the NPWT-arm (14·6%) and 21 patients in the SMWC-arm (12·1%) achieved wound closure (p=0·53). Wound closure time was not significantly different between the treatment arms (p=0·244). 96 patients in the NPWT-arm and 72 patients in the SMWC-arm had at least one adverse event (p=0·007), but only 11 events have been possibly related to NPWT. Documentation deficiencies, premature cessation of NPWT and temporary changes of the randomized treatment had a negative impact on the outcome wound closure.

Conclusions

NPWT was not superior to SMWC in diabetic foot wounds in clinical practice. Overall wound closure rate was low. Deviations from guidelines limit the treatment success.

Trial registration

Clinical Trials.gov: NCT01480362

Strengths and limitations of this study

- The DiaFu study included patients with diabetic foot ulcers both with peripheral neuropathy and peripheral arterial occlusive disease, which corresponds to the typical mixed patient population in clinical practice and enables a general statement about effectiveness and safety of NPWT in the typical medical care situation.
- The study does not provide any information on the effectiveness of NPWT in specific patient groups, which was not intended and may be seen as a limitation.
- In this health services research study hospitals and outpatient facilities were selected by means of a qualification checklist and clinical investigators were obliged to provide patients with the best clinical practice in compliance with all relevant guidelines, but there was no active monitoring of the implementation of these guidelines.
- To ensure the best quality of local wound treatment and to achieve optimal baseline conditions, the study sites were trained for both NPWT and SMWC, but treatment application was at the discretion of the clinical investigators.
- Methods against bias were applied whenever possible, but due to the nature of the compared treatment methods, a direct blinding of patients and clinical investigators was not possible and blinded outcome assessment could only be implemented for the endpoints wound closure and wound size development over time by means of wound photographs.

Background

The diabetic foot ulcer is one of the most important examples of chronic wounds which in case of severe complications can lead to leg amputation or death. It is estimated that more than 400 million people worldwide suffer from diabetes [1, 2] and about 15% of all these patients will develop a diabetic foot ulcer during their lifetime [3, 4]. Furthermore, approximately 50-70% of all lower limb amputations are due to diabetes [4]. A large number of medical products are available for wound treatment. Only a few modern moist wound dressings and topical agents have been convincingly shown to achieve higher wound closure rates compared with traditional wet gauze dressings in patients with diabetic foot wounds [5]. Also for other ulcer types there is an uncertainty which dressings and topical agents are most effective for treatment [6]. Innovative medical devices have a high potential for effective modern wound care. Negative pressure wound therapy (NPWT) is one of the most commonly used and well-established technologies with the aim to promote wound healing [7]. The first

use of vacuum sealing was described in 1993 by Fleischmann et al. [8] and the commercially available product was developed later in the 1990s [9, 10]. Positive effects of NPWT on wound healing have been suggested in various basic studies [10, 11]. At the time of planning the DiaFu-study, the clinical evidence largely consisted of clinician perception, case reports and series, small cohort studies, and weakly-powered or low-quality randomized trials that documented broad use of NPWT in various clinical settings and constituted a substantial number of publications but an overall small amount of evidence [12-15]. Two trials performed by Armstrong 2005 [16] and Blume 2008 [17] provided a solid basis for planning a study that meets national and international quality requirements. Several systematic and technical reviews on the use of NPWT for post-surgical and chronic wounds have been performed in recent years.

A specific review for the use of NPWT in diabetic foot wounds performed by Dumville et al in 2013 [18], an assessment in the home setting by Rhee at al. in 2014 [19] and a health technology assessment particularly issued for the evaluation of NPWT for managing diabetic foot ulcers [20] in 2014, as well as the most recent work of Liu et al in 2017 [21, 22] all concluded that although NPWT may have a positive effect, the trials that have been performed have methodological flaws and sufficient, unbiased evidence of whether wounds heal better or worse with NPWT than with conventional treatment is still missing.

In Germany, the issue of evidence for efficacy and safety of NPWT in acute and chronic wounds was first addressed in 2002 when it was to be decided whether NPWT could be reimbursed without restrictions in outpatient care. The German Federal Joint Committee (German: Gemeinsamer Bundesausschuss [G-BA]) commissioned systematic reviews and meta-analyzes to the national institute for quality and efficiency in health care (German: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG]). Reports were published in 2006 and 2007 by the IQWiG and the G-BA concluded that the body of evidence available was insufficient to clearly proof an additional benefit of NPWT.

Finally in 2007, the G-BA decided to evaluate the treatment method NPWT within a so-called model project. This included the conduct of clinical studies. The G-BA defined basic requirements for the overall project. Further quality requirements were based on IQWiG's general methods [23]. This essentially concerned the formulation of a study hypothesis that supports G-BA's overall question if NPWT can be reimbursed in German outpatient care without any limitation; the selection of a comparator that represents the current treatment standard in Germany; and implementation of all measures to ensure a sufficient certainty of results.

Following the announcement of the G-BA, the German statutory health insurance funds initiated an overall project through a European tender in which the treatment benefit of NPWT should be evaluated in acute and chronic wounds. The diabetic foot ulcer has been chosen to be evaluated as representative for chronic wounds in

a randomized controlled clinical superiority study comparing the effectiveness of NPWT and SMWC in clinical practice.

Methods

Aim of the study

The aim of our DiaFu-study was to evaluate whether the effectiveness and safety of NPWT is superior to standard moist wound care (SMWC) in real-life clinical practice. Unlike previous studies, in this health care research study with a pragmatic approach the question should be answered as to whether the treatment method is effective and safe when used under routine conditions.

Study Design

The DiaFu-study was a German-national, multicenter, randomized controlled clinical superiority trial with blinded assessment of wound closure, wound size and wound tissue qualities using photographs. This German national study was conducted both in hospital departments and outpatient facilities with a special qualification for diabetic foot care. Study treatment was allowed to be started both in in- and outpatient care and should be continued outpatient whenever possible. Ethical approval of the Lead Ethical Committee of the University of Witten/Herdecke has been fully granted without any conditions. More detailed information on the study design can be found in the study protocol publication that is available open access [24].

Patient and Public Involvement

Patients were not involved in the design, recruitment or conduct of the study. The results of this study will not be disseminated directly to study participants.

Participants

In order to conduct a pragmatic trial comparing NPWT and SMWC in patients with diabetes and foot wounds, a patient population was included that largely corresponded to clinical routine. In- and exclusion criteria have been selected based on manufacturers' contraindications and FDA warnings, the necessity to excluded patients in need of protection and who are unable to give their consent, and the intention to avoid general study-related influences on the results.

Adult patients (age >18 years) with at least 4-week-old chronic diabetic foot ulcers corresponding to Wagner 2 to 4 were screened for study participation by the local investigators. Before inclusion, the study protocol required either a debridement or, if necessary, an amputation of foot parts, or at least a thorough wound cleansing, depending on the individual needs of the patients, in order to achieve the optimal outcome of wound treatment.

Thus, chronic diabetic foot wounds after adequate wound pretreatment as well as post-surgical amputation wounds below the upper ankle joint were eligible for inclusion. The initially planned minimum ulcer age of 6 weeks was reduced to 4 weeks during the course of the study. Patients estimated to be at risk of non-compliance with study requirements, with wounds with necrotic tissue present that could not be removed by debridement or amputation, with exposed blood vessels within or directly surrounding the wound not possible to be sufficiently covered or with an increased risk of bleeding with hemodynamic consequences, and outpatients receiving anticoagulation therapy or suffering from a high grade impaired clotting function with a heightened risk of bleeding with hemodynamic consequences were excluded from the DiaFu-study. The use of NPWT devices on the study wound within six weeks prior to study start represented an exclusion criterion in order to demonstrate a clear therapeutic effect of each treatment arm.

Written informed consent was obtained from every participant after being informed about all aspects of the trial and before randomization and any trial-related procedure. As the statutory health insurance funds provided integrated care contracts for outpatient NPWT, it was only possible to include patients in the study who were members of a participating health insurance fund.

Basic data were collected for all patients considered for study participation during screening and have been updated during the randomization visit. Study sites have been selected based on their qualifications and experiences using a pre-study qualification checklist and annual quality reports of the respective institution (if available).

Randomization and masking

Patients were randomly allocated to the treatment arms in a 1:1 ratio using a computer generated list located on a centralized web-based tool. The randomization list consisted of permuted blocks of variable length (4, 6) which were randomly arranged. Patients were stratified by study site and by Wagner-Armstrong stage within each site (<Wagner-Armstrong stage 2C and ≥ Wagner-Armstrong stage 2C). The randomization lists were generated with the help of a self-created Java program and integrated into the study database. Each registered investigator received individual access to the randomization tool via the study website, but without knowledge of future treatment assignment, which provided adequate allocation concealment. The investigators were responsible for adequately implementing the assigned therapy. Due to the physical differences between the treatment regimens it was not possible to blind either participant or physician to the treatment assignment. Verification of complete wound closure was performed by independent, blinded assessment of wound photographs. Determination of

wound size and percentage wound tissue quality was also performed by central, blinded outcome assessors based on the wound photographs using the Wound Healing Analyzing Tool (W.H.A.T.).

Procedures

Before randomization and start of study treatment all patients underwent one or more of the following no longer than six hours before randomization: amputation, debridement or thorough wound cleansing. Patients received an extensive examination of overall health status, specific diabetes associated disorders, and relevant influence factors on wound healing during screening with an update at the randomization visit. Study therapy was allowed to be started either in-hospital or as outpatient and was intended to be continued in outpatient care whenever possible.

In the intervention group commercially available CE-marked NPWT devices of the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew were used in the discretion of the clinical investigator according to clinical routine and manufacturer's instructions [24]. Recommendations for use can be found on the manufacturers' websites. As part of the European tender for the overall project, the German statutory health insurance funds awarded lots for the provision of the medical products by the respective manufacturers. Germany was divided into 4 supply areas. During the award procedure, Smith & Nephew received 1 lot and KCI 3 lots. Thus, devices and consumables of Smith& Nephew were used for the north and northern east region of Germany and for the rest of Germany the therapy systems of KCI were used. Within the study, NPWT was required to be used for wound bed preparation in order to achieve at least 95% granulation of the wound area. After optimal preparation of the wound, complete closure could be achieved either by secondary intention with dressings or by surgical closure with subsequent removal of the suture. Control therapy was defined as any SMWC according to local clinical standards and guidelines [25, 26]. Healthcare providers were obligated to provide patients with best practice. In the control arm it was permitted to apply any local wound treatment standard used in the respective study site that did not have an experimental status or was NPWT. To ensure the best quality of local wound treatment, the study sites were trained for both the intervention arm by the manufacturers and the control arm by the German Society for Wound Healing and Wound Treatment which provided parts of its curriculum and experienced instructors.

The maximum study treatment time was 16 weeks after randomization. Study visits needed to be performed at week one, three, five, 12 and 16 and included a complete wound examination. Wound closure was possible to be achieved at any time within the study treatment period of 42 days and had to be documented in a wound closure visit as well as in a wound closure confirmation visit after 14 days. Study participants were followed up until 6

months after randomization. The initially planned follow-up period of 12 months was reduced to 6 months in the course of the study. The amendment to the study protocol was endorsed by the Ethics Committee and immediately communicated to all participating study sites.

Outcomes

Our primary outcome comprised the two primary effectiveness endpoints wound closure rate and the time until complete wound closure within a maximum study treatment period of 16 weeks. Complete wound closure was defined as 100% epithelialization of the wound, no drainage, no suture material and no need for wound dressing or adjuvants. Wound closure needed to sustain a minimum of 14 days after the first diagnosis and to be confirmed by independent blinded observers using wound photographs. If wound closure was achieved by surgical methods, the endpoint was not reached until the above criteria were met (e.g. only after removal of the suture). The determination of sufficient wound bed conditioning and the indication for surgical closure was carried out by the treating physician, as in clinical practice. The treating physician was not blinded to treatment allocation. During study planning, the following concomitant diseases and therapeutic measures with a possible influence on the primary study outcome wound closure (confounders) were identified:

diabetic neuropathic osteoarthropathy (DNOAP), severity of the foot wound according to Wagner Armstrong peripheral arterial occlusive disease , chronic venous insufficiency (CVI), extreme foot deformities and malpositions, untreated or therapy-refractory inflammation in the wound area, chronic anemia, heel necrosis, lymphedema, infection, heightened glycated hemoglobin (HbA1c) level, dialysis, hyperbaric oxygen (HBO) or normothermal therapy, application of recombinant or autologous growth factors to the study wound, and application of skin or dermal substitutes and with living cells that produce growth factors.

Secondary outcomes were wound closure rate after six months; time until optimal preparation of the wound bed (a minimum of 95% granulation), amputations and resections, wound size and wound tissue composition, pain and quality of life within 16 weeks; and recurrence within six months. The initial planned secondary endpoint of time until wound closure within 6 months was abandoned during the course of the study. It was found that a time-to-event survey was not possible outside the active study treatment period. This was mostly due to the fact that after this 16-week period weekly study visits were no longer an obligation and further patient care was no longer bound to the study site. Only one follow-up visit was planned and carried out after 6 months, in which wound or healing status and recurrences were documented.

Minor and major amputations were considered separately, whereas the disarticulation at the midtarsal joint (Chopart's amputation) was considered still to be minor. Wound size and wound tissue composition (percentage

of granulation tissue, fibrin and necrosis) were monitored at each study visit. Quality of life (QoL) was measured using the questionnaire Euro Quol 5D (EQ5D) at inclusion, end of the maximum treatment time or end of the therapy and at the six-month follow-up visit. At each study visit participants were asked to provide their assessment of wound-associated pain on a numerical rating scale (0 to 10). The incidence of serious adverse events (SAEs) within six months and the incidence of device-related and wound-related adverse events occurring within 16 weeks or until wound closure confirmation were safety endpoints of this trial.

Statistical analysis

Sample size calculation was performed using the expected difference between wound closure rates in both treatment arms based on information extracted from previously published studies. Armstrong and Lavery described a rate of complete wound closure in 56% of patients with NPWT and in 39% of patients in the corresponding control group [16]. Blume showed a rate of complete wound closure in 43% of patients treated with NPWT and 29% of patients in the control group [17]. We assumed a complete wound closure rate of 45% for NPWT and 30% in the SMWC group, resulting in a minimum difference of 15% after a treatment time of 16 weeks. Based on a type one error of $\alpha = 0.05$ and a type two error of $\beta = 0.2$ (corresponding to a power of 80%) a total sample size of 162 patients per group was calculated. The computer program of Dupont and Plummer was used for sample size calculation [27].

We performed all analyses based on a modified intention-to-treat (ITT) population that includes all randomized participants who have a valid baseline and at least one valid post baseline wound assessment. As a secondary approach a per-protocol (PP) analysis has been performed excluding patients with any serious protocol deviations, temporary changes from SMWC to NPWT, permanent wound treatment changes or without valid documentation until wound closure confirmation or end of maximum treatment time (EOMT). Safety data are presented on an ‘as treated’ basis. Subgroup analysis is presented for small vs big wound subpopulations. There was no interim analysis.

The superiority hypothesis was tested in parallel for wound closure rate and time to wound closure within16 weeks. Incidence of complete wound closure was analyzed using a chi-squared test (Fisher's exact test) comparing the two treatment arms. Time to complete wound closure was compared between the two treatment arms using a log-rank test. The method of Bonferroni-Holm was used for adjustment of the α-error for parallel confirmatory testing of both primary endpoints. Missing values have been incorporated as censored values.

Covariates thought to influence wound closure were analyzed for their effect on the two primary endpoints. Covariates were excluded from the analysis if the number of missing values was too high. First, the relevant

covariates were tested by means of a univariate analysis with regard to their effect on wound closure rate and time without consideration of the treatment arms. If there was a significant influence, the frequency of occurrence in the treatment arms was analyzed. Secondary, multivariate analyses were performed for both primary endpoints, taking into account treatment assignment and including all relevant covariates. The multivariate analysis of the primary endpoint wound closure rate was performed with binary logistic regression to describe the influence of the independent covariates (regressors) on the dependent dichotomous variable wound closure. The multivariate analysis of the primary endpoint time to wound closure was performed using a COX regression model.

Safety and secondary endpoints were analyzed using conventional univariate testing.

Within a priori planned subgroup analysis the ITT population was divided into a group of small wounds and a group of big wounds based on the wound surface area documented during the randomization visit. Wounds smaller than or equal to the total median wound surface (483 mm²) were assigned to the subgroup "small wounds". Patients with wound surface areas larger than the median value were assigned to the subgroup "large wounds". Since no citable scientific definition of a large wound was available at the time of study planning and the clinical experts involved could not make a decision, the median of all wounds was chosen as the criterion for the division into the two subgroups. Confirmatory analysis of primary and secondary endpoints was repeated for the subgroups.

Missing values for the following outcome parameters were replaced using the Last Observation Carried Forward (LOCF) method: wound closure rate, wound size and wound tissue quality, recurrence and amputation. The outcome parameters time to wound closure and time until optimal preparation of the wound bed did not require data replacement, since missing values are included in the analysis as right-censored values. If the wound closure is not confirmed to be closed after a minimum of 14 days, the wound is considered as an unsustained wound closure. All missing quality of life values (EQ-5D) were replaced with the overall quality of life assessment (visual analogue scale), if available. If there was no quality of life assessment, there was no replacement. For missing values of the demographic and baseline characteristics, which are necessary for the estimation of the regression coefficients, no replacement was performed.IBM SPSS Statistics (version 23) was used for all analyses.

This study is registered with ClinicalTrials.gov· number NCT01480362 and in the German Clinical Trial Registry, number DRKS00003347.

A data monitoring committee was formed to oversee overall study performance and safety.

Role of the funding source

Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds, which provided integrated care contracts for all study participants and for up to 7000 patients with acute and chronic wounds in Germany; defined basic rules for study design based on the requirements of the German authorities; and provided a critical review of the study protocol and the final report. The study was funded by the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary support and information about the used material. The manufacturers had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

Results

Between Dec 23, 2011 and August 12, 2014 386 patients were enrolled and randomly assigned to receive NPWT (181) or SMWC (187) in the DiaFu-study (**Error! Reference source not found.**) in overall 40 study sites, which recruited minimum 1 patient and maximum 76 patients. A full list of investigator can be found in the appendix. 13 clinical investigators randomized more than 10 patients. 23 study sites enrolled only between 1 and 4 patients. Most of these study sites refused further study participation due lack of time and staff for adequately performing the documentation. In the further course of the trial research nurses have been hired by the independent scientific institute overseeing the trial in order to support the documentation in the study sites whenever needed.

Baseline characteristics of the patients in the NPWT-and the SMWC-arm are similar in the ITT population (**Error! Reference source not found.**).

Baseline parameters (ITT population)	**Total N=345 (100 %)**	**NPWT N=171 (49·6%)**	**SMWC N=174 (50·4%)**
Male	267 of 345 (77·4%)	133of 171 (77·8%)	134 of 174(77·0%)
Female	78 of 345 (22·6%)	38 of 171(22·2%)	40 of 174(23·0%)
Age (years) (N=345)	67·8 (11·9)	67·6 of 171(12·3)	68·1 (11·5)
Height (N=340) (in cm)	174·1 (12·4)	173·4 (14·6)	174·8 (9·9)
Weight (N=335) (in kg)	93·3 (22)	92·7 (21·5)	93·8 (22·6)
Alcohol	N=341	N=169	N=172
Occasionally	157 (46%)	83 (48·5%)	74 (42·3%)
Chronic	10 (2·9%)	3 (1·8%)	7 (4·0%)
No	174 (51%)	83 (48·5%)	91 (52%)
Smoking	N=342	N=169	N=173
No	49 (14·3%)	25 (14·6%)	24 (13·7%)
Yes	293 (85·7%)	144 (84·3%)	149 (85·1%)
Number of years (Mean· SD)	34·8 (13·5)	36·5 (14·9)	33·1 (12·1)
Packs / day (Mean)	1·1	1·1	1·2
Drugs	N=341	N=169	N=172
Occasionally	1 (0·3%)	1 (0·6%)	0
Chronic	2 (0·6%)	0	2 (1·1%)
No	338 (97·7%)	168 (98·2%)	170 (97·1%)
Allergies	N=343	N=170	N=173
Yes	37 (10·7%)	16 (9·4%)	21 (12·0%)

No	306 (88·4%)	154 (90·1%)	152 (86·9%)
Subjective assessment of nutritional condition	N=342	N=169	N=173
Well-nourished	325 (94·2%)	162 (94·7%)	163 (93·7%)
Moderately malnourished or suspected malnutrition	11 (3·2%)	4 (2·3%)	7 (4%)
Malnourished	0 (0%)	0 (0%)	0 (0%)
Localization of the ulcer			
Regio calcanea	39 (11·3%)	17 (9·9%)	22 (12·6%)
Dorsum pedis	20 (5·8%)	13 (7·6%)	7 (4%)
Planta pedis	56 (16·2%)	30 (17·5%)	26 (14·9%)
Metatarsalia	147 (42·6%)	73 (42·7%)	74 (42·5%)
Phalanges distales	64 (18·6%)	31 (18·1%)	33 (19%)
Phalanges mediales	28 (8·1%)	14 (8·2%)	14 (8%)
Phalanges proximales	40 (11·6%)	21 (12·3%)	19 (10·9%)
Hallux	42 (12·2%)	24 (14%)	18 (10·3%)
Digitus pedis II	22 (6·4%)	10 (5·8%)	12 (6·9%)
Digitus pedis III	14 (4·1%)	7 (4·1%)	7 (4%)
Digitus pedis IV	20 (5·8%)	7 (4·1%)	13 (7·5%)
Digitus minimus	25 (7·2%)	12 (7%)	13 (7·5%)
Type of ulcer			
Primary ulcer	279 of 342 (80·9%)	136 of 170 (79·5%)	143 of 172 (82·2%)
Recurrence	63 of 342 (18·3%)	34 of 170 (19·9%)	29 of 172 (16·7%)
Duration of ulcer (days)			
N	335	168	167
Mean (SD)	189·7 (360·2)	217·1 (458·1)	162·1 (220)
Median	83	81	85
Min – Max	0 – 4468	0 – 4468	0 – 1826
Wound surface area at randomization (cm^2)			
Mean (SD)	1101 (2543)	1060 (1536)	1141 (3247)
Min-Max	[12 – 40773]	[20 – 13188]	[12 – 40773]

Table 1: The table shows patient demographics and baseline characteristics of the ITT- population. Data are N (%), Mean (SD), and Minimum – Maximum [Min – Max]. "N=" is stating the number of patients with actual available information. Findings, diagnoses and procedures documented by the investigators are presented.

The baseline of the identified factors possibly influencing wound closure is shown in Table 2.

Confounders at baseline (ITT population)	**Total N=345 (100 %)**	**NPWT N=171 (49·6%)**	**SMWC N=174 (50·4%)**
Presence of neuropathy (sensation loss according to the PEDIS classification system	250 of 334 (72·5%)	125 of 166 (73·1%)	125 of 168 (71·8%)
Presence of a diabetic neuropathic osteoarthropathy (DNOAP)	61 (17·7%)	30 (17·5%)	31 (17·8%)
Wagner grading of the ulcer			
1 - Superficial ulcer of skin or subcutaneous tissue	6 (1·7%)	2 (1·2%)	4 (2·3%)
2 - Ulcers extend into tendon, bone, or capsule	225 (65·2%)	110 (64·3%)	115 (66·1%)
3 - Deep ulcer with osteomyelitis, or abscess	85 (24·6%)	45 (26·3%)	40 (23%)
4 - Gangrene of toes or forefoot	26 (7·5%)	13 (7·6%)	13 (7·5%)
5 - Midfoot or hindfoot gangrene	3 (0·9%)	1 (0·6%)	2 (1·1%)
Presence of peripheral arterial occlusive disease (PAOD)	244 of 345 (70·7%)	121 of 171 (70·8%)	123 of 174 (70·7%)
Rutherford classification for chronic limb ischemia (Grade/Category)			
0/0 Asymptomatic—no hemodynamically significant occlusive disease	20 of 244 (8·2%)	8 of 121 (6·6%)	12 of 123 (9·8%)
I/1 Mild claudication	31 of 244 (12·7%)	16 of 121 (13·2%)	15 of 123 (12·2%)
I/2 Moderate claudication	20 of 244 (8·2%)	6 of 121 (5·0%)	14 of 123 (11·4%)
I/3 Severe claudication	5 of 244 (2·0%)	2 of 121 (1·7%)	3 of 123 (2·4%)
II/4 Ischemic rest pain	1 of 244 (0·4%)	1 of 121 (0·8%)	0 of 123 (0·0%)
III/5 Minor tissue loss—non-healing ulcer· focal gangrene with diffuse pedal ischemia	163 of 244 (66·8%)	87 of 121 (71·9%)	76 of 123 (61·8%)
III/6 Major tissue loss—extending above transmetatarsal level· functional foot no longer salvageable	4 of 244 (1·6%)	1 of 121 (0·8%)	3 of 123 (2·4%)
No chronic venous insufficiency (CVI)	259 of 302 (75·1%)	132 of 150 (77·2%)	127 of 152 (73%)
CVI Widmer I	25 of 302 (7·2%)	11 of 150 (6·4%)	14 of 152 (8%)
CVI Widmer II	12 of 302 (3·5%)	3 of 150 (1·8%)	9 of 152 (5·2%)
CVI Widmer III	6 of 302 (1·7%)	4 of 150 (2·3%)	2 of 152 (1·1%)
Presence of extreme foot deformities and malpositions of toes, foot or the entire limb	59 of 342 (17·1%)	26 of 170 (15·2%)	33 of 172 (19%)
Untreated or therapy-refractory inflammation in the wound area	15 of 343 (4·3%)	7 of 170 (4·1%)	8 of 173 (4·6%)
Presence of a heel necrosis	23 of 342 (6·7%)	10 of 168 (5·8%)	13 of 174 (7·5%)

No lymphedema Primary lymphedema Secondary lymphedema	282 of 340 (81·7%) 12 of 340 (3·5%) 46 of 340 (13·3%)	139 of 167 (81·3%) 5 of 167 (2·9%) 23 of 167 (13·5%)	143 of 173 (82·2%) 7 of 173 (4%) 23 of 173 (13·2%)
Clinical signs of inflammation (suspected infection)	159 of 344 (46·1%)	83 of 170 (48·5%)	76 of 174 (43·7%)
Local wound swab as part of the clinical routine	248 of 343 (71·9%)	126 of 170 (73·7%)	122 of 173 (70·1%)
Detection of germs within the local wound swab	205 of 247 (59·4%)	104 of 125 (60·8%)	101 of 122 (58%)
Hemoglobin N Mean (SD)	 177 of 345 9·5 (3,2)	 86 of 171 9·6 (3·1)	 91 of 174 9·4 (3·3)
Hemoglobin A1c (HbA1c) N Mean (SD)	 32 of 345 15·6 (18,3)	 13 of 171 16·8 (16,7)	 19 of 174 14·7 (19·6)
Requiring dialysis	29 of 343 (8·4 %)	15 of 170 (8·8%)	14 of 173 (8·0%)
Application of skin or dermal substitutes and with living cells that produce growth factors	0 of 341 (0%)	0 of 169 (0%)	0 of 172 (0%)

Table 2: The table shows the baseline of the identified factors possibly influencing wound closure in the ITT- population. Findings, diagnoses and procedures documented by the investigators are presented. Data are N (%), Mean (SD), and Minimum – Maximum [Min – Max].

Revascularization before study start	**Total** **N=345 (100 %)**	**NPWT** **N=171 (49·6%)**	**SMWC** **N=174 (50·4%)**
Performed revascularization before study start	23 of 345 (6·7%)	9 of 171 (5·3%)	14 of 174 (8·0%)
Percutaneous transluminal angioplasty (PTA)	13 of 23 (57%)	6 of 9 (67%)	7 of 9 (50%)
PTA + Stent	1 of 23 (4%)	0 of 9 (0%)	1 of 9 (7%)
Veins-Bypass	5 of 23 (22%)	2 of 9 (22%)	3 of 9 (21%)
Polytetrafluoroethylene (PTFE) Bypass	1 of 23 (4%)	0 of 9 (0%)	1 of 9 (7%)
Thromboendarterectomy and patch plastic	2 of 23 (9%)	0 of 9 (0%)	2 of 9 (14%)
Revascularization with influence on the wound	22 of 23 (96%)	9 of 9 (100%)	13 of 14 (93·9%)

Sufficient revascularization result	20 of 23 (88%)	7 of 9 (78%)	13 of 14 (93%)
Insufficient revascularization result	2 of 23 (9%)	1 of 9 (11%)	1 of 14 (7%)
Revascularization result not assessable	1 of 23 (4%)	1 of 9 (11%)	0 of 14 (0%)

Table 3: The table shows revascularization performed in the ITT- population before study start. Data are N (%).

Results for the primary outcomes in the ITT population

In the ITT population, the overall number of patients with wounds closed within 16 weeks was 46 of 345 (13·3%). Wound closure rate was higher in the NPWT arm (14·6%) than in the SMWC arm (12·1%) but this was not significant (p 0·53) as the difference in healing rate between the two groups was only four patients (2·5%) (Table 4). Wounds treated with NPWT were approximately at the same risk of remaining open like patients receiving SMWC (RR 0·97 [95% CI: 0·89-1·06]).

Wound closure rate	**Total N=345**	**NPWT N=171**	**SMWC N=174**	**p**
Patients with wound closure within 16 weeks N (%) [95% CI]	46 (13·3 %) [9·76 – 17·78]	25 (14·6%) [9·5 – 21·6]	21 (12·1%) [7·5 – 18·4]	0·53 (F)

Table 4: The table shows the wound closure rate for the ITT-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms. Wound closures within the maximum study treatment time of 16 weeks are shown with the number (N), the percentage (%) of patients, and the 95% Confidence Interval (CI). F=Fisher's Exact Test.

Beginning in week five the number of study patients with open wounds in the NPWT-arm was lower than in the SMWC-arm (Figure 2). There is no significant difference in the wound healing time between the two treatment arms (p = 0.244, Log Rank Test). Since the cumulative number of patients with open wounds was more than 70% after 16 weeks, we were not able to calculate medians for time to wound closure.

Results for the secondary outcomes in the ITT population

After 6 months the wound closure rate was higher in the SMWC- than in the NPWT-arm (36 of 174 [20·7 %] vs 24 of 171 [14· 0 %]), but the difference was not significant (p 0·12).

The time until optimal preparation of the wound for further treatment to achieve a complete epithelization (min 95 % granulation tissue) was significantly shorter for patients treated with NPWT (p 0·021) (Table 5).

Time until optimal preparation of the wound bed (min 95 % granulation tissue)	**Total N=183**	**NPWT N=100**	**SMWC N=83**	**p**
Mean (SD)	42·7 (39·0)	35·6 (34·6)	51·4 (42·6)	**0·008**
Median (IQR)	31 (64)	22·0 (48·0)	49·0 (53·6)	
Min - Max	0 - 127	0 - 127	0 - 115	

Table 5: The table shows time until optimal preparation of the wound for further treatment (min 95 % granulation tissue for the ITT-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms. Time until optimal preparation of the wound is described with mean (SD); median (IQR); and minimum (min) and maximum (max).

In the ITT-population wound surface area and wound volume decreased continuously during the study treatment time of 16 weeks in both treatment arms. The values are largely scattered. Detailed information about the course of wound surface area, volume and composition of tissues for both study populations can be found in the respective tables in the appendix. Wound surface area at each observation time point until end of maximum study treatment time of maximum of 16 weeks is separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis. The results of the blinded photo analysis using the Wound Healing Analyzing Tool (W.H.A.T.) were smaller than the values documented by the clinical investigators. Starting from a similar wound volume, the values also decreased continuously both in the NPWT- and in the SMWC-arm, wherein the values are smaller in the NPWT-arm than in the SMWC-arm at each observation time point.

Wound tissue composition is similar in both treatment arm s at baseline. Granulation tissue values increase during the study treatment period of 16 weeks and fibrin values decrease, with clinically documented values showing only minor differences between treatment arms. The values for necrotic tissue were very low and did not differ relevantly between the treatment arms. The results of the W.H.A.T. evaluation for granulation and fibrin deviate markedly from the values documented by the clinical investigators. Contrary to the clinically documented values, the W.H.A.T. evaluation shows low values for granulation and high values for fibrin.

No recurrences occurred during the study treatment time of 16 weeks. Between the end of the maximum study treatment time and the follow up at 6 months, 11 recurrences (6·4 %) occurred in the 171 patients in the NPWT arm. One patient had two recurrences. In the SMWC arm, five of 174 patients (2·9 %) had a recurrence. The difference is not significant (RR 2·24 [95%CI: 0·80-6·31]; (p 0·131)). , but the overall number of 17 recurrences in 16 patients was very low.

A total of 102 amputations or resections were performed in 71 patients (table 6). There were 45 amputations in 35 (20·5%) patients in the NPWT arm and 57 amputations in 36 (20·7 %) patients in the control arm. There is no significant difference in the number of patients with amputation or resection (p 1·00) or the overall number of performed interventions (p 0· 89) between NPWT and SMWC arm. Patients treated with NPWT were approximately at the same risk of undergoing an amputation or resection like patients treated with SMWC (RR: 0·99 [95%CI: 0·65-1·50]). A total of 69 patients (20 %) underwent a minor amputation (NPWT 33 [19·3 %] SMWC 36 [20·7 %], p 0·79). Two patients in the NPWT arm and no patient of the SMWC arm underwent a major amputation (p 0·25).

	Total **N=345**	**UWT** **N=171**	**SWT** **N=174**	**p**
Study participants with amputation or resection	71 20·6% [16·3 – 24,8]	35 20·5% [14,4 – 26,5]	36 20.7% [14·7 – 26,7]	1·00 (F)
Total number of amputations and resections	102	45	57	0·89 (U)
Number of amputations and resections per study participant				0·89 (U)
one event	49 (14·2%)	25 (14·6%)	24 (13·8%)	
two events	16 (4·6%)	10 (5·8%)	6 (3·4%)	
three events	4 (1·2%)	0 (0%)	4 (2·3%)	
four events	1 (0·3%)	0 (0%)	1 (0·6%)	
five events	1 (0·3%)	0 (0%)	1 (0·6%)	
Study participants with minor amputation	69 (20·0%)	33 (19·3%)	36 (20·7%)	0·79 (F)
Study participants with major amputation	2 (0·6%)	2 (1·2%)	0 (0%)	0·25 (F)

Table 6: The table shows the number of study participants with amputations / resections and the number of amputations / resections performed for the ITT-population. Data show the number (N) of participants, the percentage with the 95% Confidence Interval (95%CI), or the number of events accompanied with the respective percentage values in total and for both treatment arms. F = Fisher's Exact Test; U = Mann-Whitney U-Test.

Overall, pain levels were very low and decreased further during the study treatment time. The values hardly differ between the treatment arms at any observation time point. A table with pain levels can be found in the appendix.

At baseline Quality of life (EQ5D) had significant limitations in both treatment arms. Patients reaching the end of treatment within 16 weeks showed improved EQ5D levels in the NPWT arm and in the SMWC arm. Similar results have been found for patients who reached the end of the maximum treatment time without successful end of therapy. At the follow-up time after 6-months all patients still show increased EQ5D levels in both treatment arms. A table with detailed results for the EQ5D is provided in the appendix.

Safety results

269 adverse events (AE) (NPWT 167; SMWC 102) occurred during the active study treatment period of 112 days. For 96 (56· 1%) patients in the NPWT group and 72 patients (41· 4%) in the SMWC group at least one adverse event has been documented (p 0·007) but only 16 (10· 2%) of the AEs in the NPWT group were decided by the investigators to have a definite relation to the medical device. A total of 163 AEs occurring within the study observation period of 6 months were classified as serious adverse events (SAE) in the opinion of the investigators (NPWT 87, SMWC 76). In the NPWT arm, 63 patients (36·8 %) had at least one documented SAE. 45 patients had one and 18 patients had two or more SAEs. In the SMWC arm, 58 patients (33·3%) had a minimum of one SAE (45 patients with one SAE; 13 patients with two or more SAEs). The difference between the treatment arms was not significant (p 0·50). None of the SAEs in the NWPT group were documented as definitely or possibly related to the medical device by investigators. In one case in the SMWC group the investigator documented a definite relationship between the SAE and SMWC. In one case the investigator documented a possible relationship to SMWC in the NPWT group. Table 7 gives a detailed overview on the AEs documented within the study treatment time of 112 days.

Adverse Events (AE)	**NPWT**	**SMWC**

N=269	N=167	N=102
Day of occurrence (N) Mean (SD) Median (IQR)	167 37·5 (28,6) 30·0 (40·0)	102 42·7 (29·2) 38·0 (50·0)
Duration in days (N) Mean (SD) Median (IQR)	157 19·7 (29·0) 10·0 (20·0)	97 25·3 (38·6) 13·0 (22·0)
Severity (N) Mild Moderate Severe	161 64 (39·8%) 54 (33·5%) 43 (26·7%)	102 24 (23·5%) 38 (37·3%) 40 (39·2%)
AE expected / unexpected (N) Expected Unexpected	159 52 (32·7%) 107 (67·3%)	100 27 (27·0%) 73 (73·0%)
Relationship to the medical device (N) Yes Possible No Not assessable	157 16 (10· 2%) 11 (7·0%) 117 (74·5%) 13 (8·3%)	100 0 (0%) 2 (2·0%)* 94 (94·0%) 4 (4·0%)
* No treatment change to NPWT has been documented.		
Relationship to SMWC (N) Yes Possible No Not assessable	110 0 (0%) 5 (4·5%) 96 (87·3%) 9 (8·2%)	75 2 (2·7%) 0 (0%) 67 (89·3%) 6 (8·0%)
Relationship to treatment procedure (N) Yes Possible No Not assessable	148 6 (4·1%) 15 (10·1%) 111 (75·0%) 16 (10·8%)	96 4 (4·2%) 2 (2·1%) 80 (83·3%) 10 (10·4%)
Action taken (N) No Yes Cessation of therapy Temporary interruption of therapy Adaptation of therapy / treatment Other	146 23 (15·8%) 123 (84·2%) 10 of 123 (8·1%) 28 of 123 (22·8%) 52 of 123 (42·3%) 33 of 123 (26·8%)	94 23 (24·5%) 71 (75·5%) 0 of 71 (0%) 2 of 71 (2·8%) 48 of 71 (67·6%) 21 of 71 (29·6%)
Outcome (N) Fixed without consequences Condition improved	148 72 (48·6%) 32 (21·6%)	96 43 (44·8%) 26 (27·1%)

Fixed with consequences	22 (14·9%)	12 (12·5%)
Not fixed	4 (2·7%)	3 (3·1%)
Death	9 (6·1%)	6 (6·3%)
Unknown	9 (6·1%)	6 (6·3%)

Table 7: The table shows the adverse events in the active study treatment time of 112 days after randomization. Data are N (%), Mean (SD), and Median (IQR). "N=" is stating the number of patients with actual available information.

Secondary analyses and subgroups

The univariate analysis of predefined covariates potentially influencing wound closure in the ITT population showed that only the presence of an infection at the time of randomization was significantly associated with both the wound closure rate and time. The influencing factor "infection" was almost equally represented in both treatment arms (NPWT 35·1 [27·9 – 42·2] % N=60; SCWT 32·8 [25·8 – 39·7] % N= 57), so the treatment comparison was not influenced by this confounder. Of the a priori defined factors potentially influencing wound closure nine factors needed to be excluded because the number of missing values was too high or they were never documented by the investigators. The covariate peripheral arterial occlusive disease had significant influence on the time until wound closure (p 0·026) and infection had a significant influence on the wound healing rate (p 0·012). However, both influencing factors were almost evenly distributed over both study arms by randomization. Thus the group comparison has not been influenced by these confounders.

In the ITT population in 173 study participants the median wound surface area was smaller than 484 mm² and in 172 study participants wounds were bigger than 484 mm². In the NPWT arm 48·5% (N=83) of patients had small wounds and 51·5% (N=88) of patients had large wounds. The SMWC arm had 51·7% (N=90) small wounds and 48·3% (N=84) big wounds. The differences between the treatment arms were not significant.

An overview of the measures for small and big wounds and detailed results for this subgroup analysis can be found in the appendix. In the subgroup of big wounds, wound closure rate was significantly higher in the NPWT arm within 16 weeks (p 0·08). Patients with big wounds have a lower risk of not achieving wound closure within 16 weeks when treated with NPWT (RR 0·91 [95%CI: 0·82-1·0]). In the subgroup of big wounds a significantly faster wound closure was achieved in the NPWT arm (p 0·027) (Figure 3). Time until complete, sustained and verified wound closure was not significantly different between the treatment arms in the subgroup of small wounds (Figure 4).

In the subgroup of small wounds the time to reach 95 % granulation tissue was significantly shorter for the patients treated with NPWT (p 0·005). Time until optimal wound bed preparation was shorter in the NPWT arm in the subgroup of big wounds, but did not significantly differ to the result of the SMWC arm (p 0·27). There are no relevant or significant differences in the overall number of patients with amputation or resection between the

treatment arms in both subgroups. Both major amputations were performed in patients with big wounds treated with NPWT. Due to the low overall number of recurrences (N=16) we were not able to perform a subgroup analysis for this outcome parameter.

Results for the primary and secondary outcomes in the PP population

In the PP-population patients treated with NPWT showed a 14·5 % higher wound closure rate within 16 weeks than patients treated with SMWC (Appendix), but the difference was not significant (p 0·053). Wounds treated with NPWT had a lower risk of remaining open after 16 weeks (RR 0·82 [95%CI: 0·66-1·03]) than wounds treated with SMWC. Time to wound closure in the NPWT arm was significantly shorter (p=0·004) (Figure 5). After 6 months, wound closure rate in the SMWC-arm was higher than in the NPWT-arm, but the difference was not significant (p 0·84). As in the ITT population, optimal wound bed preparation was achieved significantly faster in patients receiving NPWT (p<0·001). Patients receiving NPWT had a higher risk of recurrence than those in the control group (RR 1·50 [95%CI: 0·37-6·01]), however there was no significant difference between the treatment arms regarding the total number of recurrences (p 0.38) or the number of patients with recurrences (p 0·69). 9 patients in the NPWT group and 21 (21·4%) patients in the SMWC group had an amputation or resection (NPWT RR 1·07 [95%CI: 0·53-2·15]). Neither the number of patients with amputations or resections (NPWT 9 (20·5%) SMWC 21 (21·4%) p 0·83) nor the number of amputations or resections performed (NPWT 11 SMWC 28 p 0·86) differ significantly between the treatment arms. No major amputations were performed in the PP population. In the PP-population wound surface area started at smaller baseline levels and decreased faster than in the ITT-population whereas the measures were smaller in the NPWT arm than in the SMWC arm. Wound volume started higher in the NPWT arm and ended at similar levels for the treatment arms after decreasing continuously during the treatment period. This effect was stronger in the SMWC arm. Wound volume measures were lower in the PP-population than in the ITT-population. Wound tissues had a similar course over time like in the ITT population but showed higher values for granulation as well as lower values for fibrin and necrosis in the PP population. Like in the ITT population, pain levels were very low, showing no relevant difference between the treatment arms, and further decreased during the study treatment period. In the PP-population EQ5D values are higher than in the ITT population during screening, but still show that all patients have significant problems. In the NPWT arm QoL measures are similar to those of the SMWC arm for patients reaching end of maximum treatment time before end of therapy. EQ5D shows higher values for patients reaching the end of therapy during the study treatment time of 16 weeks. Detailed results for the PP population can be found in the appendix.

Additional results on treatment compliance and documentation quality

29 (17·0%) patients in the NPWT group had a temporary therapy change to SMWC (mean duration 20·5 ± 21·6 days). In the SMWC group, 17 (9·8%) patients had a temporary therapy change to NPWT (mean duration 28·9 ± 21·6 days). For only 2 of the 29 NPWT patients (6·9%) with a temporary therapy change to SMWC the wound closure was achieved within 16 weeks, whereas 16·2% (23 von 142) of the wounds of the NPWT patients without therapy change were completely closed.

A total of 57·3% (98 of 171) of the patients randomized to NPWT completed treatment before achieving a granulation surface of the wound of at least 95%. Fewer patients with this premature end of NPWT (4·7%, N=8) achieved a complete wound closure than patients with no premature end of therapy (9·9, N=17). Mean NPWT-duration until premature end of therapy was 28.5 days (SD 24·1), while a mean granulation area of 59.6% (SD 30· 5) was achieved.

For 131 patients (76· 6 %) in the NPWT arm less than the required three dressing changes per week were documented. 19 patients (14· 5 %) with this protocol violation achieved a complete wound closure. Six (15·4%) of the 39 NPWT patients who received at least 3 therapy changes per week achieved a complete wound closure.

In the electronic Case Report Forms (eCRF) a wound closure was documented for 96 patients (NPWT 56 of 171; SMWC 40 of 174), but only for 46 patients (NPWT 25; SMWC 21) all criteria for a complete, verified and sustained wound closure have been met. For the wound closure visit seven wound photographs (NPWT 7; SMWC 0) and for the wound closure confirmation visit four photographs (NPWT 3; SMWC 1) were missing. In addition, two of the existing wound photographs for the wound closure (NPWT 0; SMWC 2) and two photographs for the wound closure confirmation (NPWT 1, SMWC 3) were not assessable by the blinded observers due to serious quality issues. Furthermore 23 (NPWT 15; SMWC 8) existing and assessable wound photographs were not able to confirm the wound closure and 3 (NPWT 1; SMWC 2) photographs were not able to confirm the wound closure after 14 days.

Discussion

The DiaFu-study did not demonstrate significant superiority in wound closure rate or time to complete wound closure for either NPWT or SMWC. Wound closure rates were higher in the NPWT arm but did not significantly differ from those in the SMWC arm. Optimal preparation of the wound bed (95% granulation tissue) was achieved significantly earlier when using NPWT in both study populations (ITT and PP), but the overall rate of wound closures was low. Time to wound healing in the NPWT group is lower than in the SMWC arm while the difference between the treatment groups becomes statistically significant only in the PP population. Thus, with this study we were not able to confirm our hypothesis that wound closure can be achieved more often and faster with NPWT than with SMWC when used in the complex treatment process for diabetic foot ulcers in clinical practice. Findings of previous RCTs that showed a significant superiority in healing when using NPWT on amputation and chronic wounds [16, 17] could not be confirmed by this trial. We were able to show that although significantly more adverse events have been documented in the NPWT group only a small number of these events were related to the medical device according to the investigator`s assessment. Mortality rates were very low in both groups and there was no significant difference between the treatment arms regarding amputations and resections performed during the study. Only two major amputations have been performed in patients with big wounds treated with NPWT. None of the two treatments resulted in an additional impairment of the patients' quality of life during study treatment time or follow up. Time until complete wound closure was significantly shorter with NPWT than with SMWC in the subgroup of big wounds, which indicates that NPWT has the potential to be valuable treatment method for this kind of wounds.

The DiaFu-study was designed to evaluate effectiveness and safety of NPWT for chronic diabetic foot wounds in real-life clinical practice while avoiding any bias that have been described by several systematic reviews [18-22]. Methods against bias have been implemented whenever possible, but within this study shortcomings in documentation quality and missing compliance to therapy guidelines negatively impact the results.

None of the previous studies examined the influence of therapy adherence and target-oriented therapy application on the clinical outcome. Our study is the first to show that temporary therapy changes and premature therapy cessation have a negative impact on reaching the patient relevant therapy outcome complete wound healing in study participants treated with NPWT. The results of this additional therapy compliance analysis indicate that if NPWT is not used with a clear focus and applied consistently under consideration of all prescriptions of the authorities and the manufacturers, the desired treatment outcome will not be reached. Together with the poor documentation quality, these circumstances could have led to the fact that the expected superiority of the NPWT, which was shown in previous studies, could not be achieved in DiaFu-study.

Not addressing and analyzing all factors influencing the overall treatment outcome like targeted pressure relief, infection control and adequate treatment of the underlying disease during the study treatment and observation period may be seen as a limitation of this health care research study. Study sites have been selected based on a self-disclosure by means of a qualification checklist and cross checks using quality reports. This ensured that all prerequisites were met for guideline-compliant patient care. Nevertheless, even in the application of NPWT there were deviations from the standards. Anyway, questioning the quality of investigators' treatment was not the main focus of this health services research trial. Evaluating the individual treatment quality within a single RCT is neither feasible nor effective.

Other than previous studies the DiaFu-study evaluated the effectiveness of NPWT most closely to real-life using a patient population as diverse as in clinical practice. The DiaFu-study therefore included patients with chronic diabetic foot ulcers of neuropathic and angiopathic origin, regardless of whether a simple wound cleansing, tissue debridement or even amputation was necessary prior to application of wound therapy targeted to achieve complete wound closure. Thus, results can easier be generalized and applied in routine practice settings, but the problems of the clinical routine also affect data quality and statements about specific patient groups are not possible.

Some of the previous studies did choose granulation tissue formation for primary outcome. Wound bed preparation and granulation tissue formation are important prerequisites for wound healing, but the selection of a patient-relevant primary endpoint and the implementation of adequate measures against bias as required by the German authorities have been a priority during planning. Preparing the wound bed significantly faster with NPWT is an important result for the therapeutic approach, but is not a proof of effectiveness and cannot serve as a basis for the benefit assessment of NPWT. Thus, complete wound closure needed to be chosen to be the primary outcome rather than the evaluation of the functionality within in the purpose of the evaluated medical device, which is still part of a complex treatment process.

In order to support the decision making process of the German G-BA on general reimbursement of NPWT in German outpatient care the DiaFu-study was conducted with a population according to the clinical routine without excluding specific patient groups; with therapy application in the discretion of the attending physician; and with evaluation of patient relevant outcome. Within this setting we were not able to show a significant superiority of NPWT for achieving wound closure, but despite all limitations NPWT showed a significant superiority in optimal wound bed preparation. This indicates that NPWT works according to its intended use and has at least a potential to be a valuable treatment alternative. Anyway, in the complex treatment process of the diabetic wound a satisfactory rate of wound closure was reached with neither NPWT or with SMWC.

Conclusions

NPWT is not superior to SMWC when evaluated in German real-life clinical practice. Missing compliance with therapy guidelines and poor documentation quality led to restrictions in achieving the patient-relevant endpoint complete wound closure and prevents a clear proof of effectiveness. The question if NPWT is superior to SMWC for treating diabetic foot wounds remains unanswered due to the limitations of the DiaFu-study. An overall low number of wound closures indicate problems with the overall treatment quality. The results of the PP-population suggest that without the negative impact of premature treatment cessation, temporary changes of the randomized therapy and partly incomplete documentation, NPWT may be more effective for treating diabetic foot wounds than SMWC. NPWT should be evaluated again after implementation of a sufficient, well-considered and widely-accepted concept for quality control. In a future health care research study the treatment outcome before and after the implementation of these quality measures should be evaluated, for which the results of this trial may serve as a basis. Practitioners worldwide should review their processes with regard to the problems described here.

Ethics approval and consent to participate

Ethical approval of the main ethical committee (EC): Ethical Committee of the University of Witten-Herdecke, has been fully granted without any conditions. Due to performing the trial according to § 23b MPG (German Medical Device Act), participating study sites in Germany only received a consultation for the main clinical investigator according to professional law by the respective EC. All investigators have been fully approved by the respective ECs. An evaluation of the study's content by ECs of participating study sites in Germany was not applicable. All study participants gave written informed consent prior to randomization and any trial related procedure.

Data sharing

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Datasets are available in German language.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare:

The German statutory health insurance companies commissioned the Witten/Herdecke University (UW/H) to plan, conduct, analyze and publish the study. Dörthe Seidel is an employee of the UW/H. The study has been financed by the manufacturers KCI (Acelity) and Smith&Nephew. Dörthe Seidel received a consulting fee for the presentation of the study during an event organized by the manufacturer Hartmann. During study planning and conduct Edmund Neugebauer was an employee of the UW/H. He was the director of the IFOM.

The clinical investigators Martin Storck, Holger Lawall, Gernold Wozniak, Peter Maukner, Dirk Hochlenert, Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink received a case fee of 1000 € for each patient included in the DiaFu-study in order to compensate for the additional organizational and especially the documentation effort during trial conduct. Furthermore all investigators received compensation for travelling to the investigator meetings. The institutions of the investigators used integrated care contracts for NPWT during study conduct in order to provide best practice for the study participants during outpatient care.

Gernold Wozniak and Walter Wetzel-Roth are members of the scientific advisory board of the manufacturer Kinetic Concepts Incorporated (KCI) (now Acelity).

Funding

Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds, which provided integrated care contracts for all study participants and for up to 7000 patients with acute and chronic wounds in Germany; defined basic rules for study design based on the requirements of the German authorities; and provided a critical review of the study protocol and the final report. The study was funded by the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary support and information about the used material. The manufacturers had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

Authors' contributions

Dörthe Seidel was the principal coordinating investigator. She conceived the study, reviewed the scientific literature, and was responsible for study design, data analysis, data interpretation, writing and reviewing of the report. She is the lead author and takes overall responsibility for this report. She affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Martin Storck and Holger Lawall were study investigators and contributed to study design, data collection and interpretation, and reviewed the report.

Gernold Wozniak, Peter Maukner, Walter Wetzel-Roth and Dirk Hochlenert were study investigators and contributed to data collection and data interpretation and reviewed the report.

Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink were study investigators and contributed to data collection and reviewed the report.

Edmund Neugebauer contributed to study design and data interpretation and reviewed the report.

All authors approved the final version of the report.

Acknowledgements

The authors thank all investigators, nurses, patients and partners for supporting the study.

At least one patient was included in the following facilities: HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für Gefäßchirurgie Ludwig-Erhard-Straße 100 65199 Wiesbaden; Asklepios Westklinikum Hamburg Zentrum für

Gefäßmedizin Suurheid 20 22559 Hamburg; Knappschaftskrankenhaus Bottrop Gefäßchirurgische Klinik Osterfelderstraße 157 46242 Bottrop; Städtisches Klinikum Karlsruhe Klinik für Gefäß- und Thoraxchirurgie Moltkestraße 90 76133 Karlsruhe; Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Merheimer Straße 217 50733 Köln; Klinikum Döbeln Abt. für Gefäßchirurgie Sörmitzer Straße 10 04720 Döbeln; Klinikum Bielefeld Mitte Klinik für Allgemeine Innere Medizin Teutoburger Straße 50 33604 Bielefeld; Klinikum Frankfurt/Oder Klinik für Gefäßchirurgie Müllroser Chaussee 7 15236 Frankfurt/Oder; Weißeritztal-Kliniken GmbH Medizinische Klinik III Bürgerstraße 7 01705 Freital; Krankenhaus Porz am Rhein Klinik für Gefäßchirurgie Urbacher Weg 19 51149 Köln; St. Remigius Krankenhaus Opladen Innere Medizin An St. Remigius 26 51379 Leverkusen; Marien Hospital Dortmund-Hombruch Klinik für Innere Medizin/Diabetologie Gablonzstraße 9 44225 Dortmund; Zentrum für Chirurgie Klinik für Gefäß- und Endovascularchirurgie Theodor-Stern-Kai 7, Haus 23C/EG 60590 Frankfurt am Main; Facharzt für Chirurgie Thorax-Kardiovaskularchirurgie Hindenburgstraße 1 86807 Buchloe; Helfenstein Klinik Geisslingen Allgemein- und Viszeralchirurgie Eybstraße 16 73312 Geislingen/Steige; Paracelsus-Klinik am Silbersee Wundzentrum Hannover Oertzeweg 24 30851 Langenhagen; Klinikum Darmstadt Chirurgische Klinik III Grafenstraße 9 64283 Darmstadt; Ortenau Klinikum Offenburg-Ebertplatz Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ebertplatz 12 77654 Offenburg; Thüringen-Kliniken "Georgius Agricola" GmbH Klinik für Gefäßchirurgie Rainweg 68 07318 Saalfeld; Klinikum Dorothea Christiane Erxleben GmbH Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ditfurter Weg 24 06484 Quedlinburg; Franziskus-Krankenhaus Berlin Abt. für Innere Medizin Budapester Straße 15-19 10787 Berlin; Hegau-Bodensee Klinikum Radolfzell (HBK) Klinik für Innere Medizin Hausherrenstraße 12 78315 Radolfzell; Diabetologische Schwerpunktpraxis Dr. med. Hansjörg Mühlen & Partner Ruhrorter Straße 195 47119 Duisburg; Kliniken Maria Hilf Mönchengladbach Klinik für Gefäßchirurgie und Angiologie Sandradstraße 43 41061 Mönchengladbach; Städtisches Klinikum München/Bogenhausen Klinik für Endokrinologie, Diabetologie und Angiologie Englschalkingerstraße 77 81925 München; Gerhard Rothenaicher Facharzt für Chirurgie Cosimastraße 2 81927 München; Bürgerhospital Frankfurt am Main Interdisziplinäres Zentrum Diabetischer Fuß (DDG) Nibelungenallee 37- 41 60318 Frankfurt am Main; Gemeinschaftspraxis für Chirurgie und Gefäßmedizin Drs. Alter/Pourhassan/Heim Klosterstraße 12 46145 Oberhausen; Ev. KH Königin Elisabeth Herzberge gGmbH Abt. für Kardiologie, Angiologie und Diabetologie Herzbergstraße 79 10365 Berlin; Städtisches Klinikum Neunkirchen gGmbH Abt. für Gefäßchirurgie & Phlebologie Brunnenstraße 20 66538 Neunkirchen; Westküstenklinikum Heide Klinik für Viszeral- und Gefäßchirurgie Esmarchstraße 50 25746 Heide/Holstein; Chir. Praxisgemeinschaft am Bayenthalgürtel Praxis Dr. med. Gerald Engels Bayenthalgürtel 45 50968 Köln; Malteser Krankenhaus – St.

Franziskus-Hospital Medizinische Klinik I, Abt. für Diabetologie Waldstraße 17 24939 Flensburg; St. Marienkrankenhaus Siegen gGmbH Klinik für Gastroenterologie Kampenstraße 51 57072 Siegen; Krankenhaus Bietigheim Klinik für Innere Medizin, Kardiologie, Endokrinologie, Diabetologie und Internistische Intensivmedizin Riedstraße 12 74321 Bietigheim-Bissingen; Asklepios Kliniken Harburg Eißendorfer Pferdeweg 52 21075 Hamburg; Diabetologikum Ludwigshafen Diabetes-Schwerpunktpraxis Ludwigsplatz 9 67059 Ludwigshafen; Mariannen-Hospital Werl Abt. für Chirurgie Unnaer Straße 15 59457 Werl; Diabetes Klinik GmbH & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim; Institut für Diabetesforschung Münster GmbH Hohenzollernring 70 48145 Münster.

The study was initiated by a consortium of 19 statutory German health insurance funds represented by the AOK federal association (AOK-Bundesverband – AOK-BV), the association of alternative health insurance funds (Verband der Ersatzkrankenkassen – vdek) and the minors (Knappschaft). In order to guarantee outpatient care for all study participants without any restrictions, the contracting health insurance companies provided integrated care contracts for outpatient negative pressure wound therapy.

A project advisory board was implemented to coordinate all processes and project partners. The board comprised two representatives each from the statutory health insurance funds, the management company and the sponsor as well as one representative each from the participating medical device manufacturers (KCI and smith & nephew). Representing the contracting authority (statutory German health insurance funds) Dr. Gerhard Schillinger (AOK-BV) and Ute Leonhard (vdek) acted as contact persons for all aspects of the project.

The management company “Gesundheitsforen Leipzig” has been entirely responsible for the logistics of the study. Central tasks of the management company included the recruitment of study sites and patients, the development of the IT infrastructure including the documentation, communication and invoicing software as well as the processing of all payments.

The manufacturers Kinetic Concepts Incorporated (KCI) (Acelity) and smith & nephew provided the NPWT devices as well as support and training for the investigators and financed the study.

The Private University of Witten/Herdecke gGmbH acted as the Sponsor of the trial and the Institute for Research in Operative Medicine with its former director Prof. E.A.M. Neugebauer, the current interim head Prof. Rolf Lefering and the head of the division for clinical research Dörthe Seidel was responsible for the scientific conception, the evaluation as well as the reporting and publication of the study. Prof. Dr. Rolf Lefering was responsible for the statistical planning and analysis. PD Dr. Peter Krüger was responsible for the data management of the study. Special thanks are going to Stefan Bauer, who supported the data management as well as the statistical analysis and reporting.

We would like to thank Sophie Thorn, who checked the article as a native English speaker with regard to spelling and grammar.

List of figures:

References

1. World Health Organization, *Global report on diabetes.* 2016, WHO: http://www.who.int/diabetes/global-report/en/.
2. International Diabetes Federation, *IDF Diabetes Atlas*. 2015, IDF: www.diabetesatlas.org.
3. Yazdanpanah, L., M. Nasiri, and S. Adarvishi, *Literature review on the management of diabetic foot ulcer.* World J Diabetes, 2015. **6**(1): p. 37-53.
4. Leone, S., et al., *[Epidemiology of diabetic foot].* Infez Med, 2012. **20 Suppl 1**: p. 8-13.
5. Wu, L., et al., *Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews.* Cochrane Database Syst Rev, 2015(7): p. CD010471.
6. Norman, G., et al., *Dressings and topical agents for treating venous leg ulcers.* Cochrane Database Syst Rev, 2018. **6**: p. CD012583.
7. Wu, S.C., W. Marston, and D.G. Armstrong, *Wound care: the role of advanced wound-healing technologies.* J Am Podiatr Med Assoc, 2010. **100**(5): p. 385-94.
8. Fleischmann, W., et al., *[Vacuum sealing as treatment of soft tissue damage in open fractures].* Unfallchirurg, 1993. **96**(9): p. 488-92.
9. Argenta, L.C. and M.J. Morykwas, *Vacuum-assisted closure: a new method for wound control and treatment: clinical experience.* Ann Plast Surg, 1997. **38**(6): p. 563-76; discussion 577.
10. Morykwas, M.J., et al., *Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation.* Ann Plast Surg, 1997. **38**(6): p. 553-62.
11. Morykwas, M.J., et al., *Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine.* Ann Plast Surg, 2001. **47**(5): p. 547-51.
12. Gregor, S., et al., *Negative pressure wound therapy: a vacuum of evidence?* Arch Surg, 2008. **143**(2): p. 189-96.
13. Peinemann, F. and S. Sauerland, *Negative-pressure wound therapy: systematic review of randomized controlled trials.* Dtsch Arztebl Int, 2011. **108**(22): p. 381-9.
14. Ubbink Dirk, T., et al. *Topical negative pressure for treating chronic wounds*. Cochrane Database of Systematic Reviews, 2008. DOI: 10.1002/14651858.CD001898.pub2.
15. Vikatmaa, P., et al., *Negative pressure wound therapy: a systematic review on effectiveness and safety.* Eur J Vasc Endovasc Surg, 2008. **36**(4): p. 438-48.
16. Armstrong, D.G. and L.A. Lavery, *Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial.* Lancet, 2005. **366**(9498): p. 1704-10.
17. Blume, P.A., et al., *Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial.* Diabetes Care, 2008. **31**(4): p. 631-6.
18. Dumville, J.C., et al., *Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus.* Cochrane Database Syst Rev, 2013(10): p. CD010318.
19. Rhee, S.M., et al., *Negative Pressure Wound Therapy Technologies for Chronic Wound Care in the Home Setting*. 2014, Johns Hopkins University Evidence-based Practice Center: Rockville (MD).
20. Canadian Agency for Drugs and Technologies in Health, *Negative Pressure Wound Therapy for Managing Diabetic Foot Ulcers: A Review of the Clinical Effectiveness, Cost-effectiveness, and Guidelines*. 2014: Ottawa (ON).
21. Liu, S., et al., *Evaluation of negative-pressure wound therapy for patients with diabetic foot ulcers: systematic review and meta-analysis.* Ther Clin Risk Manag, 2017. **13**: p. 533-544.
22. Liu, Z., et al., *Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus.* Cochrane Database Syst Rev, 2018. **10**: p. CD010318.
23. IQWiG. *General Methods*. 2018; Available from: https://www.iqwig.de/en/methods/methods-paper.3020.html.
24. Seidel, D., et al., *Negative pressure wound therapy versus standard wound care in chronic diabetic foot wounds: study protocol for a randomized controlled trial.* Trials, 2014. **15**: p. 334.

25. Bauer, H., et al. *Typ-2-Diabetes: Präventions- und Behandlungsstrategien für Fußkomplikationen*. Nationale Versorgungs Leitlinien, 2010.

26. Ruttermann, M., et al., *Local treatment of chronic wounds: in patients with peripheral vascular disease, chronic venous insufficiency, and diabetes.* Dtsch Arztebl Int, 2013. **110**(3): p. 25-31.

27. Dupont, W.D. and W.D. Plummer, Jr., *Power and sample size calculations. A review and computer program.* Control Clin Trials, 1990. **11**(2): p. 116-28.

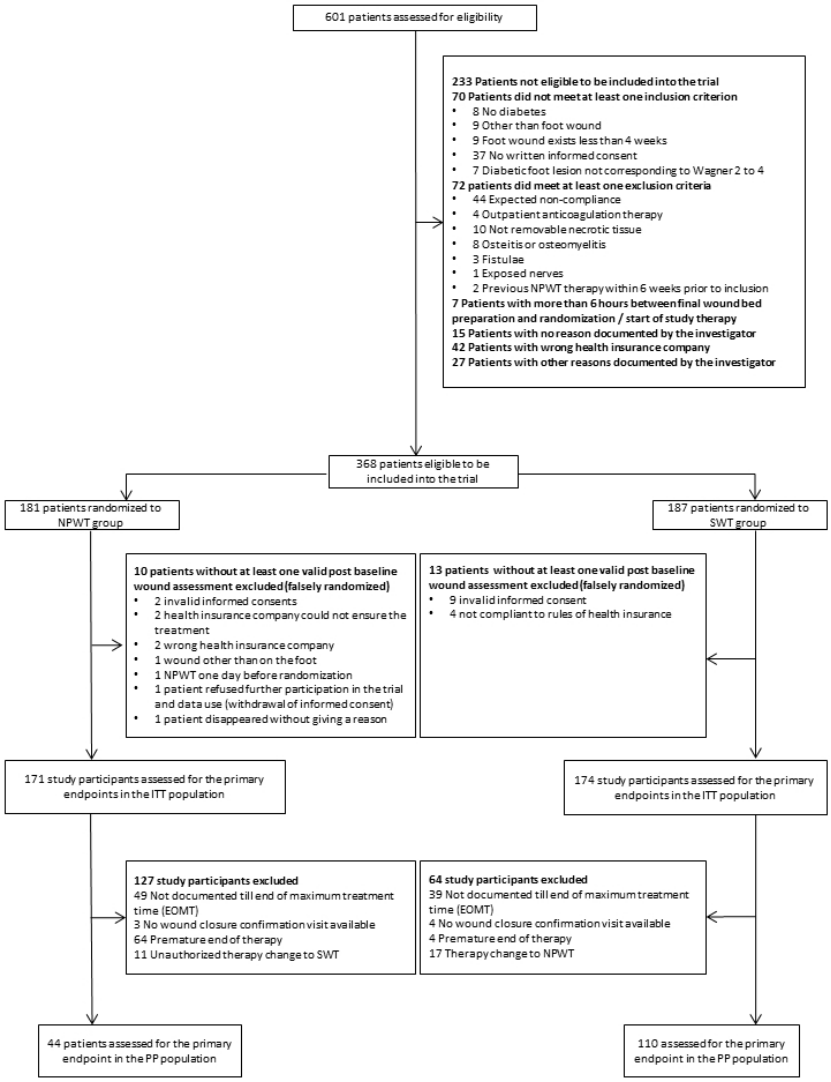


Figure 1: Trial profile (CONSORT)

190x275mm (96 x 96 DPI)

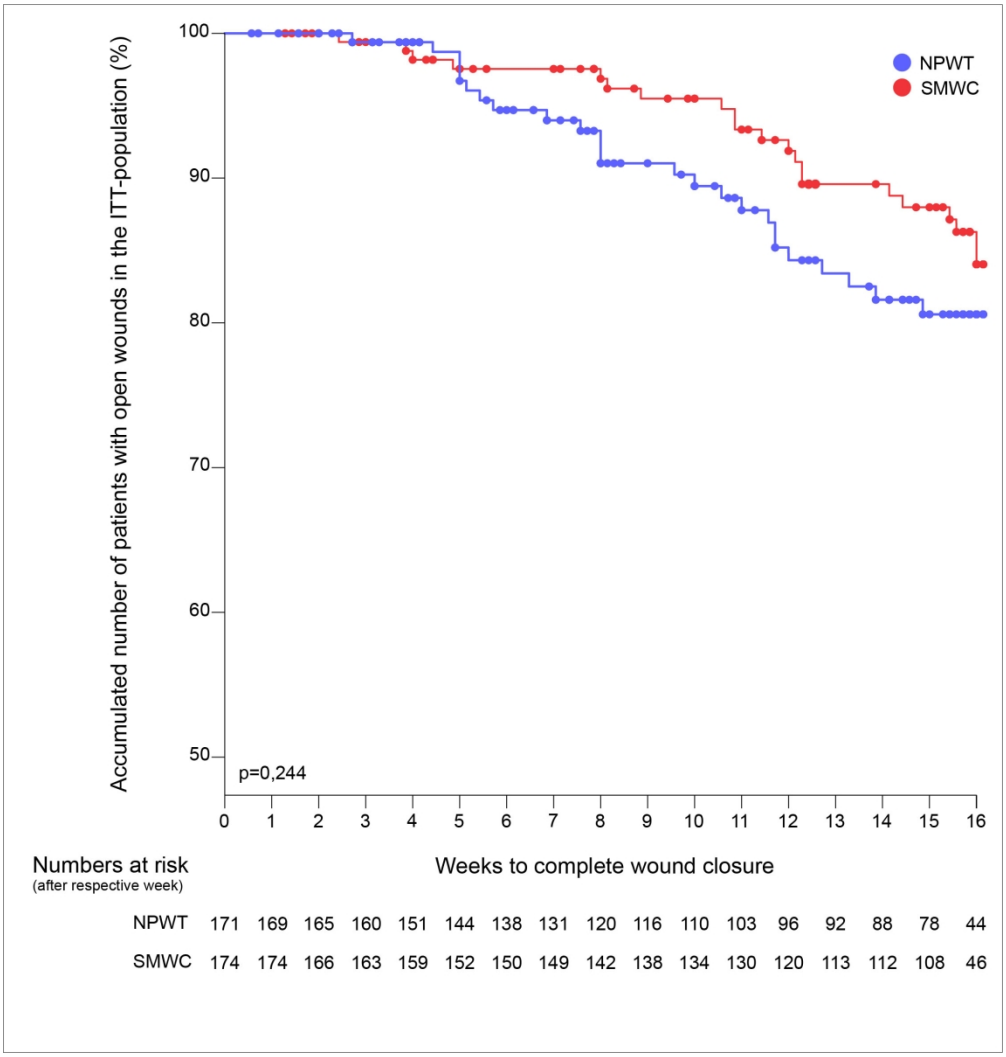


Figure 2: Time to wound closure in the ITT-population

189x198mm (300 x 300 DPI)

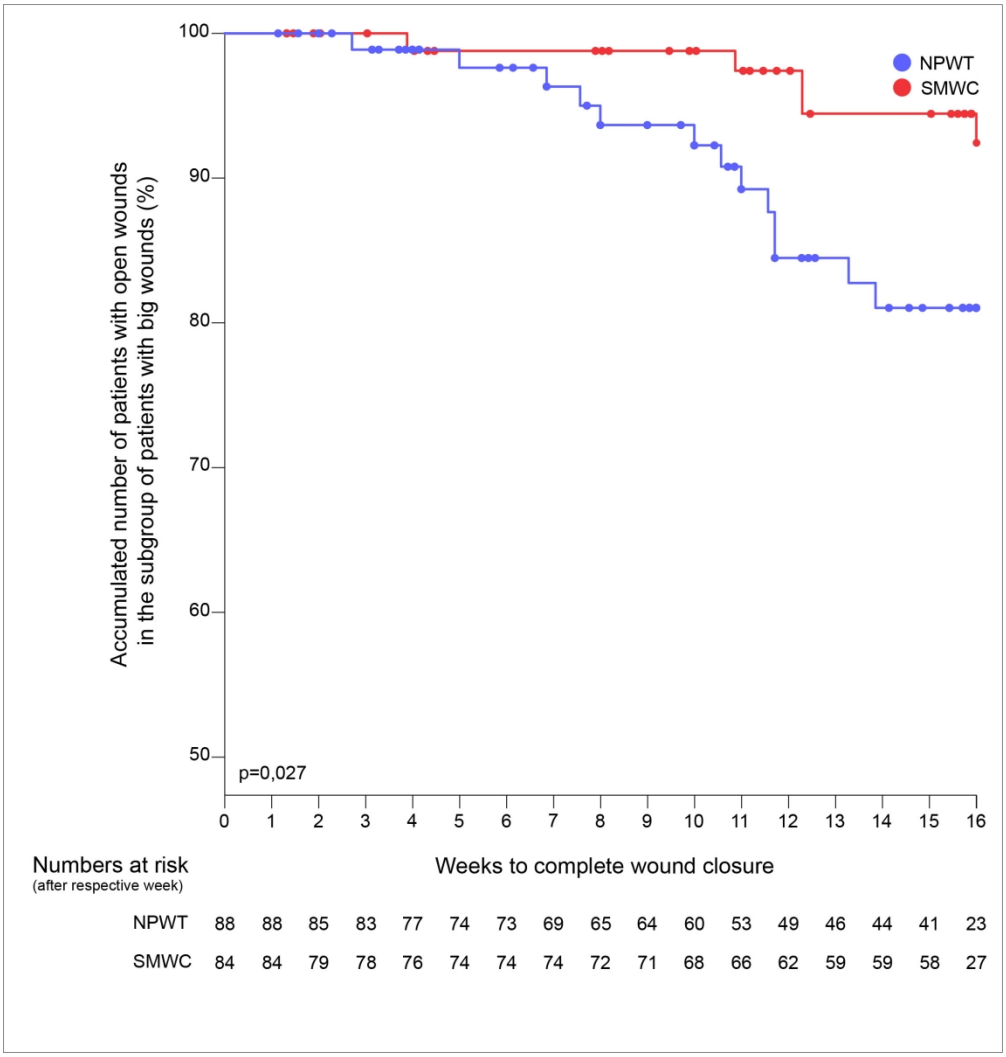


Figure 3: Time to wound closure in the subgroup of big wounds

189x198mm (300 x 300 DPI)

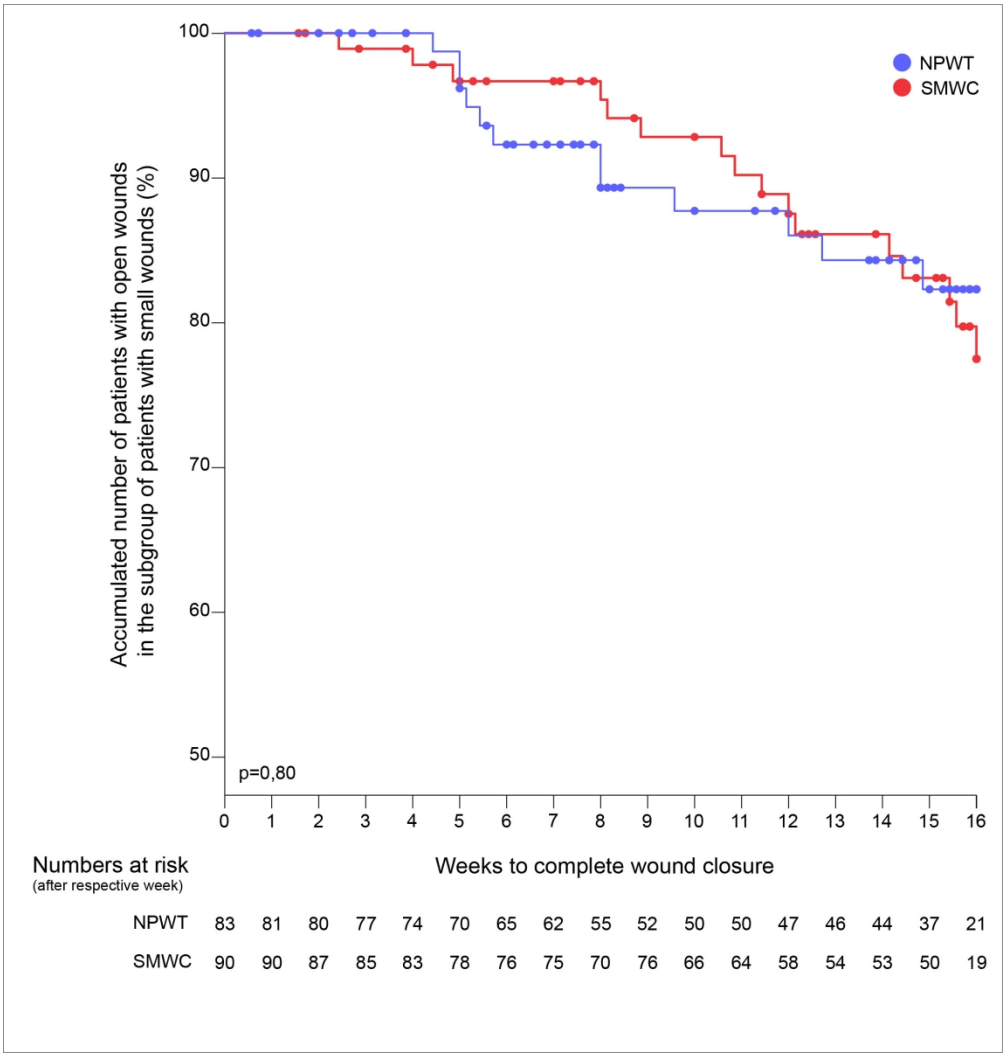


Figure 4: Time to wound closure in the subgroup of small wounds

189x198mm (300 x 300 DPI)

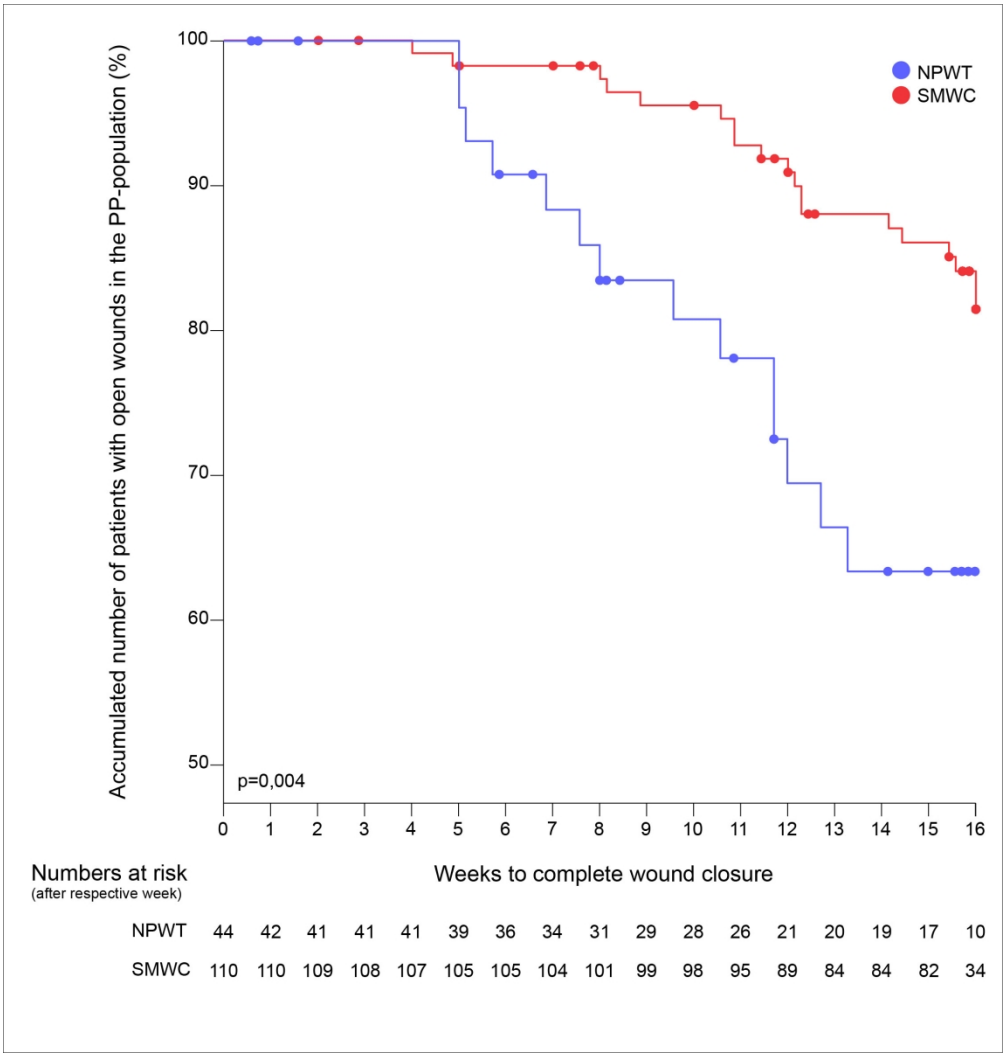


Figure 5: Time to wound closure in the PP-population

189x198mm (300 x 300 DPI)

Supplementary Appendix

Table of contents:

List of investigators:

At least one patient was included in the following facilities:

1. PD Dr. med. Achim Neufang	HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für Gefäßchirurgie Ludwig-Erhard-Straße 100 65199 Wiesbaden
2. Dr. med. Holger Lawall	Asklepios Westklinikum Hamburg Zentrum für Gefäßmedizin Suurheid 20 22559 Hamburg
3. Prof. Dr. med. Gernold Wozniak	Knappschaftskrankenhaus Bottrop Gefäßchirurgische Klinik Osterfelderstraße 157 46242 Bottrop
4. Prof. Dr. med. Martin Storck	Städtisches Klinikum Karlsruhe Klinik für Gefäß- und Thoraxchirurgie Moltkestraße 90 76133 Karlsruhe
5. Dr. med. Dirk Hochlenert	Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Merheimer Straße 217 50733 Köln
6. Dr. med. Gudrun Hetzel	Klinikum Döbeln Abt. für Gefäßchirurgie Sörmitzer Straße 10 04720 Döbeln
7. Dr. med. Karsten Jungheim	Klinikum Bielefeld Mitte Klinik für Allgemeine Innere Medizin Teutoburger Straße 50 33604 Bielefeld
8. Dr. med. Michael Petzold	Klinikum Frankfurt/Oder Klinik für Gefäßchirurgie Müllroser Chaussee 7 15236 Frankfurt/Oder

9. PD Dr. med. Matthias Weck	Weißeritztal-Kliniken GmbH Medizinische Klinik III Bürgerstraße 7 1705 tal
10. Dr. med. Alexandra Zidek	Krankenhaus Porz am Rhein Klinik für Gefäßchirurgie Urbacher Weg 19 51149 Köln
11. Dr. med. Peter Mauckner	St. Remigius Krankenhaus Opladen Innere Medizin An St. Remigius 26 51379 Leverkusen
12. Dr. med. Klemens M. Sondern	Marien Hospital Dortmund-Hombruch Klinik für Innere Medizin/Diabetologie Gablonzstraße 9 44225 Dortmund
13. Prof. Dr. med. Thomas Schmitz-Rixen	Universitätsklinikum Frankfurt Zentrum für Chirurgie Klinik für Gefäß- und Endovascularchirurgie Theodor-Stern-Kai 7, Haus 23C/EG 60590 Frankfurt am Main
14. Dr. med. Walter Wetzel-Roth	Facharztpraxis für Chirurgie Hindenburgstraße 1 86807 Buchloe
15. Dr. med. Matthias Hahn	Helfenstein Klinik Geisslingen Allgemein- und Viszeralchirurgie Eybstraße 16 73312 Geislingen/Steige
16. Dr. med. Karsten Glockemann	Paracelsus-Klinik am Silbersee Wundzentrum Hannover Oertzeweg 24 30851 Langenhagen
17. PD Dr. med. Farzin Adili	Klinikum Darmstadt Chirurgische Klinik III Grafenstraße 9 64283 Darmstadt
18. Dr. med. Andreas Riemer	Ortenau Klinikum Offenburg-Ebertplatz Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ebertplatz 12 77654 Offenburg

19. Dr. med. Thomas Krönert	Thüringen-Kliniken "Georgius Agricola" GmbH Klinik für Gefäßchirurgie Rainweg 68 7318 feld
20. Dr. med. Matthias Holfeld	Klinikum Dorothea Christiane Erxleben GmbH Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ditfurter Weg 24 6484 linburg
21. Prof. Dr. med. Jan Andre´ Schmidt-Lucke	Franziskus-Krankenhaus Berlin Abt. für Innere Medizin Budapester Straße 15-19 10787 Berlin
22. Dr. med. Wolf-Rüdiger Klare	Hegau-Bodensee Klinikum Radolfzell (HBK) Klinik für Innere Medizin Hausherrenstraße 12 78315 Radolfzell
23. Dr. med. Hansjörg Mühlen	Diabetologische Schwerpunktpraxis Dr. med. Hansjörg Mühlen & Partner Ruhrorter Straße 195 47119 Duisburg
24. Dr. med. Christian Reinhold	Kliniken Maria Hilf Mönchengladbach Klinik für Gefäßchirurgie und Angiologie Sandradstraße 43 41061 Mönchengladbach
25. Dr. med. Makarios Paschalidis	Städtisches Klinikum München/Bogenhausen Klinik für Endokrinologie, Diabetologie und Angiologie Englschalkingerstraße 77 81925 München
26. Gerhard Rothenaicher	Facharztpraxis für Chirurgie Cosimastraße 2 81927 München
27. Dr. med. Elke Anne Klug	Bürgerhospital Frankfurt am Main Interdisziplinäres Zentrum Diabetischer Fuß (DDG) Nibelungenallee 37- 41 60318 Frankfurt am Main
28. Dr. med. Siamak Pourhassan	Gemeinschaftspraxis für Chirurgie und Gefäßmedizin Drs. Alter / Pourhassan / Heim Klosterstraße 12 46145 Oberhausen
29. Dr. med. Jan Theil	Evangelisches Krankenhaus Königin Elisabeth Herzberge gGmbH Abt. für Kardiologie, Angiologie und Diabetologie

	Herzbergstraße 79 10365 Berlin
30. Dr. med. Martin Adolph	Städtisches Klinikum Neunkirchen gGmbH Abt. für Gefäßchirurgie & Phlebologie Brunnenstraße 20 66538 Neunkirchen
31. Dr. med. Frank von Feldmann	Westküstenklinikum Heide Klinik für Viszeral- und Gefäßchirurgie Esmarchstraße 50 25746 Heide/Holstein
32. Dr. med. Gerald Engels	Chir. Praxisgemeinschaft am Bayenthalgürtel Praxis Dr. med. Gerald Engels Bayenthalgürtel 45 50968 Köln
33. Dr. med. Joachim Oldenburg	Malteser Krankenhaus – St. Franziskus-Hospital Medizinische Klinik I Abt. für Diabetologie Waldstraße 17 24939 Flensburg
34. Dr. med. Philipp Kneppe	St. Marienkrankenhaus Siegen gGmbH Klinik für Gastroenterologie Kampenstraße 51 57072 Siegen
35. Dr. med. Steffen Hering	Krankenhaus Bietigheim Klinik für Innere Medizin, Kardiologie, Endokrinologie, Diabetologie und Internistische Intensivmedizin Riedstraße 12 74321 Bietigheim-Bissingen
36. Dr. med. Harald Daum	Asklepios Kliniken Harburg Eißendorfer Pferdeweg 52 21075 Hamburg
37. Dr. med. Lutz Stemler	Diabetologikum Ludwigshafen Diabetes-Schwerpunktpraxis Ludwigsplatz 9 67059 Ludwigshafen
38. Dr. med. Thomas Müller	Mariannen-Hospital Werl Abt. für Chirurgie Unnaer Straße 15 59457 Werl
39. Dr. med. Karl Zink	Diabetes Klinik GmbH & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim

40. Dr. med. Dirk Lammers	Institut für Diabetesforschung Münster GmbH Hohenzollernring 70 48145 Münster

Supplementary Discussion

As direct blinding of patients and investigators was not possible due to the nature of the applied treatment methods, issues of blinding have been addressed using independent blinded outcome assessors and the W.H.A.T. for evaluating the wound photographs. For wound size and wound tissue the values documented by the investigators reflect the expected course much better than the W.H.A.T. results. During study planning the W.H.A.T. (http://www.what-world.com/) was the only available validated instrument that was able to measure both wound size and wound tissue composition (granulation, fibrin, and necrosis). For the wound surface area, the difference between the clinical measurements and the W.H.A.T. results may have been caused by the different evaluation methods. An elliptical wound surface area was calculated by the investigators using length and width, but most wounds are not elliptical. The independent blinded assessors marked the wound margin on the photograph and the W.H.A.T. calculates the wound surface area automatically afterwards, thus if the wound photo is of good quality the W.H.A.T. is more precise. In addition, the depth of the wound cannot be assessed using a wound photo, thus wound volume has only been evaluated using the clinical measurements provided by the investigators. The values for granulation tissue and fibrin differ significantly between the clinical estimations and the W.H.A.T. results. This may be caused by the quality of the wound photography, the reliability and precision of both the clinical investigator and the W.H.A.T. system and the wound itself. Wounds with invisible, deeper areas cannot be detected without manipulation. Both circumstances possibly affect the results.

Supplementary tables

Demographic and baseline parameters (PP-Population)	**Total** **N=154 (100%)**	**NPWT** **N=44** **(28·6%)**	**SMWC** **N=110** **(71·4%)**
Sex	N=154	N=44	N=110
Male	113 (73·4%)	29 (65·9%)	84 (76·4%)
Female	41 (26·6%)	15 (34·1%)	26 (23·6%)
Age in years Mean (SD)	N=154 67·4 (10·6)	N=44 66·5 (11·0)	N=110 67·8 (10·4)
Height in cm Mean (SD)	N=153 173·8 (12·9)	N=43 173·5 (17·4)	N=110 174·0 (10·7)
Weight in kg Mean (SD)	N=150 95·4 (23·3)	N=42 96·2 (21·6)	N=108 95·1 (24·0)
Alcohol	N=153	N=44	N=109
Occasionally	71 (46·4%)	22 (50·0%)	49 (45·0%)

Chronic	3 (2·0%)	1 (2·3%)	2 (1·8%)
No	79 (51·6%)	21 (47·7%)	58 (53·2%)
Smoking	N=154	N=44	N=110
No	16 (10·4%)	2 (4·5%)	14 (12·7%)
Yes	138 (89·6%)	42 (95·5%)	96 (87·3%)
Number of years (Mean (SD))	37·0 (9·2)	42·0 (2·8)	36·3 (9·7)
Packs / day (Mean)	1·0	1·0	1·0
Drugs	N=153	N=44	N=109
Occasionally	0 (0%)	0 (0%)	0 (0%)
Chronic	1 (0·7%)	0 (0%)	1 (0·9%)
No	152 (99·3%)	44 (100%)	108 (99·1%)
Requiring dialysis	N=154	N=44	N=110
Yes	11 (7·1 %)	2 (4·5%)	9 (8·2%)
No	143 (92·9%)	42 (95·5%)	101 (91·8%)
Allergies	N=154	N=44	N=110
Yes	16 (10·4%)	6 (13·6%)	10 (9·1%)
No	138 (89·6%)	38 (86·4%)	100 (90·9%)
Subjective assessment of nutritional condition	N=150	N=43	N=107
Well-nourished	147 (98·0%)	42 (97·7%)	105 (98·1%)
Moderately malnourished or suspected malnutrition	3 (2·0%)	1 (2·3%)	2 (1·9%)
Malnourished	0 (0%)	0 (0%)	0 (0%)
Peripheral arterial occlusive disease (PAOD)	N=109 (70·8%)	N=29 (65·9%)	N=80 (72·7%)
without critical limb ischemia	103 (94·5%)	28 (96·6%)	75 (93·8%)
with critical limb ischemia	6 (5·5%)	1 (3·4%)	5 (6·3%)
Rutherford classification for chronic limb ischemia (Grade/Category)	N=109	N=29	N=80
0/0 Asymptomatic—no hemodynamically significant occlusive disease	13 (11·9%)	4 (13·8%)	9 (11·3%)
I/1 Mild claudication	13 (11·9%)	2 (6·9%)	11 (13·8%)
I/2 Moderate claudication	8 (7·3%)	0 (0·0%)	8 (10·0%)
I/3 Severe claudication	4 (3·7%)	1 (3·4%)	3 (3·8%)
II/4 Ischemic rest pain	1 (0·9%)	1 (3·4%)	0 (0%)
III/5 Minor tissue loss—non healing ulcer, focal gangrene with	67 (61·5%)	21 (72·4%)	46 (57·5%)

diffuse pedal ischemia			
III/6 Major tissue loss—extending above transmetatarsal level, functional foot no longer salvageable	3 (2·8%)	0 (0·0%)	3 (3·8%)
Revascularisation before study start	N=9 (5·8%)	N=1 (2·3%)	N=8 (7·3%)
Percutaneous transluminal angioplasty (PTA)	5 (55·6%)	0 (0·0%)	5 (62·5%)
PTA + Stent	0 (0%)	0 (0%)	0 (0%)
Veins-Bypass	1 (11·1%)	1 (100·0%)	0 (11·1%)
Polytetrafluoroethylene (PTFE) Bypass	1 (11·1%)	0 (0%)	1 (12·5%)
Thromboendarterectomy and patch plastic	2 (22·2%)	0 (0%)	2 (25·0%)
Revascularization with influence on the wound	9 of 9 (100%)	1 of 1 (100%)	0 of 8 (100%)
Sufficient revascularization result	9 of 9 (100%)	1 of 1 (100%)	8 of 8 (100%)
Insufficient revascularization result	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)
Revascularization result not assessable	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)

Table S1: Patient demographics and baseline characteristics of the Per-Protocol (PP) population. Data are N (%) and Mean (SD). "N=" is stating the number of patients with actual available information. Findings, diagnoses and procedures documented by the investigators are presented.

	Wound surface NPWT		**Wound surface SMWC**	
Observation time point	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**
Randomization	1060 (1536) 550 (1236) N=171 (2)	687 (879) 321 (760) N=118 (10)	1141 (3247) 471 (1007) N=174 (0)	664 (1050) 316 (658) N=129 (13)
Week 1	847 (1489) 397 (801) N=171 (15)	643 (820) 329 (750) N=118 (32)	1085 (3234) 395 (867) N=174 (25)	713 (1065) 307 (749) N=129 (36)
Week 3	810 (1472) 314 (860) N=171 (24)	590 (742) 273 (633) N=118 (28)	1025 (3242) 390 (913) N=174 (22)	701 (1212) 266 (768) N=129 (35)
Week 5	717 (1379) 275 (769) N=171 (37)	607 (828) 231 (843) N=118 (42)	759 (1466) 267 (824) N=174 (41)	610 (1119) 219 (635) N=129 (38)
Week 8	636 (1322) 220 (712)	495 (770) 182 (561)	674 (1410) 186 (783)	501 (937) 165 (481)

	N=171 (52)	N=118 (48)	N=174 (42)	N=129 (42)
Week 12	549 (858) 165 (964) N=171 (110)	457 (742) 134 (494) N=118 (88)	570 (940) 169 (632) N=174 (124)	493 (950) 133 (498) N=129 (104)
Week 16	440 (810) 79 (471) N=171 (80)	334 (649) 114 (363) N=118 (66)	493 (1095) 69 (415) N=174 (63)	351 (750) 77 (320) N=129 (56)

Table S2: Wound surface area at each observation time point in the ITT-population. Wound surface area at each observation time point until end of maximum study treatment time of 16 weeks is separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis. An elliptical wound surface area has been calculated from the documented width and length (eCRF) [(pi / 4) x length x width = area]. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	**Wound volume NPWT (mm^3)**	**Wound volume SMWC (mm^3)**
Randomization	22498 (58930) 4710 (15048) N=171 (2)	21740 (74181) 4759 (12888) N=174 (0)
Week 1	13203 (28709) 2487 (6908) N=171 (15)	19979 (73143) 3533 (11407) N=174 (26)
Week 3	10708 (28521) 1884 (6857) N=171 (24)	16217 (67494) 2293 (8831) N=174 (23)
Week 5	7700 (19719) 1166 (5338) N=171 (37)	11286 (32566) 1365 (7539) N=174 (42)
Week 8	5592 (11535) 785 (4604) N=171 (78)	8772 (27674) 812 (5258) N=174 (67)
Week 12	5333 (12422) 565 (3913) N=171 (119)	6639 (16454) 625 (4083) N=174 (133)
Week 16	3880 (10534) 141 (1890) N=171 (83)	5465 (14874) 200 (1587) N=174 (64)

Table S3: Wound volume at each observation time point during the study treatment time of maximum 16 weeks in the ITT-population. Wound volume (length x width x depth) was calculated from width, length and depth as documented in the eCRF. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	NPWT Granulation		NPWT Fibrin		NPWT Necrosis		SMWC Granulation		SMWC Fibrin		SMWC Necrosis	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.
Rando	34 (36) 20 (70) 171 (2)	22 (25) 12 (37) 118 (8)	21 (28) 10 (30) 170 (4)	71 (27) 79 (46) 118 (8)	3 (10) 0 (0) 169 (5)	7 (15) 0 (5) 118 (8)	34 (37) 20 (71) 174 (3)	24 (26) 14 (39) 129 (12)	22 (29) 10 (40) 174 (1)	69 (28) 79 (44) 129 (12)	2 (9) 0 (0) 172 (2)	7 (14) 0 (8) 129 (12)
Week 1	58 (35) 70 (70) 171 (16)	21 (25) 10 (36) 118 (32)	19 (22) 10 (30) 71 (19)	73 (27) 81 (47) 118 (32)	5 (13) 0 (2) 169 (23)	6 (12) 0 (5) 118 (32)	49 (35) 50 (70) 174 (28)	21 (25) 10 (36) 129 (36)	24 (27) 15 (31) 174 (27)	74 (26) 85 (40) 129 (36)	6 (15) 0 (5) 172 (30)	5 (9) 0 (5) 129 (36)
Week 3	67 (31) 80 (55) 171 (26)	16 (23) 5 (25) 118 (27)	18 (22) 10 (30) 171 (30)	80 (25) 91 (30) 118 (27)	5 (13) 0 (0) 169 (28)	4 (11) 0 (1) 118 (27)	57 (32) 60 (60) 174 (24)	21 (25) 10 (36) 129 (35)	25 (26) 20 (35) 174 (25)	77 (25) 85 (36) 129 (35)	5 (13) 0 (3) 172 (30)	3 (7) 0 (1) 129 (35)
Week 5	70 (30) 80 (45) 171 (36)	15 (22) 6 (21) 118 (43)	18 (24) 10 (25) 171 (38)	83 (22) 91 (26) 118 (43)	4 (13) 0 (0) 169 (42)	2 (8) 0 (1) 118 (43)	62 (31) 63 (50) 174 (44)	18 (26) 4 (32) 129 (36)	23 (25) 10 (39) 174 (47)	80 (26) 93 834) 129 (36)	4 (12) 0 (0) 172 (46)	3 (10) 0 (0) 129 (36)
Week 8	74 (30) 90 (40) 171 (53)	16 (23) 4 (27) 118 (48)	17 (24) 10 (20) 171 (56)	82 (24) 93 (33) 118 (48)	4 (13) 0 (0) 171 (59)	2 (6) 0 (0) 118 (48)	70 (29) 80 (40) 174 (44)	17 (24) 3 (33) 129 (43)	17 (21) 10 (20) 174 (49)	80 (25) 92 (36) 129 (43)	5 (13) 0 (0) 174 (52)	3 (11) 0 (0) 129 (43)
Week 12	75 (30) 90 (40) 171(115)	15 (23) 4 (22) 118 (89)	17 (25) 5 (20) 171(118)	83 (24) 96 (23) 118 (89)	4 (13) 0 (0) 171(119)	1 (5) 0 (0) 118 (89)	73 (29) 80 (38) 174(124)	16 (23) 3 (29) 129(102)	16 (20) 10 (20) 174(125)	82 (23) 93 (32) 129(102)	5 (13) 0 (0) 172(126)	2 (6) 0 (0) 129(102)
Week 16	77 (30) 90 (40) 171 (78)	13 (22) 1 (17) 118 (66)	14 (22) 2 (20) 171 (79)	86 (24) 98 (19) 118 (66)	3 (10) 0 (0) 171 (82)	1 (6) 0 (0) 118 (66)	76 (30) 90 (40) 174 (62)	17 (24) 4 (31) 129 (576	15 (24) 5 (20) 174 (65)	81 (24) 93 (35) 129 (56)	3 (13) 0 (0) 174 (66)	2 (6) 0 (0) 129 (56)

Table S1: Wound tissue composition at each observation time point during the study treatment time of maximum 16 week in the ITT-population. Wound tissue (granulation, fibrin, and necrosis) is separately shown for the data documented in the eCRF and for the data derived from the photo analysis using the Wound Healing Analyzing Tool (W.H.A.T.). Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Pain Total N=344	Pain NPWT N=171	Pain SMWC N=173
Screening	2·1 (2·4) 1 (4) N=344 (0)	2·1 (2·3) 1 (4) N=171 (0)	2·1 (2·4) 1 (4) N=173 (0)
Week 1	1·7 (2·2) 1 (3) N=344 (6)	1·6 (2·2) 0 (2) N=171 (1)	1·8 (2·2) 1 (3) N=173 (5)
Week 3	1·5 (2·0) 1 (2) N=344 (27)	1·3 (1·9) 0 (2) N=171 (11)	1·7 (2·1) 1 (3) N=173 (16)
Week 5	1·3 (1·9) 0 (2) N=344 (45)	1·2 (1·9) 0 (2) N=171 (21)	1·4 (2·0) 0 (2) N=173 (24)
Week 8	1·3 (1·9) 0 (2) N=344 (70)	1·2 (1·9) 0 (2) N=171 (38)	1·3 (1·9) 0 (2) N=173 (32)
Week 12	1·1 (1·8) 0 (2) N=344 (115)	1·2 (1·9) 0 (2) N=171 (64)	1·1 (1·8) 0 (2) N=173 (51)
Week 16	1·0 (1·7) 0 (1) N=344 (129)	1·0 (1·7) 0 (2) N=171 (76)	0·9 (1·7) 0 (1) N=173 (53)

Table S2: Pain in the course of the study treatment time of maximum 16 weeks in the ITT-population. Pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	EQ5D NPWT	EQ5D SMWC
Screening	0,53 (0,27) 0,53 (0,2) N=156 (2)	0,53 (0,24) 0,53 (0,18) N=159 (3)
End of therapy	0,67 (0,24) 0,77 (0,29) N=62 (2)	0,72 (0,17) 0,66 (0,35) N=13 (0)

End of maximum study treatment time	0,66 (0,22) 0,66 (0,28) N=63 (2)	0,61 (0,25) 0,63 (0,24) N=95 (2)
Follow up after 6 months	0,69 (0,26) 0,77 (0,35) N=93 (3)	0,67 (0,23) 0,63 (0,39) N=97 (2)

Table S3: Quality of life (EQ5D) in the course of the study treatment time of 16 week in the ITT-population. Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT-population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Wound surface area	**Small wounds**				**Big wounds**			
mm^2	**Total N=173**	**NPWT N=83**	**SMWC N=90**	**p**	**Total N=172**	**NPWT N=88**	**SMWC N=84**	**p**
N (LOCF)	2	2	0	0·232	0	0	0	0·193
Mean (SD)	213 (136)	212 (138)	213 (135)		1995 (3377)	1860 (1805)	2135 (4474)	
Median (IQR)	188 (220)	176 (220)	196 (222)		1276 (1482)	1364 (1242)	1242 (1708)	
Min - Max	12-484	20-484	12-471		491-40773	520-13188	491-40773	

Table S4: Wound surface area for small and big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms, the number (N) of values substituted by the last observation carried forward (LOCF) method; mean (SD), median (IQR); and minimum (min) and maximum (max).

Wound closure rate **Small wounds**	**NPWT (N=171)** **N=83**	**SMWC (N=174)** **N=90**	**p**
Within 16 weeks maximum study treatment time	12 (14·5 %)	16 (17·8 %)	0·6
At follow up after 6 months	13 (15·7 %)	24 (26·7 %)	0·10

Table S5: Wound closure rates within the maximum study treatment time of 16 weeks and within the study observation time of 6 months for small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number of patients with wound closure (N) within 16 weeks and after 6 months as well the percentage (%) of patients achieving the endpoints within both treatment arms.

Wound closure rate **Big wounds**	**NPWT (N=171)** **N=88**	**SMWC (N=174)** **N=84**	**P**
Within 16 weeks maximum study treatment time	13 (14·8 %)	5 (6·0 %)	0·08
At follow up after 6 months	11 (12·5 %)	12 (14·3 %)	0·82

Table S6: Wound closure rates within the maximum study treatment time of 16 weeks and within the study observation time of 6 months for big wounds. Data show the number (N) of participants available for the analysis in total and for both

treatment arms and the number of patients with wound closure (N) within 16 weeks and after 6 months as well the percentage (%) of patients achieving the endpoints within both treatment arms.

Time until min. 95 % granulation tissue for small wounds	**Total (N=100)**	**NPWT (N=52)**	**SMWC (N=48)**	**p**
Mean (SD)	38·6 (37·4)	28·5 (30·0)	49·5 (41·6)	0·005
Median (IQR)	26·5 (50·0)	20·0 (28·0)	48·0 (79·0)	
Min-Max	0-114	0-113	0-114	

Table S7: Time until optimal preparation of the wound bed (min. 95 % granulation tissue) for the subgroup of small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Time until min 95 % granulation tissue for big wounds	**Total (N=80)**	**NPWT (N=47)**	**SMWC (N=33)**	**p**
Mean (SD)	47·8 (40·8)	43·4 (37·9)	54·0 (44·6)	0·27
Median (IQR)	36·5 (70·0)	35·0 (61·0)	56·0 (105·0)	
Min-Max	0-127	0-127	0-115	

Table S 8: Time until optimal preparation of the wound bed (min 95 % granulation tissue) for the subgroup of big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Amputations & Resections **Small wounds**	**Total** **N=173**	**NPWT** **N=83**	**SMWC** **N=90**	**p**
No. of patients with amputations or resections [N (%)]	35 (20·2%)	19 (22·9%)	16 (17·8%)	0·45 (F)
No. of performed amputations and resections [N]	50	22	28	0·51 (U)
No. of patients with minor amputations [N (%)]	35 (20·2%)	19 (22·9%)	16 (17·8%)	0·45 (F)
No. of patients with major amputations [N (%)]	0 (0%)	0 (0%)	0 (0%)	-

Table S9: Amputations and resections in the subgroup of small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

Amputations & Resections **Big wounds**	**Total** **N=172**	**NPWT** **N=88**	**SMWC** **N=84**	**p**

No. of patients with amputations or resections [N (%)]	36 (20·9%)	16 (18·2%)	20 (23·8%)	0·45 (F)
No. of performed amputations and resections [N]	52	45	57	0·41 (U)
No. of patients with minor amputations [N (%)]	34 (19·8%)	14 (15·9%)	20 (23·8%)	0·25 (F)
No. of patients with major amputations [N (%)]	2 (1·2%)	2 (2·3%)	0 (0%)	0·50 (F)

Table S10: Amputations and resections in the subgroup of big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

Wound closure rate	**Total N=154**	**NPWT N=44**	**SMWC N=110**	**p**
Wound closures [N (%)] within 16 weeks	33 (21·4 %)	14 (31·8%)	19 (17·3%)	0·053
Wound closures [N (%)] after 6 months	41 (26·6 %)	11 (25·0%)	30 (27·3%)	0·84

Table S11: Wound closure rate after 6 months and in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with wound closures within 16 weeks and after 6 months.

Time until min. 95 % granulation tissue	**Total (N=100)**	**NPWT (N=38)**	**SMWC (N=62)**	**p**
Mean (SD)	43·8 (42·3)	23·8 (31·7)	56·0 (43·5)	<0·001
Median (IQR)	30·0 (76)	8·5 (28·0)	56·0 (96·0)	
Min - Max	0 - 127	0 - 127	0 - 115	

Table S12: Time until optimal preparation of the wound for further treatment (min 95 % granulation tissue) in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Recurrences	**Total (N=154)**	**NPWT (N=44)**	**SMWC (N=110)**	**p**
No. of patients with recurrences [N (%)]	8 (5·2 %)	3 (8·1 %)	5 (5·3%)	0·69
No. of recurrences [N]	9	4	5	0·38

Table S13: Recurrences in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with recurrences.

Amputations & Resections	**Total (N=154)**	**NPWT (N=44)**	**SMWC (N=110)**	**p**
No. of patients with amputation or resection [N (%)]	30 (19·5%)	9 (20·5%)	21 (21·4%)	0·83

No. of amputations or resections [N]	39	11	28	0·86
No. of patients with Minor-Amputations [N (%)]	30 (18·9%)	9 (12·8%)	21 (21·4%)	0·83
No. of patients with Major-Amputations [N (%)]	0 (0%)	0 (0%)	0 (0%)	-

Table S14: Amputations and resections in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

	Wound surface NPWT		**Wound surface SMWC**	
Observation time point	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**	**Observation time point**	**Calculated from width and length (according to eCRF entry)**
Randomization	964 (1392) 345 (1426) N= 44 (1)	633 (795) 299 (705) N=41 (3)	878 (1266) 373 (889) N= 110 (0)	669 (1143) 294 (692) N=102 (9)
Week 1	525 (696) 224 (408) N= 44 (5)	524 (614) 318 (561) N=41 (8)	827 (1238) 306 (863) N= 110 (16)	706 (1138) 289 (775) N=102 (27)
Week 3	428 (635) 176 (378) N= 44 (6)	477 (737) 165 (424) N=41 (9)	803 (1306) 238 (867) N= 110 (7)	714 (1316) 259 (656) N=102 (26)
Week 5	355 (590) 100 (291) N= 44 (8)	418 (602) 165 (435) N=41 (15)	650 (1157) 161 (670) N= 110 (18)	607 (1212) 167 (545) N=102 (29)
Week 8	284 (528) 53 (217) N= 44 (8)	320 (530) 83 (264) N=41 (16)	569 (1072) 106 (443) N= 110 (17)	479 (990) 123 (397) N=102 (29)
Week 12	283 (580) 14 (130) N= 44 (24)	289 (537) 62 (175) N=41 (32)	528 (1024) 79 (419) N= 110 (71)	474 (1006) 111 (407) N=102 (80)
Week 16	190 (416) 0 (95) N= 44 (14)	179 (333) 30 (204) N=41 (25)	386 (1124) 31 (159) N= 110 (19)	319 (724) 65 (256) N=102 (42)

Table S18: Wound surface area at each observation time point during the study treatment time of maximum 16 weeks separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis using W.H.A.T. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Wound volume NPWT (mm^3)	Wound volume SMWC (mm^3)
Randomization	33359 (95749) 5746 (17330) N=44 (1)	14742 (36523) 3905 (11189) N=110 (0)
Week 1	11606 (26991) 1824 (6113) N=44 (5)	13525 (34844) 2470 (9479) N=110 (16)
Week 3	8636 (24698) 777 (3199) N=44 (6)	11907 (32047) 1864 (8039) N=110 (7)
Week 5	5480 (13967) 271 (1790) N=44 (7)	8981 (25570) 1027 (4745) N=110 (18)
Week 8	3955 (9056) 192 (809) N=44 (16)	6899 (18607) 506 (3915) N=110 (29)
Week 12	6052 (16114) 71 (681) N=44 (25)	5964 (15930) 361 (1890) N=110 (77)
Week 16	3246 (11245) 0 (319) N=44 (15)	3396 (10783) 57 (609) N=110 (19)

Table S15: Wound volume (length x width x depth) for each observation time point during the study treatment time of maximum 16 weeks calculated from width· length and depth as documented in the eCRF. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	NPWT Granulation		NPWT Fibrin		NPWT Necrosis		SMWC Granulation		SMWC Fibrin		SMWC Necrosis	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.		eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF
Rando	32 (37)	23 (26)	18 (27)	68 (27)	2 (7)	9 (15)	38 (38)	26 (27)	21 (29)	67 (29)	1 (7)	7 (15)
	10 (68)	13 (37)	3 (28)	69 (45)	0 (0)	0 (15)	25 (80)	16 (42)	10 (33)	77 (56)	0 (0)	0 (8)
	44 (1)	41 (2)	44 (1)	41 (2)	44 (1)	41 (2)	110 (0)	102 (9)	110 (0)	102 (9)	108 (2)	102 (9)
Week 1	72 (37)	22 (26)	7 (13)	70 (28)	2 (7)	9 (15)	54 (35)	24 (27)	22 (24)	72 (27)	5 (14)	5 (9)
	90 (50)	9 (41)	0 (10)	75 (50)	0 (0)	0 (11)	63 (70)	13 (42)	13 (28)	78 (42)	0 (1)	0 (6)
	44 (5)	41 (8)	44 (6)	41 (8)	44 (7)	41 (8)	110 (16)	102 (27)	110 (16)	102 (27)	108 (19)	102 (27)
Week 3	77 (32)	16 (24)	11 (19)	79 (26)	1 (4)	6 (14)	61 (31)	24 (27)	25 (25)	75 (26)	4 (11)	3 (7)
	93 (34)	2 (29)	0 (20)	91 (37)	0 (0)	0 (1)	70 (50)	15 (42)	20 (35)	83 (41)	0 (0)	0 (1)
	44 (6)	41 (9)	44 (7)	41 (9)	44 (7)	41 (9)	110 (9)	102 (26)	110 (10)	102 (26)	108 (13)	102 (26)
Week 5	82 (29)	10 (16)	9 (19)	87 (17)	1 (4)	3 (9)	65 (29)	19 (27)	24 (24)	78 (27)	3 (9)	3 (11)
	95 (20)	4 (11)	2 (10)	93 (21)	0 (0)	0 (1)	73 (46)	4 (34)	13 (37)	93 (35)	0 (0)	0 (0)
	44 (7)	41 (16)	44 (8)	41 (16)	44 (9)	41 (16)	110 (19)	102 (27)	110 (22)	102 (27)	108 (22)	102 (27)
Week 8	85 (27)	15 (25)	6 (13)	82 (26)	2 (6)	3 (8)	74 (27)	20 (26)	18(21)	77 (27)	3 (10)	3 (12)
	100 (20)	1 (16)	0 (5)	96 (35)	0 (0)	0 (0)	80 (31)	3 (38)	10 (18)	91 (43)	0 (0)	0 (0)
	44 (9)	41 (16)	44 (10)	41 (16)	44 (9)	41 (16)	110 (18)	102 (30)	110 (21)	102 (30)	108 (25)	102 (30)
Week 12	86 (26)	13 (24)	6 (14)	85 (26)	2 (9)	2 (6)	77 (27)	18 (25)	16 (20)	80 (25)	3 (11)	2 (6)
	100 (18)	1 (13)	0 (4)	99 (20)	0 (0)	0 (0)	85 (29)	3 (36)	10 (20)	92 (36)	0 (0)	0 (0)
	44 (26)	41 (34)	44 (26)	41 (32)	44 (28)	41 (32)	110 (72)	101 (78)	110 (73)	102 (79)	108 (73)	102 (80)
Week 16	87 (25)	12 (22)	6 (14)	86 (24)	0·1 (1)	1 (6)	80 (30)	19 (25)	14 (24)	80 (26)	2 (11)	1 (5)
	100 (15)	0 (14)	0 (1)	100 (20)	0 (0)	0 (0)	95 (20)	5 (36)	0 (20)	92 (36)	0 (0)	0 (0)
	44 (14)	41 (25)	44 (16)	41 (25)	44 (15)	41 (25)	110 (18)	102 (42)	110 (21)	102 (42)	108 (24)	102 (42)

Table S20: Wound tissue (granulation, fibrin, necrosis) at each observation time point during the study treatment time of maximum 16 weeks separately shown for the data documented in the eCRF and for the data derived from the photo analysis using the wound healing analyzing too (W.H.A.T.). Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Pain Total N=344	Pain NPWT N=171
Screening	1·3 (2·1) 0 (2) N=44 (0)	1·8 (2·3) 1 (3) N=110 (0)
Week 1	0·7 (1·5) 0 (1) N=44 (0)	1·4 (2·1) 0 (3) N=110 (5)
Week 3	0·4 (0·7) 0 (1) N=44 (4)	1·3 (1·8) 0 (2) N=110 (3)
Week 5	0·3 (0·8) 0 (0) N=44 (2)	1·0 (1·6) 0 (2) N=110 (5)
Week 8	0·4 (1·1) 0 (0) N=44 (4)	0·9 (1·5) 0 (2) N=110 (9)
Week 12	0·3 (1·0) 0 (0) N=44 (11)	0·7 (1·3) 0 (1) N=110 (18)
Week 16	0·2 (0·7) 0 (0) N=44 (14)	0·5 (1·2) 0 (0) N=110 (13)

Table S16: Pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	EQ5D NPWT	EQ5D SMWC
Screening	0·61 (0·23) 0·63 (0·24) N=42 (1)	0·60 (0·20) 0·59 (0·25) N=100 (3)
End of therapy	0·65 (0·20) 0·78 (0·20) N=26 (2)	0·81 (0·14) 0·87 (0·26) N=8 (0)
End of maximum study treatment time	0·65 (0·25)	0·66 (0·21)

	0·66 (0·43) N=19 (0)	0·63 (0·28) N=73 (2)
Follow up after 6 months	0·75 (0·22) 0·78 (0·30) N=26 (0)	0·70 (0·23) 0·77 (0·34) N=73 (2)

Table S17: Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Supplementary Appendix

Table of contents:

List of investigators:

At least one patient was included in the following facilities:

1. PD Dr. med. Achim Neufang	HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für Gefäßchirurgie Ludwig-Erhard-Straße 100 65199 Wiesbaden
2. Dr. med. Holger Lawall	Asklepios Westklinikum Hamburg Zentrum für Gefäßmedizin Suurheid 20 22559 Hamburg
3. Prof. Dr. med. Gernold Wozniak	Knappschaftskrankenhaus Bottrop Gefäßchirurgische Klinik Osterfelderstraße 157 46242 Bottrop
4. Prof. Dr. med. Martin Storck	Städtisches Klinikum Karlsruhe Klinik für Gefäß- und Thoraxchirurgie Moltkestraße 90 76133 Karlsruhe
5. Dr. med. Dirk Hochlenert	Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Merheimer Straße 217 50733 Köln
6. Dr. med. Gudrun Hetzel	Klinikum Döbeln Abt. für Gefäßchirurgie Sörmitzer Straße 10 04720 Döbeln
7. Dr. med. Karsten Jungheim	Klinikum Bielefeld Mitte Klinik für Allgemeine Innere Medizin Teutoburger Straße 50 33604 Bielefeld
8. Dr. med. Michael Petzold	Klinikum Frankfurt/Oder Klinik für Gefäßchirurgie Müllroser Chaussee 7 15236 Frankfurt/Oder

9. PD Dr. med. Matthias Weck	Weißeritztal-Kliniken GmbH Medizinische Klinik III Bürgerstraße 7 1705 tal
10. Dr. med. Alexandra Zidek	Krankenhaus Porz am Rhein Klinik für Gefäßchirurgie Urbacher Weg 19 51149 Köln
11. Dr. med. Peter Mauckner	St. Remigius Krankenhaus Opladen Innere Medizin An St. Remigius 26 51379 Leverkusen
12. Dr. med. Klemens M. Sondern	Marien Hospital Dortmund-Hombruch Klinik für Innere Medizin/Diabetologie Gablonzstraße 9 44225 Dortmund
13. Prof. Dr. med. Thomas Schmitz-Rixen	Universitätsklinikum Frankfurt Zentrum für Chirurgie Klinik für Gefäß- und Endovascularchirurgie Theodor-Stern-Kai 7, Haus 23C/EG 60590 Frankfurt am Main
14. Dr. med. Walter Wetzel-Roth	Facharztpraxis für Chirurgie Hindenburgstraße 1 86807 Buchloe
15. Dr. med. Matthias Hahn	Helfenstein Klinik Geisslingen Allgemein- und Viszeralchirurgie Eybstraße 16 73312 Geislingen/Steige
16. Dr. med. Karsten Glockemann	Paracelsus-Klinik am Silbersee Wundzentrum Hannover Oertzeweg 24 30851 Langenhagen
17. PD Dr. med. Farzin Adili	Klinikum Darmstadt Chirurgische Klinik III Grafenstraße 9 64283 Darmstadt
18. Dr. med. Andreas Riemer	Ortenau Klinikum Offenburg-Ebertplatz Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ebertplatz 12 77654 Offenburg

19. Dr. med. Thomas Krönert	Thüringen-Kliniken "Georgius Agricola" GmbH Klinik für Gefäßchirurgie Rainweg 68 7318 feld
20. Dr. med. Matthias Holfeld	Klinikum Dorothea Christiane Erxleben GmbH Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ditfurter Weg 24 6484 linburg
21. Prof. Dr. med. Jan Andre´ Schmidt-Lucke	Franziskus-Krankenhaus Berlin Abt. für Innere Medizin Budapester Straße 15-19 10787 Berlin
22. Dr. med. Wolf-Rüdiger Klare	Hegau-Bodensee Klinikum Radolfzell (HBK) Klinik für Innere Medizin Hausherrenstraße 12 78315 Radolfzell
23. Dr. med. Hansjörg Mühlen	Diabetologische Schwerpunktpraxis Dr. med. Hansjörg Mühlen & Partner Ruhrorter Straße 195 47119 Duisburg
24. Dr. med. Christian Reinhold	Kliniken Maria Hilf Mönchengladbach Klinik für Gefäßchirurgie und Angiologie Sandradstraße 43 41061 Mönchengladbach
25. Dr. med. Makarios Paschalidis	Städtisches Klinikum München/Bogenhausen Klinik für Endokrinologie, Diabetologie und Angiologie Englschalkingerstraße 77 81925 München
26. Gerhard Rothenaicher	Facharztpraxis für Chirurgie Cosimastraße 2 81927 München
27. Dr. med. Elke Anne Klug	Bürgerhospital Frankfurt am Main Interdisziplinäres Zentrum Diabetischer Fuß (DDG) Nibelungenallee 37- 41 60318 Frankfurt am Main
28. Dr. med. Siamak Pourhassan	Gemeinschaftspraxis für Chirurgie und Gefäßmedizin Drs. Alter / Pourhassan / Heim Klosterstraße 12 46145 Oberhausen
29. Dr. med. Jan Theil	Evangelisches Krankenhaus Königin Elisabeth Herzberge gGmbH Abt. für Kardiologie, Angiologie und Diabetologie

	Herzbergstraße 79 10365 Berlin
30. Dr. med. Martin Adolph	Städtisches Klinikum Neunkirchen gGmbH Abt. für Gefäßchirurgie & Phlebologie Brunnenstraße 20 66538 Neunkirchen
31. Dr. med. Frank von Feldmann	Westküstenklinikum Heide Klinik für Viszeral- und Gefäßchirurgie Esmarchstraße 50 25746 Heide/Holstein
32. Dr. med. Gerald Engels	Chir. Praxisgemeinschaft am Bayenthalgürtel Praxis Dr. med. Gerald Engels Bayenthalgürtel 45 50968 Köln
33. Dr. med. Joachim Oldenburg	Malteser Krankenhaus – St. Franziskus-Hospital Medizinische Klinik I Abt. für Diabetologie Waldstraße 17 24939 Flensburg
34. Dr. med. Philipp Kneppe	St. Marienkrankenhaus Siegen gGmbH Klinik für Gastroenterologie Kampenstraße 51 57072 Siegen
35. Dr. med. Steffen Hering	Krankenhaus Bietigheim Klinik für Innere Medizin, Kardiologie, Endokrinologie, Diabetologie und Internistische Intensivmedizin Riedstraße 12 74321 Bietigheim-Bissingen
36. Dr. med. Harald Daum	Asklepios Kliniken Harburg Eißendorfer Pferdeweg 52 21075 Hamburg
37. Dr. med. Lutz Stemler	Diabetologikum Ludwigshafen Diabetes-Schwerpunktpraxis Ludwigsplatz 9 67059 Ludwigshafen
38. Dr. med. Thomas Müller	Mariannen-Hospital Werl Abt. für Chirurgie Unnaer Straße 15 59457 Werl
39. Dr. med. Karl Zink	Diabetes Klinik GmbH & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim

40. Dr. med. Dirk Lammers	Institut für Diabetesforschung Münster GmbH Hohenzollernring 70 48145 Münster

Supplementary Discussion

As direct blinding of patients and investigators was not possible due to the nature of the applied treatment methods, issues of blinding have been addressed using independent blinded outcome assessors and the W.H.A.T. for evaluating the wound photographs. For wound size and wound tissue the values documented by the investigators reflect the expected course much better than the W.H.A.T. results. During study planning the W.H.A.T. (http://www.what-world.com/) was the only available validated instrument that was able to measure both wound size and wound tissue composition (granulation, fibrin, and necrosis). For the wound surface area, the difference between the clinical measurements and the W.H.A.T. results may have been caused by the different evaluation methods. An elliptical wound surface area was calculated by the investigators using length and width, but most wounds are not elliptical. The independent blinded assessors marked the wound margin on the photograph and the W.H.A.T. calculates the wound surface area automatically afterwards, thus if the wound photo is of good quality the W.H.A.T. is more precise. In addition, the depth of the wound cannot be assessed using a wound photo, thus wound volume has only been evaluated using the clinical measurements provided by the investigators. The values for granulation tissue and fibrin differ significantly between the clinical estimations and the W.H.A.T. results. This may be caused by the quality of the wound photography, the reliability and precision of both the clinical investigator and the W.H.A.T. system and the wound itself. Wounds with invisible, deeper areas cannot be detected without manipulation. Both circumstances possibly affect the results.

Supplementary tables

Demographic and baseline parameters (PP-Population)	**Total** **N=154 (100%)**	**NPWT** **N=44** **(28·6%)**	**SMWC** **N=110** **(71·4%)**
Sex	N=154	N=44	N=110
Male	113 (73·4%)	29 (65·9%)	84 (76·4%)
Female	41 (26·6%)	15 (34·1%)	26 (23·6%)
Age in years Mean (SD)	N=154 67·4 (10·6)	N=44 66·5 (11·0)	N=110 67·8 (10·4)
Height in cm Mean (SD)	N=153 173·8 (12·9)	N=43 173·5 (17·4)	N=110 174·0 (10·7)
Weight in kg Mean (SD)	N=150 95·4 (23·3)	N=42 96·2 (21·6)	N=108 95·1 (24·0)
Alcohol	N=153	N=44	N=109
Occasionally	71 (46·4%)	22 (50·0%)	49 (45·0%)

Chronic	3 (2·0%)	1 (2·3%)	2 (1·8%)
No	79 (51·6%)	21 (47·7%)	58 (53·2%)
~~Nicotine~~Smoking	N=154	N=44	N=110
No	16 (10·4%)	2 (4·5%)	14 (12·7%)
Yes	138 (89·6%)	42 (95·5%)	96 (87·3%)
Number of years (Mean (SD))	37·0 (9·2)	42·0 (2·8)	36·3 (9·7)
Packs / day (Mean)	1·0	1·0	1·0
Drugs	N=153	N=44	N=109
Occasionally	0 (0%)	0 (0%)	0 (0%)
Chronic	1 (0·7%)	0 (0%)	1 (0·9%)
No	152 (99·3%)	44 (100%)	108 (99·1%)
Requiring dialysis	N=154	N=44	N=110
Yes	11 (7·1 %)	2 (4·5%)	9 (8·2%)
No	143 (92·9%)	42 (95·5%)	101 (91·8%)
Allergies	N=154	N=44	N=110
Yes	16 (10·4%)	6 (13·6%)	10 (9·1%)
No	138 (89·6%)	38 (86·4%)	100 (90·9%)
Subjective assessment of nutritional condition	N=150	N=43	N=107
Well-nourished	147 (98·0%)	42 (97·7%)	105 (98·1%)
Moderately malnourished or suspected malnutrition	3 (2·0%)	1 (2·3%)	2 (1·9%)
Malnourished	0 (0%)	0 (0%)	0 (0%)
Peripheral arterial occlusive disease (PAOD)	N=109 (70·8%)	N=29 (65·9%)	N=80 (72·7%)
without critical limb ischemia	103 (94·5%)	28 (96·6%)	75 (93·8%)
with critical limb ischemia	6 (5·5%)	1 (3·4%)	5 (6·3%)
Rutherford classification for chronic limb ischemia (Grade/Category)	N=109	N=29	N=80
0/0 Asymptomatic—no hemodynamically significant occlusive disease	13 (11·9%)	4 (13·8%)	9 (11·3%)
I/1 Mild claudication	13 (11·9%)	2 (6·9%)	11 (13·8%)
I/2 Moderate claudication	8 (7·3%)	0 (0·0%)	8 (10·0%)
I/3 Severe claudication	4 (3·7%)	1 (3·4%)	3 (3·8%)
II/4 Ischemic rest pain	1 (0·9%)	1 (3·4%)	0 (0%)
III/5 Minor tissue loss—non healing ulcer, focal gangrene with	67 (61·5%)	21 (72·4%)	46 (57·5%)

diffuse pedal ischemia			
III/6 Major tissue loss—extending above transmetatarsal level, functional foot no longer salvageable	3 (2·8%)	0 (0·0%)	3 (3·8%)
Revascularisation before study start	N=9 (5·8%)	N=1 (2·3%)	N=8 (7·3%)
Percutaneous transluminal angioplasty (PTA)	5 (55·6%)	0 (0·0%)	5 (62·5%)
PTA + Stent	0 (0%)	0 (0%)	0 (0%)
Veins-Bypass	1 (11·1%)	1 (100·0%)	0 (11·1%)
Polytetrafluoroethylene (PTFE) Bypass	1 (11·1%)	0 (0%)	1 (12·5%)
Thromboendarterectomy and patch plastic	2 (22·2%)	0 (0%)	2 (25·0%)
Revascularization with influence on the wound	9 of 9 (100%)	1 of 1 (100%)	0 of 8 (100%)
Sufficient revascularization result	9 of 9 (100%)	1 of 1 (100%)	8 of 8 (100%)
Insufficient revascularization result	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)
Revascularization result not assessable	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)

Table S1: Patient demographics and baseline characteristics of the Per-Protocol (PP) population. Data are N (%) and Mean (SD). "N=" is stating the number of patients with actual available information. Findings, diagnoses and procedures documented by the investigators are presented.

	Wound surface NPWT		**Wound surface SMWC**	
Observation time point	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**
Randomization	1060 (1536) 550 (1236) N=171 (2)	687 (879) 321 (760) N=118 (10)	1141 (3247) 471 (1007) N=174 (0)	664 (1050) 316 (658) N=129 (13)
Week 1	847 (1489) 397 (801) N=171 (15)	643 (820) 329 (750) N=118 (32)	1085 (3234) 395 (867) N=174 (25)	713 (1065) 307 (749) N=129 (36)
Week 3	810 (1472) 314 (860) N=171 (24)	590 (742) 273 (633) N=118 (28)	1025 (3242) 390 (913) N=174 (22)	701 (1212) 266 (768) N=129 (35)
Week 5	717 (1379) 275 (769) N=171 (37)	607 (828) 231 (843) N=118 (42)	759 (1466) 267 (824) N=174 (41)	610 (1119) 219 (635) N=129 (38)
Week 8	636 (1322) 220 (712)	495 (770) 182 (561)	674 (1410) 186 (783)	501 (937) 165 (481)

	N=171 (52)	N=118 (48)	N=174 (42)	N=129 (42)
Week 12	549 (858) 165 (964) N=171 (110)	457 (742) 134 (494) N=118 (88)	570 (940) 169 (632) N=174 (124)	493 (950) 133 (498) N=129 (104)
Week 16	440 (810) 79 (471) N=171 (80)	334 (649) 114 (363) N=118 (66)	493 (1095) 69 (415) N=174 (63)	351 (750) 77 (320) N=129 (56)

Table S2: WChange of wound surface area in the course of the study treatment time of maximum 16 weeksat each observation time point -in the ITT-population. WChange of wound surface area at each observation time point until end of maximum study treatment time in the course of the study treatment time of maximum of 16 weeks is separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis. An elliptical wound surface area has been calculated from the documented width and length (eCRF) [(pi / 4) x length x width = area]. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	**Wound volume NPWT (mm^3)**	**Wound volume SMWC (mm^3)**
Randomization	22498 (58930) 4710 (15048) N=171 (2)	21740 (74181) 4759 (12888) N=174 (0)
Week 1	13203 (28709) 2487 (6908) N=171 (15)	19979 (73143) 3533 (11407) N=174 (26)
Week 3	10708 (28521) 1884 (6857) N=171 (24)	16217 (67494) 2293 (8831) N=174 (23)
Week 5	7700 (19719) 1166 (5338) N=171 (37)	11286 (32566) 1365 (7539) N=174 (42)
Week 8	5592 (11535) 785 (4604) N=171 (78)	8772 (27674) 812 (5258) N=174 (67)
Week 12	5333 (12422) 565 (3913) N=171 (119)	6639 (16454) 625 (4083) N=174 (133)
Week 16	3880 (10534) 141 (1890)	5465 (14874) 200 (1587)

	N=171 (83)	N=174 (64)

Table S3: WChange of wound volume in the course ofat each observation time point during the study treatment time of maximum 16 weeks in the ITT-population. Change of wWound volume (length x width x depth) in the course of the study treatment time of maximum 16 weeks was calculated from width, length and depth as documented in the eCRF. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	NPWT Granulation		NPWT Fibrin		NPWT Necrosis		SMWC Granulation		SMWC Fibrin		SMWC Necrosis	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.
Rando	34 (36) 20 (70) 171 (2)	22 (25) 12 (37) 118 (8)	21 (28) 10 (30) 170 (4)	71 (27) 79 (46) 118 (8)	3 (10) 0 (0) 169 (5)	7 (15) 0 (5) 118 (8)	34 (37) 20 (71) 174 (3)	24 (26) 14 (39) 129 (12)	22 (29) 10 (40) 174 (1)	69 (28) 79 (44) 129 (12)	2 (9) 0 (0) 172 (2)	7 (14) 0 (8) 129 (12)
Week 1	58 (35) 70 (70) 171 (16)	21 (25) 10 (36) 118 (32)	19 (22) 10 (30) 71 (19)	73 (27) 81 (47) 118 (32)	5 (13) 0 (2) 169 (23)	6 (12) 0 (5) 118 (32)	49 (35) 50 (70) 174 (28)	21 (25) 10 (36) 129 (36)	24 (27) 15 (31) 174 (27)	74 (26) 85 (40) 129 (36)	6 (15) 0 (5) 172 (30)	5 (9) 0 (5) 129 (36)
Week 3	67 (31) 80 (55) 171 (26)	16 (23) 5 (25) 118 (27)	18 (22) 10 (30) 171 (30)	80 (25) 91 (30) 118 (27)	5 (13) 0 (0) 169 (28)	4 (11) 0 (1) 118 (27)	57 (32) 60 (60) 174 (24)	21 (25) 10 (36) 129 (35)	25 (26) 20 (35) 174 (25)	77 (25) 85 (36) 129 (35)	5 (13) 0 (3) 172 (30)	3 (7) 0 (1) 129 (35)
Week 5	70 (30) 80 (45) 171 (36)	15 (22) 6 (21) 118 (43)	18 (24) 10 (25) 171 (38)	83 (22) 91 (26) 118 (43)	4 (13) 0 (0) 169 (42)	2 (8) 0 (1) 118 (43)	62 (31) 63 (50) 174 (44)	18 (26) 4 (32) 129 (36)	23 (25) 10 (39) 174 (47)	80 (26) 93 834) 129 (36)	4 (12) 0 (0) 172 (46)	3 (10) 0 (0) 129 (36)
Week 8	74 (30) 90 (40) 171 (53)	16 (23) 4 (27) 118 (48)	17 (24) 10 (20) 171 (56)	82 (24) 93 (33) 118 (48)	4 (13) 0 (0) 171 (59)	2 (6) 0 (0) 118 (48)	70 (29) 80 (40) 174 (44)	17 (24) 3 (33) 129 (43)	17 (21) 10 (20) 174 (49)	80 (25) 92 (36) 129 (43)	5 (13) 0 (0) 174 (52)	3 (11) 0 (0) 129 (43)
Week 12	75 (30) 90 (40) 171(115)	15 (23) 4 (22) 118 (89)	17 (25) 5 (20) 171(118)	83 (24) 96 (23) 118 (89)	4 (13) 0 (0) 171(119)	1 (5) 0 (0) 118 (89)	73 (29) 80 (38) 174(124)	16 (23) 3 (29) 129(102)	16 (20) 10 (20) 174(125)	82 (23) 93 (32) 129(102)	5 (13) 0 (0) 172(126)	2 (6) 0 (0) 129(102)
Week 16	77 (30) 90 (40) 171 (78)	13 (22) 1 (17) 118 (66)	14 (22) 2 (20) 171 (79)	86 (24) 98 (19) 118 (66)	3 (10) 0 (0) 171 (82)	1 (6) 0 (0) 118 (66)	76 (30) 90 (40) 174 (62)	17 (24) 4 (31) 129 (576	15 (24) 5 (20) 174 (65)	81 (24) 93 (35) 129 (56)	3 (13) 0 (0) 174 (66)	2 (6) 0 (0) 129 (56)

Table S1: WChange of wound tissue composition in the course ofat each observation time point during the study treatment time of maximum 16 week in the ITT-population. Change of Wwound tissue (granulation, fibrin, and necrosis) is in the course of the study treatment time of maximum 16 weeks separately shown for the data documented in the eCRF and for the data derived from the photo analysis using the Wound Healing Analyzing Tool (W.H.A.T.). Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Pain Total N=344	Pain NPWT N=171	Pain SMWC N=173
Screening	2·1 (2·4) 1 (4) N=344 (0)	2·1 (2·3) 1 (4) N=171 (0)	2·1 (2·4) 1 (4) N=173 (0)
Week 1	1·7 (2·2) 1 (3) N=344 (6)	1·6 (2·2) 0 (2) N=171 (1)	1·8 (2·2) 1 (3) N=173 (5)
Week 3	1·5 (2·0) 1 (2) N=344 (27)	1·3 (1·9) 0 (2) N=171 (11)	1·7 (2·1) 1 (3) N=173 (16)
Week 5	1·3 (1·9) 0 (2) N=344 (45)	1·2 (1·9) 0 (2) N=171 (21)	1·4 (2·0) 0 (2) N=173 (24)
Week 8	1·3 (1·9) 0 (2) N=344 (70)	1·2 (1·9) 0 (2) N=171 (38)	1·3 (1·9) 0 (2) N=173 (32)
Week 12	1·1 (1·8) 0 (2) N=344 (115)	1·2 (1·9) 0 (2) N=171 (64)	1·1 (1·8) 0 (2) N=173 (51)
Week 16	1·0 (1·7) 0 (1) N=344 (129)	1·0 (1·7) 0 (2) N=171 (76)	0·9 (1·7) 0 (1) N=173 (53)

Table S2: Pain in the course of the study treatment time of maximum 16 weeks in the ITT-population. Pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	EQ5D NPWT	EQ5D SMWC
Screening	0,53 (0,27) 0,53 (0,2) N=156 (2)	0,53 (0,24) 0,53 (0,18) N=159 (3)
End of therapy	0,67 (0,24) 0,77 (0,29) N=62 (2)	0,72 (0,17) 0,66 (0,35) N=13 (0)

End of maximum study treatment time	0,66 (0,22) 0,66 (0,28) N=63 (2)	0,61 (0,25) 0,63 (0,24) N=95 (2)
Follow up after 6 months	0,69 (0,26) 0,77 (0,35) N=93 (3)	0,67 (0,23) 0,63 (0,39) N=97 (2)

Table S3: Quality of life (EQ5D) in the course of the study treatment time of 16 week in the ITT-population. Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT-population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Wound surface area	**Small wounds**				**Big wounds**			
mm^2	**Total N=173**	**NPWT N=83**	**SMWC N=90**	**p**	**Total N=172**	**NPWT N=88**	**SMWC N=84**	**p**
N (LOCF)	2	2	0	0·232	0	0	0	0·193
Mean (SD)	213 (136)	212 (138)	213 (135)		1995 (3377)	1860 (1805)	2135 (4474)	
Median (IQR)	188 (220)	176 (220)	196 (222)		1276 (1482)	1364 (1242)	1242 (1708)	
Min - Max	12-484	20-484	12-471		491-40773	520-13188	491-40773	

Table S4: Wound surface area for small and big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms, the number (N) of values substituted by the last observation carried forward (LOCF) method; mean (SD), median (IQR); and minimum (min) and maximum (max).

Wound closure rate **Small wounds**	**NPWT (N=171)** **N=83**	**SMWC (N=174)** **N=90**	**p**
Within 16 weeks maximum study treatment time	12 (14·5 %)	16 (17·8 %)	0·6
At follow up after 6 months	13 (15·7 %)	24 (26·7 %)	0·10

Table S5: Wound closure rates within the maximum study treatment time of 16 weeks and within the study observation time of 6 months for small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number of patients with wound closure (N) within 16 weeks and after 6 months as well the percentage (%) of patients achieving the endpoints within both treatment arms.

Wound closure rate **Big wounds**	**NPWT (N=171)** **N=88**	**SMWC (N=174)** **N=84**	**P**
Within 16 weeks maximum study treatment time	13 (14·8 %)	5 (6·0 %)	0·08
At follow up after 6 months	11 (12·5 %)	12 (14·3 %)	0·82

Table S6: Wound closure rates within the maximum study treatment time of 16 weeks and within the study observation time of 6 months for big wounds. Data show the number (N) of participants available for the analysis in total and for both

treatment arms and the number of patients with wound closure (N) within 16 weeks and after 6 months as well the percentage (%) of patients achieving the endpoints within both treatment arms.

Time until min. 95 % granulation tissue for small wounds	**Total (N=100)**	**NPWT (N=52)**	**SMWC (N=48)**	**p**
Mean (SD)	38·6 (37·4)	28·5 (30·0)	49·5 (41·6)	0·005
Median (IQR)	26·5 (50·0)	20·0 (28·0)	48·0 (79·0)	
Min-Max	0-114	0-113	0-114	

Table S7: Time until optimal preparation of the wound bed (min. 95 % granulation tissue) for the subgroup of small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Time until min 95 % granulation tissue for big wounds	**Total (N=80)**	**NPWT (N=47)**	**SMWC (N=33)**	**p**
Mean (SD)	47·8 (40·8)	43·4 (37·9)	54·0 (44·6)	0·27
Median (IQR)	36·5 (70·0)	35·0 (61·0)	56·0 (105·0)	
Min-Max	0-127	0-127	0-115	

Table S 8: Time until optimal preparation of the wound bed (min 95 % granulation tissue) for the subgroup of big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Amputations & Resections **Small wounds**	**Total** **N=173**	**NPWT** **N=83**	**SMWC** **N=90**	**p**
No. of patients with amputations or resections [N (%)]	35 (20·2%)	19 (22·9%)	16 (17·8%)	0·45 (F)
No. of performed amputations and resections [N]	50	22	28	0·51 (U)
No. of patients with minor amputations [N (%)]	35 (20·2%)	19 (22·9%)	16 (17·8%)	0·45 (F)
No. of patients with major amputations [N (%)]	0 (0%)	0 (0%)	0 (0%)	-

Table S9: Amputations and resections in the subgroup of small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

Amputations & Resections **Big wounds**	**Total** **N=172**	**NPWT** **N=88**	**SMWC** **N=84**	**p**

No. of patients with amputations or resections [N (%)]	36 (20·9%)	16 (18·2%)	20 (23·8%)	0·45 (F)
No. of performed amputations and resections [N]	52	45	57	0·41 (U)
No. of patients with minor amputations [N (%)]	34 (19·8%)	14 (15·9%)	20 (23·8%)	0·25 (F)
No. of patients with major amputations [N (%)]	2 (1·2%)	2 (2·3%)	0 (0%)	0·50 (F)

Table S10: Amputations and resections in the subgroup of big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

Wound closure rate	**Total N=154**	**NPWT N=44**	**SMWC N=110**	**p**
Wound closures [N (%)] within 16 weeks	33 (21·4 %)	14 (31·8%)	19 (17·3%)	0·053
Wound closures [N (%)] after 6 months	41 (26·6 %)	11 (25·0%)	30 (27·3%)	0·84

Table S11: Wound closure rate after 6 months and in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with wound closures within 16 weeks and after 6 months.

Time until min. 95 % granulation tissue	**Total (N=100)**	**NPWT (N=38)**	**SMWC (N=62)**	**p**
Mean (SD)	43·8 (42·3)	23·8 (31·7)	56·0 (43·5)	<0·001
Median (IQR)	30·0 (76)	8·5 (28·0)	56·0 (96·0)	
Min - Max	0 - 127	0 - 127	0 - 115	

Table S12: Time until optimal preparation of the wound for further treatment (min 95 % granulation tissue) in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Recurrences	**Total (N=154)**	**NPWT (N=44)**	**SMWC (N=110)**	**p**
No. of patients with recurrences [N (%)]	8 (5·2 %)	3 (8·1 %)	5 (5·3%)	0·69
No. of recurrences [N]	9	4	5	0·38

Table S13: Recurrences in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with recurrences.

Amputations & Resections	**Total (N=154)**	**NPWT (N=44)**	**SMWC (N=110)**	**p**
No. of patients with amputation or resection [N (%)]	30 (19·5%)	9 (20·5%)	21 (21·4%)	0·83

No. of amputations or resections [N]	39	11	28	0·86
No. of patients with Minor-Amputations [N (%)]	30 (18·9%)	9 (12·8%)	21 (21·4%)	0·83
No. of patients with Major-Amputations [N (%)]	0 (0%)	0 (0%)	0 (0%)	-

Table S14: Amputations and resections in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

	Wound surface NPWT		**Wound surface SMWC**	
Observation time point	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**	**Observation time point**	**Calculated from width and length (according to eCRF entry)**
Randomization	964 (1392) 345 (1426) N= 44 (1)	633 (795) 299 (705) N=41 (3)	878 (1266) 373 (889) N= 110 (0)	669 (1143) 294 (692) N=102 (9)
Week 1	525 (696) 224 (408) N= 44 (5)	524 (614) 318 (561) N=41 (8)	827 (1238) 306 (863) N= 110 (16)	706 (1138) 289 (775) N=102 (27)
Week 3	428 (635) 176 (378) N= 44 (6)	477 (737) 165 (424) N=41 (9)	803 (1306) 238 (867) N= 110 (7)	714 (1316) 259 (656) N=102 (26)
Week 5	355 (590) 100 (291) N= 44 (8)	418 (602) 165 (435) N=41 (15)	650 (1157) 161 (670) N= 110 (18)	607 (1212) 167 (545) N=102 (29)
Week 8	284 (528) 53 (217) N= 44 (8)	320 (530) 83 (264) N=41 (16)	569 (1072) 106 (443) N= 110 (17)	479 (990) 123 (397) N=102 (29)
Week 12	283 (580) 14 (130) N= 44 (24)	289 (537) 62 (175) N=41 (32)	528 (1024) 79 (419) N= 110 (71)	474 (1006) 111 (407) N=102 (80)
Week 16	190 (416) 0 (95) N= 44 (14)	179 (333) 30 (204) N=41 (25)	386 (1124) 31 (159) N= 110 (19)	319 (724) 65 (256) N=102 (42)

Table S18: ~~Change of w~~Wound surface area at each observation time point during the study treatment time of maximum 16 weeks separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis using W.H.A.T. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Wound volume NPWT (mm^3)	Wound volume SMWC (mm^3)
Randomization	33359 (95749) 5746 (17330) N=44 (1)	14742 (36523) 3905 (11189) N=110 (0)
Week 1	11606 (26991) 1824 (6113) N=44 (5)	13525 (34844) 2470 (9479) N=110 (16)
Week 3	8636 (24698) 777 (3199) N=44 (6)	11907 (32047) 1864 (8039) N=110 (7)
Week 5	5480 (13967) 271 (1790) N=44 (7)	8981 (25570) 1027 (4745) N=110 (18)
Week 8	3955 (9056) 192 (809) N=44 (16)	6899 (18607) 506 (3915) N=110 (29)
Week 12	6052 (16114) 71 (681) N=44 (25)	5964 (15930) 361 (1890) N=110 (77)
Week 16	3246 (11245) 0 (319) N=44 (15)	3396 (10783) 57 (609) N=110 (19)

Table S15: W~~Change of w~~ound volume (length x width x depth) ~~in the course of~~for each observation time point during the study treatment time of maximum 16 weeks calculated from width· length and depth as documented in the eCRF. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	NPWT Granulation		NPWT Fibrin		NPWT Necrosis		SMWC Granulation		SMWC Fibrin		SMWC Necrosis	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.		eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF
Rando	32 (37)	23 (26)	18 (27)	68 (27)	2 (7)	9 (15)	38 (38)	26 (27)	21 (29)	67 (29)	1 (7)	7 (15)
	10 (68)	13 (37)	3 (28)	69 (45)	0 (0)	0 (15)	25 (80)	16 (42)	10 (33)	77 (56)	0 (0)	0 (8)
	44 (1)	41 (2)	44 (1)	41 (2)	44 (1)	41 (2)	110 (0)	102 (9)	110 (0)	102 (9)	108 (2)	102 (9)
Week 1	72 (37)	22 (26)	7 (13)	70 (28)	2 (7)	9 (15)	54 (35)	24 (27)	22 (24)	72 (27)	5 (14)	5 (9)
	90 (50)	9 (41)	0 (10)	75 (50)	0 (0)	0 (11)	63 (70)	13 (42)	13 (28)	78 (42)	0 (1)	0 (6)
	44 (5)	41 (8)	44 (6)	41 (8)	44 (7)	41 (8)	110 (16)	102 (27)	110 (16)	102 (27)	108 (19)	102 (27)
Week 3	77 (32)	16 (24)	11 (19)	79 (26)	1 (4)	6 (14)	61 (31)	24 (27)	25 (25)	75 (26)	4 (11)	3 (7)
	93 (34)	2 (29)	0 (20)	91 (37)	0 (0)	0 (1)	70 (50)	15 (42)	20 (35)	83 (41)	0 (0)	0 (1)
	44 (6)	41 (9)	44 (7)	41 (9)	44 (7)	41 (9)	110 (9)	102 (26)	110 (10)	102 (26)	108 (13)	102 (26)
Week 5	82 (29)	10 (16)	9 (19)	87 (17)	1 (4)	3 (9)	65 (29)	19 (27)	24 (24)	78 (27)	3 (9)	3 (11)
	95 (20)	4 (11)	2 (10)	93 (21)	0 (0)	0 (1)	73 (46)	4 (34)	13 (37)	93 (35)	0 (0)	0 (0)
	44 (7)	41 (16)	44 (8)	41 (16)	44 (9)	41 (16)	110 (19)	102 (27)	110 (22)	102 (27)	108 (22)	102 (27)
Week 8	85 (27)	15 (25)	6 (13)	82 (26)	2 (6)	3 (8)	74 (27)	20 (26)	18(21)	77 (27)	3 (10)	3 (12)
	100 (20)	1 (16)	0 (5)	96 (35)	0 (0)	0 (0)	80 (31)	3 (38)	10 (18)	91 (43)	0 (0)	0 (0)
	44 (9)	41 (16)	44 (10)	41 (16)	44 (9)	41 (16)	110 (18)	102 (30)	110 (21)	102 (30)	108 (25)	102 (30)
Week 12	86 (26)	13 (24)	6 (14)	85 (26)	2 (9)	2 (6)	77 (27)	18 (25)	16 (20)	80 (25)	3 (11)	2 (6)
	100 (18)	1 (13)	0 (4)	99 (20)	0 (0)	0 (0)	85 (29)	3 (36)	10 (20)	92 (36)	0 (0)	0 (0)
	44 (26)	41 (34)	44 (26)	41 (32)	44 (28)	41 (32)	110 (72)	101 (78)	110 (73)	102 (79)	108 (73)	102 (80)
Week 16	87 (25)	12 (22)	6 (14)	86 (24)	0·1 (1)	1 (6)	80 (30)	19 (25)	14 (24)	80 (26)	2 (11)	1 (5)
	100 (15)	0 (14)	0 (1)	100 (20)	0 (0)	0 (0)	95 (20)	5 (36)	0 (20)	92 (36)	0 (0)	0 (0)
	44 (14)	41 (25)	44 (16)	41 (25)	44 (15)	41 (25)	110 (18)	102 (42)	110 (21)	102 (42)	108 (24)	102 (42)

Table S20: ~~Change of~~Wound tissue (granulation, fibrin, necrosis) at each observation time point during the study treatment time of maximum 16 weeks separately shown for the data documented in the eCRF and for the data derived from the photo analysis using the wound healing analyzing too (W.H.A.T.). Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Pain Total N=344	Pain NPWT N=171
Screening	1·3 (2·1) 0 (2) N=44 (0)	1·8 (2·3) 1 (3) N=110 (0)
Week 1	0·7 (1·5) 0 (1) N=44 (0)	1·4 (2·1) 0 (3) N=110 (5)
Week 3	0·4 (0·7) 0 (1) N=44 (4)	1·3 (1·8) 0 (2) N=110 (3)
Week 5	0·3 (0·8) 0 (0) N=44 (2)	1·0 (1·6) 0 (2) N=110 (5)
Week 8	0·4 (1·1) 0 (0) N=44 (4)	0·9 (1·5) 0 (2) N=110 (9)
Week 12	0·3 (1·0) 0 (0) N=44 (11)	0·7 (1·3) 0 (1) N=110 (18)
Week 16	0·2 (0·7) 0 (0) N=44 (14)	0·5 (1·2) 0 (0) N=110 (13)

Table S16: Pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	EQ5D NPWT	EQ5D SMWC
Screening	0·61 (0·23) 0·63 (0·24) N=42 (1)	0·60 (0·20) 0·59 (0·25) N=100 (3)
End of therapy	0·65 (0·20) 0·78 (0·20) N=26 (2)	0·81 (0·14) 0·87 (0·26) N=8 (0)
End of maximum study treatment time	0·65 (0·25)	0·66 (0·21)

	0·66 (0·43) N=19 (0)	0·63 (0·28) N=73 (2)
Follow up after 6 months	0·75 (0·22) 0·78 (0·30) N=26 (0)	0·70 (0·23) 0·77 (0·34) N=73 (2)

Table S17: Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6,8,9
Participants	4a	Eligibility criteria for participants	6,7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7,8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8,9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	9,10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12 Fig. 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig. 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12,13,14Tab. 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig. 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14-20
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	14-20
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	18-19
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	19-20
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3,21-22
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	21
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10-11

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Negative Pressure Wound Therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026345.R2
Article Type:	Original research
Date Submitted by the Author:	07-Nov-2019
Complete List of Authors:	Seidel, Dörthe; Universitat Witten/Herdecke, Institut für Forschung in der Operativen Medizin (IFOM) Storck, Martin; Stadtisches Klinikum Karlsruhe gGmbH, Klinik für Gefäß- und Thoraxchirurgie Lawall, Holger; Praxis für Herzkreislauferkrankungen; Max-Grundig Klinik Wozniak, Gernold; Knappschaftskrankenhaus Bottrop GmbH, Gefäßchirurgische Klinik Mauckner, Peter; St. Remigius Krankenhaus Opladen, Innere Medizin Hochlenert, Dirk; Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Wetzel-Roth, Walter; Chirurgische Praxis Wetzel-Roth Sondern, Klemens; Marien Hospital Dortmund-Hombruch, Klinik für Innere Medizin/Diabetologie Hahn, Matthias; Helfenstein Klinik, Allgemein- und Viszeralchirurgie Rothenaicher, Gerhard; Chirurgische Praxis Rothenaicher Krönert, Thomas; Thüringen-Kliniken "Georgius Agricola" GmbH, Klinik für Gefäßchirurgie Zink, Karl; Diabetes Klinik Neugebauer, Edmund; Universitat Witten/Herdecke Department fur Humanmedizin; Medizinische Hochschule Brandenburg -Theodor Fontane
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Surgery, Evidence based practice, Dermatology
Keywords:	negative pressure wound therapy, wound healing, benefit assessment, wound treatment, Diabetic foot < DIABETES & ENDOCRINOLOGY, wound care

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Negative Pressure Wound Therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT

Dörthe Seidel, Martin Storck, Holger Lawall, Gernold Wozniak, Peter Mauckner, Dirk Hochlenert, Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert, Karl Zink, Edmund Neugebauer

Institut für Forschung in der Operativen Medizin (IFOM), University of Witten/Herdecke, Köln, Germany (D Seidel MD), Doerthe.Seidel@uni-wh.de

Klinik für Gefäß- und Thoraxchirurgie, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany (Prof M Storck MD), Martin.Storck@klinikum-karlsruhe.de

Praxis für Herzkreislauferkrankungen, Ettlingen und Max-Grundig Klinik Bühlerhöhe, Germany (Dr med H Lawall MD), holger.lawall@gmail.com

Gefäßchirurgische Klinik, Knappschaftskrankenhaus, Bottrop, Germany (Prof G Wozniak MD), gernold.wozniak@kk-bottrop.de

Innere Medizin, St. Remigius Krankenhaus Opladen, Leverkusen, Germany (Dr med P Mauckner MD), peter-mauckner@live.de

Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock, Köln, Germany (Dr med D Hochlenert MD), dirk.hochlenert@web.de

Chirurgische Praxis Wetzel-Roth, Buchloe, Germany (Dr med W Wetzel-Roth MD), info@wetzel-roth.de

Klinik für Innere Medizin/Diabetologie, Marien Hospital Dortmund-Hombruch, Dortmund, Germany (Dr med Sondern MD), klemens.sondern@marien-hospital-dortmund.de

Allgemein- und Viszeralchirurgie, Helfenstein Klinik, Geisslingen, Germany (Dr med M Hahn, MD), matthias.hahn@af-k.de

Chirurgische Praxis Rothenaicher, München, Germany (G Rothenaicher MD), rothenaicher@arcor.de

Klinik für Gefäßchirurgie, Thüringen-Kliniken "Georgius Agricola" GmbH, Saalfeld, Germany (Dr med T Krönert MD), tkroenert@thueringen-kliniken.de

Diabetes Klinik, Bad Mergentheim, Germany (Dr med K Zink MD), zink@diabetes-zentrum.de

University of Witten/Herdecke, Köln, Germany (Prof E Neugebauer), Edmund.Neugebauer@uni-wh.de

Correspondence to:

Dörthe Seidel*

Institut für Forschung in der Operativen Medizin (IFOM)

University of Witten/Herdecke

Ostmerheimerstraße 200 Haus 38

Köln (Cologne)

51109 Germany

Doerthe.Seidel@uni-wh.de

Abstract

Objectives

The aim of the DiaFu-study was to evaluate effectiveness and safety of negative pressure wound therapy (NPWT) in patients with diabetic foot wounds in clinical practice.

Design

In this controlled clinical superiority trial with blinded outcome assessment patients were randomized in a 1:1 ratio stratified by study site and ulcer severity grade using a web-based-tool.

Setting

This German-national study was conducted in 40 surgical and internal medicine in- and outpatient facilities specialized in diabetes foot care.

Participants

368 patients were randomized and 345 participants were included in the modified ITT population. Adult patients suffering from a diabetic foot ulcer at least for 4 weeks and without contraindication for NPWT were allowed to be included.

Interventions

NPWT was compared with standard moist wound care (SMWC) according to local standards and guidelines.

Primary and secondary outcome measures

Primary endpoints were wound closure rate and time to closure within 16 weeks. Secondary endpoints were wound- and treatment-related adverse events (AEs), amputations, time until optimal wound bed preparation, wound size and wound tissue composition, pain, and quality of life within 16 weeks, and recurrences and wound closure rate within 6 months.

Results

In the ITT population 25 patients in the NPWT-arm (14·6%) and 21 patients in the SMWC-arm (12·1%) achieved wound closure (p=0·53). Wound closure time was not significantly different between the treatment arms (p=0·24). 96 patients in the NPWT-arm and 72 patients in the SMWC-arm had at least one AE (p=0·007), but only 11 AEs have been possibly related to NPWT. Documentation deficiencies, premature cessation of NPWT and temporary changes of the randomized treatment negatively impacted the outcome wound closure.

Conclusions

NPWT was not superior to SMWC in diabetic foot wounds in clinical practice. Overall wound closure rate was low. Deviations from guidelines limit the treatment success.

Trial registration

Clinical Trials.gov: NCT01480362

Strengths and limitations of this study

- The DiaFu study included patients with diabetic foot ulcers both with peripheral neuropathy and peripheral arterial occlusive disease, which corresponds to the typical mixed patient population in real-life clinical practice and enables a general statement about effectiveness and safety of NPWT in the typical medical care situation.
- The study does not provide any information on the effectiveness of NPWT in specific patient groups, which was not intended and may be seen as a limitation.
- In this health services research study hospitals and outpatient facilities were selected by means of a qualification checklist and clinical investigators were obliged to provide patients with the best clinical practice in compliance with all relevant guidelines, but there was no active monitoring of the implementation of these guidelines.
- To ensure the best quality of local wound treatment and to achieve optimal baseline conditions, the study sites were trained for both NPWT and SMWC, but treatment application was at the discretion of the clinical investigators.
- Methods against bias were applied whenever possible, but due to the nature of the compared treatment methods, a direct blinding of patients and clinical investigators was not possible and blinded outcome assessment could only be implemented for the endpoints wound closure and wound size development over time by means of wound photographs.

Background

More than 400 million people worldwide suffer from diabetes [1, 2] and about 15% of all these patients will develop a diabetic foot ulcer (DFU) during their lifetime [3, 4]. Approximately 50-70% of all lower limb amputations are due to diabetes [4]. DFUs represent complex chronic wounds with a major impact on patients` morbidity, mortality and quality of life. Beside an optimal diabetes and infection control, pressure relieving strategies and restoring pulsatile blood flow, effective local wound care is part of the holistic approach necessary to optimally treat patients with DFUs. Only a few modern moist wound dressings and topical agents have been convincingly shown to achieve higher wound closure rates compared with traditional wet gauze dressings in patients with diabetic foot wounds [5]. Also, for other ulcer types there is an uncertainty which dressings and topical agents are most effective for treatment [6]. Negative pressure wound therapy (NPWT) is an innovative treatment option and one of the most commonly used and well-established technologies with the aim to promote wound healing [7]. The first use of vacuum sealing was described in 1993 by Fleischmann et al. [8] and the

commercially available product was developed later in the 1990s [9, 10]. Positive effects of NPWT on wound healing have been suggested in various basic studies [10, 11]. At the time of planning the DiaFu-study, the clinical evidence largely consisted of clinician perception, case reports and series, small cohort studies, and weakly-powered or low-quality randomized trials that documented broad use of NPWT in various clinical settings and constituted a substantial number of publications but an overall small amount of evidence [12-15]. Two randomized controlled trials (RCTs) performed by Armstrong 2005 [16] and Blume 2008 [17] provided a solid basis for planning a study.

In the recent years, a specific review for the use of NPWT in diabetic foot wounds performed by Dumville et al in 2013 [18], an assessment in the home setting by Rhee at al. in 2014 [19] and a health technology assessment particularly issued for the evaluation of NPWT for managing diabetic foot ulcers [20] in 2014, as well as the most recent work of Liu et al in 2017 [21, 22] all concluded that although NPWT may have a positive effect, the trials that have been performed have methodological flaws and sufficient, unbiased evidence of whether wounds heal better or worse with NPWT than with conventional treatment is still missing.

In Germany, the issue of evidence for efficacy and safety of NPWT in acute and chronic wounds was first addressed in 2002 when the German Federal Joint Committee (German: Gemeinsamer Bundesausschuss [G-BA]) needed to decide whether NPWT could be reimbursed without restrictions in outpatient care.

Finally, in 2007 taking into account all available evidence the G-BA decided that the benefits of the treatment method NPWT should be evaluated in a so-called model project. This included the conduct of clinical studies for which the G-BA defined basic requirements. This essentially concerned the formulation of a study hypothesis that supports G-BA's overall question if NPWT can be reimbursed in German outpatient care without any limitation; the selection of a comparator that represents the current treatment standard in Germany; and implementation of all measures to ensure a sufficient certainty of the results.

Following the announcement of the G-BA, the German statutory health insurance funds initiated an overall project through a European tender. The DFU has been chosen to be the representative for chronic wounds in a RCT comparing NPWT and standard moist wound care (SMWC) in clinical practice.

Methods

Aim of the study

The aim of the DiaFu-study was to evaluate whether the effectiveness and safety of NPWT is superior to SMWC in German real-life clinical practice.

Study Design

The DiaFu-study was a German-national, multicenter, randomized controlled clinical superiority trial with blinded assessment of wound closure, wound size and wound tissue qualities using photographs. This German national study was conducted both in hospital departments and outpatient facilities with a special qualification for diabetic foot care. Study treatment was allowed to be started both in in- and outpatient care and should be continued outpatient whenever possible. Ethical approval of the Lead Ethical Committee of the University of Witten/Herdecke has been fully granted without any conditions. More detailed information on the study design can be found in the study protocol publication that is available open access [23].

Patient and Public Involvement

Patients were not involved in the design, recruitment or conduct of the study. The results of this study will not be disseminated directly to study participants.

Participants

Following a pragmatic approach with the aim to include a patient population best representing real-life clinical practice, in- and exclusion criteria have been selected based on manufacturers' contraindications and FDA warnings, the necessity to excluded patients in need of protection and who are unable to give their consent, and the intention to avoid general study-related influences on the results.

Adult patients (age >18 years) with at least 4-week-old chronic diabetic foot ulcers corresponding to Wagner 2 to 4 were screened for study participation by the local investigators. Before inclusion, the study protocol required either a debridement or, if necessary, an amputation of foot parts, or at least a thorough wound cleansing, depending on the individual needs of the patients, in order to achieve the optimal outcome of wound treatment. Thus, chronic diabetic foot wounds after adequate wound pretreatment as well as post-surgical amputation wounds below the upper ankle joint were eligible for inclusion. The initially planned minimum ulcer age of 6 weeks was reduced to 4 weeks during the course of the study. Patients estimated to be at risk of non-compliance with study requirements,

with wounds with necrotic tissue present that could not be removed by debridement or amputation, with exposed blood vessels within or directly surrounding the wound not possible to be sufficiently covered or with an increased risk of bleeding with hemodynamic consequences (mainly relevant for posterior tibial artery dorsalis pedis artery), and outpatients receiving anticoagulation therapy or suffering from a high-grade impaired clotting function with a heightened risk of bleeding with hemodynamic consequences were excluded from the DiaFu-study. The use of NPWT devices on the study wound within six weeks prior to study start represented an exclusion criterion in order to demonstrate a clear therapeutic effect of each treatment arm.

Written informed consent was obtained from every participant after being informed about all aspects of the trial and before randomization and any trial-related procedure. As the statutory health insurance funds provided integrated care contracts for outpatient NPWT, it was only possible to include patients in the study who were members of a participating health insurance fund.

Basic data were collected for all patients considered for study participation during screening and have been updated during the randomization visit. Study sites have been selected based on their qualifications and experiences using a pre-study qualification checklist and annual quality reports of the respective institution (if available).

Randomization and masking

Patients were randomly allocated to the treatment arms in a 1:1 ratio using a computer-generated list located on a centralized web-based tool. The randomization list consisted of permuted blocks of variable length (4, 6) which were randomly arranged. Patients were stratified by study site and by Wagner-Armstrong stage within each site (<Wagner-Armstrong stage 2C and ≥ Wagner-Armstrong stage 2C). The randomization lists were generated with the help of a self-created Java program and integrated into the study database. Each registered investigator received individual access to the randomization tool via the study website, but without knowledge of future treatment assignment, which provided adequate allocation concealment. The investigators were responsible for adequately implementing the assigned therapy. Due to the physical differences between the treatment regimens it was not possible to blind either participant or physician to the treatment assignment. Verification of complete wound closure was performed by independent, blinded assessment of wound photographs. Determination of wound size and percentage wound tissue quality was also performed by central, blinded outcome assessors based on the wound photographs using the Wound Healing Analyzing Tool (W.H.A.T.). The determination of sufficient wound bed conditioning and the indication for surgical closure was carried out by the treating physician, as in clinical practice. The treating physician was not blinded to treatment allocation.

Procedures

Before randomization and start of study treatment all patients underwent one or more of the following no longer than six hours before randomization: amputation, debridement or thorough wound cleansing. Patients received an extensive examination of overall health status, specific diabetes associated disorders, and relevant influence factors on wound healing during screening with an update at the randomization visit. Pedal perfusion was assessed by Ankle Brachial Index (ABI), ankle and pedal Doppler arterial waveforms, and either toe systolic pressure or transcutaneous oxygen pressure (TcPO2). Infection diagnosis followed the approach involving clinical evaluation and laboratory testing, and in case of suspected diabetic foot osteomyelitis (DFO) a probe to bone test and a stepwise approach to imaging modalities in order to confirm and to determine the best treatment regimen for the study participants. Study therapy was allowed to be started either in-hospital or as outpatient and was intended to be continued in outpatient care whenever possible.

In the intervention arm commercially available CE-marked NPWT devices of the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew were used in the discretion of the clinical investigator according to clinical routine and manufacturer's instructions [23]. Recommendations for use can be found on the manufacturers' websites. As part of the European tender for the overall project, the German statutory health insurance funds awarded lots for the provision of the medical products by the respective manufacturers. Germany was divided into 4 supply areas. During the award procedure, Smith & Nephew received 1 lot and KCI 3 lots. Thus, devices and consumables of Smith& Nephew were used for the north and northern east region of Germany and for the rest of Germany the therapy systems of KCI were used. Within the study, NPWT was required to be used for wound bed preparation in order to achieve at least 95% granulation of the wound area. After optimal preparation of the wound, complete closure could be achieved either by secondary intention with dressings or by surgical closure with subsequent removal of the suture.

Control therapy was defined as any SMWC according to local clinical standards and guidelines [24, 25]. Healthcare providers were obligated to provide patients with best practice. In the control arm it was permitted to apply any local wound treatment standard used in the respective study site that did not have an experimental status or was NPWT. To ensure the best quality of local wound treatment, the study sites were trained for both the intervention arm by the manufacturers and the control arm by the German Society for Wound Healing and Wound Treatment which provided parts of its curriculum and experienced instructors.

The maximum study treatment time was 16 weeks after randomization. Study visits needed to be performed at week one, three, five, 12 and 16 and included a complete wound examination. Wound closure was possible to be achieved at any time within the study treatment period of 42 days and had to be documented in a wound closure

visit as well as in a wound closure confirmation visit after 14 days. Study participants were followed up until 6 months after randomization. The initially planned follow-up period of 12 months was reduced to 6 months in the course of the study. The amendment to the study protocol was endorsed by the Ethics Committee and immediately communicated to all participating study sites.

Outcomes

The primary outcomes were wound closure rate and the time until complete wound closure within a maximum study treatment period of 16 weeks. Complete wound closure was defined as 100% epithelialization of the wound, no drainage, no suture material and no need for wound dressing or adjuvants. Wound closure needed to sustain a minimum of 14 days after the first diagnosis and to be confirmed by independent blinded observers using wound photographs. If wound closure was achieved by surgical methods, the endpoint was not reached until the above criteria were met (e.g. only after removal of the suture).

Secondary outcomes were wound closure rate after six months; time until optimal preparation of the wound bed (a minimum of 95% granulation), amputations and resections, wound size and wound tissue composition, pain and quality of life within 16 weeks; and recurrence within six months. The initial planned secondary endpoint of time until wound closure within 6 months was abandoned during the course of the study. It was found that a time-to-event survey was not possible outside the active study treatment period. This was mostly due to the fact that after this 16-week period weekly study visits were no longer an obligation and further patient care was no longer bound to the study site.

Minor and major amputations were considered separately, whereas the disarticulation at the midtarsal joint (Chopart's amputation) was considered still to be minor. Wound size and wound tissue composition (percentage of granulation tissue, fibrin and necrosis) were monitored at each study visit. Quality of life (QoL) was measured using the questionnaire Euro Quol 5D (EQ5D) at inclusion, end of the maximum treatment time or end of the therapy and at the six-month follow-up visit. At each study visit participants were asked to provide their assessment of wound-associated pain on a numerical rating scale (0 to 10). The incidence of serious adverse events (SAEs) within six months and the incidence of device-related and wound-related adverse events occurring within 16 weeks or until wound closure confirmation were safety endpoints of this trial.

Statistical analysis

Sample size calculation was performed using the expected difference between wound closure rates in both treatment arms based on information extracted from previously published studies by Armstrong and Lavery [16]

and [17]. We assumed a complete wound closure rate of 45% for NPWT and 30% in the SMWC group, resulting in a minimum difference of 15% after a treatment time of 16 weeks. Based on a type one error of $\alpha = 0.05$ and a type two error of $\beta = 0.2$ (corresponding to a power of 80%) a total sample size of 162 patients per group was calculated. The computer program of Dupont and Plummer was used for sample size calculation [26].

We performed all analyses based on a modified intention-to-treat (ITT) population that includes all randomized participants who have a valid baseline and at least one valid post baseline wound assessment. As a secondary approach a per-protocol (PP) analysis has been performed excluding patients with any serious protocol deviations, temporary changes from SMWC to NPWT, permanent wound treatment changes or without valid documentation until wound closure confirmation or end of maximum treatment time (EOMT). Safety data are presented on an 'as treated' basis. Subgroup analysis is presented for small vs big wound subpopulations. There was no interim analysis.

The superiority hypothesis was tested in parallel for wound closure rate and time to wound closure within16 weeks. Incidence of complete wound closure was analyzed using a chi-squared test (Fisher's exact test) comparing the two treatment arms. Time to complete wound closure was compared between the two treatment arms using a log-rank test. The method of Bonferroni-Holm was used for adjustment of the α-error for parallel confirmatory testing of both primary endpoints. Missing values have been incorporated as censored values.

During study planning, the following concomitant diseases and therapeutic measures with a possible influence on the primary study outcome wound closure (confounders) were identified: presence of neuropathy (sensation loss according to the PEDIS classification system [27]); presence of diabetic neuropathic osteoarthropathy (DNOAP) (anatomical classification according to Sanders [28] and progression stages according to Levin [29]
), Wagner [30] grading of the ulcer; presence of peripheral arterial occlusive disease (Rutherford classification for chronic limb ischemia [31]), chronic venous insufficiency (CVI) (Widmer I-III [32]), presence of extreme foot deformities and malpositions of toes, foot or the entire limb; untreated or therapy-refractory inflammation in the wound area; chronic anemia; heel necrosis; presence of a lymphedema; infection; heightened glycated hemoglobin (HbA1c) level; dialysis; application of hyperbaric oxygen (HBO) or normothermal therapy, application of recombinant or autologous growth factors to the study wound, and application of skin or dermal substitutes and with living cells that produce growth factors. These covariates thought to influence wound closure were analyzed for their effect on the two primary endpoints. Covariates were excluded from the analysis if the number of missing values was too high. First, the relevant covariates were tested by means of a univariate analysis with regard to their effect on wound closure rate and time without consideration of the treatment arms. If there was a significant influence, the frequency of occurrence in the treatment arms was analyzed. Secondary, multivariate analyses were

performed for both primary endpoints, taking into account treatment assignment and including all relevant covariates. The multivariate analysis of the primary endpoint wound closure rate was performed with binary logistic regression to describe the influence of the independent covariates (regressors) on the dependent dichotomous variable wound closure. The multivariate analysis of the primary endpoint time to wound closure was performed using a COX regression model.

Safety and secondary endpoints were analyzed using conventional univariate testing.

Within a priori planned subgroup analysis the ITT population was divided into a group of small wounds and a group of big wounds based on the wound surface area documented during the randomization visit. Wounds smaller than or equal to the total median wound surface (483 mm²) were assigned to the subgroup "small wounds". Patients with wound surface areas larger than the median value were assigned to the subgroup "large wounds". Since no citable scientific definition of a large wound was available at the time of study planning and the clinical experts involved could not make a decision, the median of all wounds was chosen as the criterion for the division into the two subgroups. Confirmatory analysis of primary and secondary endpoints was repeated for the subgroups.

Missing values for the following outcome parameters were replaced using the Last Observation Carried Forward (LOCF) method: wound closure rate, wound size and wound tissue quality, recurrence and amputation. The outcome parameters time to wound closure and time until optimal preparation of the wound bed did not require data replacement, since missing values are included in the analysis as right-censored values. If the wound closure is not confirmed to be closed after a minimum of 14 days, the wound is considered as an unsustained wound closure. All missing quality of life values (EQ-5D) were replaced with the overall quality of life assessment (visual analogue scale), if available. If there was no quality of life assessment, there was no replacement. For missing values of the demographic and baseline characteristics, which are necessary for the estimation of the regression coefficients, no replacement was performed. IBM SPSS Statistics (version 23) was used for all analyses.

This study is registered with ClinicalTrials.gov· number NCT01480362 and in the German Clinical Trial Registry, number DRKS00003347.

A data monitoring committee was formed to oversee overall study performance and safety.

Role of the funding source

Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds, which provided integrated care contracts for all study participants and for up to 7000 patients with acute and chronic wounds in Germany; defined basic rules for study design based on the requirements of the German authorities; and provided a critical review of the study protocol and the final report. The study was funded by the

manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary support and information about the used material. The manufacturers had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

Results

Between Dec 23, 2011 and August 12, 2014 386 patients were enrolled and randomly assigned to receive NPWT (181) or SMWC (187) in the DiaFu-study (**Error! Reference source not found.**) in overall 40 study sites, which recruited minimum 1 patient and maximum 76 patients. A full list of investigators can be found in the appendix. 13 clinical investigators randomized more than 10 patients. 23 study sites enrolled only between 1 and 4 patients. Most of these study sites refused further study participation due lack of time and staff for adequately performing the documentation. In the further course of the trial research nurses have been hired by the independent scientific institute overseeing the trial in order to support the documentation in the study sites whenever needed.

Demographics and relevant baseline characteristics of the DFU are presented in Table 1 and the appendix. Baseline characteristics of the patients in the NPWT-and the SMWC-arm are similar in the ITT population without any relevant difference between the treatment arms.

Demographics of the study population and baseline parameters of the DFU (ITT population)	**Total N=345 (100 %)**	**NPWT N=171 (49·6%)**	**SMWC N=174 (50·4%)**
Male	267 of 345 (77·4%)	133 of 171 (77·8%)	134 of 174 (77·0%)
Female	78 of 345 (22·6%)	38 of 171(22·2%)	40 of 174 (23·0%)
Age (years) (N=345) Mean (SD)	67·8 (11·9)	67·6 of 171(12·3)	68·1 (11·5)
Height (N=340) (in cm) Mean (SD)	174·1 (12·4)	173·4 (14·6)	174·8 (9·9)
Weight (N=335) (in kg) Mean (SD)	93·3 (22)	92·7 (21·5)	93·8 (22·6)
Localization of the ulcer			
Regio calcanea	39 (11·3%)	17 (9·9%)	22 (12·6%)
Dorsum pedis	20 (5·8%)	13 (7·6%)	7 (4%)
Planta pedis	56 (16·2%)	30 (17·5%)	26 (14·9%)
Metatarsalia	147 (42·6%)	73 (42·7%)	74 (42·5%)
Phalanges distales	64 (18·6%)	31 (18·1%)	33 (19%)
Phalanges mediales	28 (8·1%)	14 (8·2%)	14 (8%)
Phalanges proximales	40 (11·6%)	21 (12·3%)	19 (10·9%)
Hallux	42 (12·2%)	24 (14%)	18 (10·3%)
Digitus pedis II	22 (6·4%)	10 (5·8%)	12 (6·9%)
Digitus pedis III	14 (4·1%)	7 (4·1%)	7 (4%)
Digitus pedis IV	20 (5·8%)	7 (4·1%)	13 (7·5%)
Digitus minimus	25 (7·2%)	12 (7%)	13 (7·5%)
Type of ulcer			

Primary ulcer	279 of 342 (80·9%)	136 of 170 (79·5%)	143 of 172 (82·2%)
Recurrence	63 of 342 (18·3%)	34 of 170 (19·9%)	29 of 172 (16·7%)
Duration of ulcer (days)			
N	335	168	167
Mean (SD)	189·7 (360·2)	217·1 (458·1)	162·1 (220)
Median	83	81	85
Min – Max	0 – 4468	0 – 4468	0 – 1826
Wound surface area at randomization (cm^2)			
Mean (SD)	1101 (2543)	1060 (1536)	1141 (3247)
Min-Max	[12 – 40773]	[20 – 13188]	[12 – 40773]

Table 1: The table shows patient demographics and baseline characteristics of the ITT- population. Data are Number (N) and Percentage (%), Mean and Standard Deviation (SD), and Minimum – Maximum [Min – Max]. "N=" is stating the number of patients with actual available information. Findings, diagnoses and procedures documented by the investigators are presented.

The baseline of the identified factors possibly influencing wound closure is shown in Table 2.

Confounders at baseline (ITT population)	**Total N=345 (100 %)**	**NPWT N=171 (49·6%)**	**SMWC N=174 (50·4%)**
Presence of neuropathy (sensation loss according to the PEDIS classification system)	250 of 334 (72·5%)	125 of 166 (73·1%)	125 of 168 (71·8%)
Presence of a diabetic neuropathic osteoarthropathy (DNOAP)	61 (17·7%)	30 (17·5%)	31 (17·8%)
Wagner grading of the ulcer			
1 - Superficial ulcer of skin or subcutaneous tissue	6 (1·7%)	2 (1·2%)	4 (2·3%)
2 - Ulcers extend into tendon, bone, or capsule	225 (65·2%)	110 (64·3%)	115 (66·1%)
3 - Deep ulcer with osteomyelitis, or abscess	85 (24·6%)	45 (26·3%)	40 (23%)
4 - Gangrene of toes or forefoot	26 (7·5%)	13 (7·6%)	13 (7·5%)
5 - Midfoot or hindfoot gangrene	3 (0·9%)	1 (0·6%)	2 (1·1%)
Presence of peripheral arterial occlusive disease (PAOD)	244 of 345 (70·7%)	121 of 171 (70·8%)	123 of 174 (70·7%)
Rutherford classification for chronic limb ischemia (Grade/Category)			
0/0 Asymptomatic—no hemodynamically significant occlusive disease	20 of 244 (8·2%)	8 of 121 (6·6%)	12 of 123 (9·8%)
I/1 Mild claudication	31 of 244 (12·7%)	16 of 121 (13·2%)	15 of 123 (12·2%)

I/2 Moderate claudication	20 of 244 (8·2%)	6 of 121 (5·0%)	14 of 123 (11·4%)
I/3 Severe claudication	5 of 244 (2·0%)	2 of 121 (1·7%)	3 of 123 (2·4%)
II/4 Ischemic rest pain	1 of 244 (0·4%)	1 of 121 (0·8%)	0 of 123 (0·0%)
III/5 Minor tissue loss—non-healing ulcer· focal gangrene with diffuse pedal ischemia	163 of 244 (66·8%)	87 of 121 (71·9%)	76 of 123 (61·8%)
III/6 Major tissue loss—extending above transmetatarsal level· functional foot no longer salvageable	4 of 244 (1·6%)	1 of 121 (0·8%)	3 of 123 (2·4%)
No chronic venous insufficiency (CVI)	259 of 302 (75·1%)	132 of 150 (77·2%)	127 of 152 (73%)
CVI Widmer I	25 of 302 (7·2%)	11 of 150 (6·4%)	14 of 152 (8%)
CVI Widmer II	12 of 302 (3·5%)	3 of 150 (1·8%)	9 of 152 (5·2%)
CVI Widmer III	6 of 302 (1·7%)	4 of 150 (2·3%)	2 of 152 (1·1%)
Presence of extreme foot deformities and malpositions of toes, foot or the entire limb	59 of 342 (17·1%)	26 of 170 (15·2%)	33 of 172 (19%)
Untreated or therapy-refractory inflammation in the wound area	15 of 343 (4·3%)	7 of 170 (4·1%)	8 of 173 (4·6%)
Presence of a heel necrosis	23 of 342 (6·7%)	10 of 168 (5·8%)	13 of 174 (7·5%)
No lymphedema	282 of 340 (81·7%)	139 of 167 (81·3%)	143 of 173 (82·2%)
Primary lymphedema	12 of 340 (3·5%)	5 of 167 (2·9%)	7 of 173 (4%)
Secondary lymphedema	46 of 340 (13·3%)	23 of 167 (13·5%)	23 of 173 (13·2%)
Clinical signs of inflammation (suspected infection)	159 of 344 (46·1%)	83 of 170 (48·5%)	76 of 174 (43·7%)
Local wound swab as part of the clinical routine	248 of 343 (71·9%)	126 of 170 (73·7%)	122 of 173 (70·1%)
Detection of germs within the local wound swab	205 of 247 (59·4%)	104 of 125 (60·8%)	101 of 122 (58%)
Hemoglobin			
N	177 of 345	86 of 171	91 of 174
Mean (SD)	9·5 (3,2)	9·6 (3·1)	9·4 (3·3)
Hemoglobin A1c (HbA1c)			
N	32 of 345	13 of 171	19 of 174
Mean (SD)	15·6 (18,3)	16·8 (16,7)	14·7 (19·6)
Requiring dialysis	29 of 343 (8·4 %)	15 of 170 (8·8%)	14 of 173 (8·0%)
Application of skin or dermal substitutes and with living cells that produce growth factors	0 of 341 (0%)	0 of 169 (0%)	0 of 172 (0%)

Table 2: The table shows the baseline of the identified factors possibly influencing wound closure in the ITT- population. Findings, diagnoses and procedures documented by the investigators are presented. Data are N (%), Mean (SD), and Minimum – Maximum [Min – Max].

Details on revascularization performed before study start are shown in Table 3.

Revascularization before study start	**Total N=345 (100 %)**	**NPWT N=171 (49·6%)**	**SMWC N=174 (50·4%)**
Performed revascularization before study start	23 of 345 (6·7%)	9 of 171 (5·3%)	14 of 174 (8·0%)
Percutaneous transluminal angioplasty (PTA)	13 of 23 (57%)	6 of 9 (67%)	7 of 9 (50%)
PTA + Stent	1 of 23 (4%)	0 of 9 (0%)	1 of 9 (7%)
Veins-Bypass	5 of 23 (22%)	2 of 9 (22%)	3 of 9 (21%)
Polytetrafluoroethylene (PTFE) Bypass	1 of 23 (4%)	0 of 9 (0%)	1 of 9 (7%)
Thromboendarterectomy and patch plastic	2 of 23 (9%)	0 of 9 (0%)	2 of 9 (14%)
Revascularization with influence on the wound	22 of 23 (96%)	9 of 9 (100%)	13 of 14 (93·9%)
Sufficient revascularization result*	20 of 23 (88%)	7 of 9 (78%)	13 of 14 (93%)
Insufficient revascularization result	2 of 23 (9%)	1 of 9 (11%)	1 of 14 (7%)
Revascularization result not assessable	1 of 23 (4%)	1 of 9 (11%)	0 of 14 (0%)

Table 3: The table shows revascularization performed in the ITT- population before study start. Data are N (%). * Sufficient revascularization result was defined as successful recanalization of the tibial artery in which the foot lesion is located or, if it is technically impossible to recanalize the respective artery, achievement of an unhindered inflow into at least one of the tibial vessels.

Results for the primary outcomes in the ITT population

In the ITT population, the overall number of patients with wounds closed within 16 weeks was 46 of 345 (13·3%). Wound closure rate was higher in the NPWT arm (14·6%) than in the SMWC arm (12·1%) but this was not significant (p 0·53) as the difference in healing rate between the two groups was only four patients (2·5%) (Table 4). Wounds treated with NPWT were approximately at the same risk of remaining open like patients receiving SMWC (RR 0·97 [95% CI: 0·89-1·06]).

Wound closure rate	Total N=345	NPWT N=171	SMWC N=174	p
Patients with wound closure within 16 weeks N (%) [95% CI]	46 (13·3 %) [9·8 – 17·8]	25 (14·6%) [9·5 –21·6]	21 (12·1%) [7·5 – 18·4]	0·53 (F)

Table 4: The table shows the wound closure rate for the ITT-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms. Wound closures within the maximum study treatment time of 16 weeks are shown with the number (N), the percentage (%) of patients, and the 95% Confidence Interval (CI). F=Fisher's Exact Test.

Beginning in week five the number of study patients with open wounds in the NPWT-arm was lower than in the SMWC-arm (Figure 2). There is no significant difference in the wound healing time between the two treatment arms (p = 0·244, Log Rank Test). Since the cumulative number of patients with open wounds was more than 70% after 16 weeks, we were not able to calculate medians for time to wound closure.

Results for the secondary outcomes in the ITT population

After 6 months the wound closure rate was higher in the SMWC- than in the NPWT-arm (36 of 174 [20·7 %] vs 24 of 171 [14· 0 %]), but the difference was not significant (p 0·12).

The time until optimal preparation of the wound for further treatment to achieve a complete epithelization (min 95 % granulation tissue) was significantly shorter for patients treated with NPWT (p 0·021) (Table 5).

Time until optimal preparation of the wound bed (min 95 % granulation tissue)	Total N=183	NPWT N=100	SMWC N=83	p
Mean (SD)	42·7 (39·0)	35·6 (34·6)	51·4 (42·6)	**0·008**
Median (IQR)	31 (64)	22·0 (48·0)	49·0 (53·6)	
Min - Max	0 - 127	0 - 127	0 - 115	

Table 5: The table shows time until optimal preparation of the wound for further treatment (min 95 % granulation tissue for the ITT-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms. Time until optimal preparation of the wound is described with mean (SD); median (IQR); and minimum (min) and maximum (max).

In the ITT population wound surface area and wound volume decreased continuously during the study treatment time of 16 weeks in both treatment arms. The values are largely scattered. Detailed information about the course

of wound surface area, volume and composition of tissues for both study populations are provided in the respective tables in the appendix. Wound surface area at each observation time point until end of maximum study treatment time of maximum of 16 weeks is separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis. The results of the blinded photo analysis using the Wound Healing Analyzing Tool (W.H.A.T.) were smaller than the values documented by the clinical investigators. Starting from a similar wound volume, the values also decreased continuously both in the NPWT- and in the SMWC-arm, wherein the values are smaller in the NPWT-arm than in the SMWC-arm at each observation time point.

Wound tissue composition is similar in both treatment arm s at baseline. Granulation tissue values increase during the study treatment period of 16 weeks and fibrin values decrease, with clinically documented values showing only minor differences between treatment arms. The values for necrotic tissue were very low and did not differ relevantly between the treatment arms. The results of the W.H.A.T. evaluation for granulation and fibrin deviate markedly from the values documented by the clinical investigators. Contrary to the clinically documented values, the W.H.A.T. evaluation shows low values for granulation and high values for fibrin.

No recurrences occurred during the study treatment time of 16 weeks. Between the end of the maximum study treatment time and the follow up at 6 months, 11 recurrences (6·4 %) occurred in the 171 patients in the NPWT arm. One patient had two recurrences. In the SMWC arm, five of 174 patients (2·9 %) had a recurrence. The difference is not significant (RR 2·24 [95%CI: 0·80-6·31]; p=0·131) but the overall number of 17 recurrences in 16 patients was very low.

There was no significant difference in the number of patients with amputation or resection (p 1·00), the overall number of performed interventions (p 0· 89), and the number of study participants with minor (0·79) and major amputations 0·25 between NPWT and SMWC arm (Table 6). Patients treated with NPWT were approximately at the same risk of undergoing an amputation or resection like patients treated with SMWC (RR: 0·99 [95%CI: 0·65-1·50]).

Amputations and resections	**Total** **N=345**	**UWT** **N=171**	**SMWC** **N=174**	**p**

Study participants with amputation or resection	71 20·6% [16·3 – 24,8]	35 20·5% [14,4 – 26,5]	36 20.7% [14·7 – 26,7]	1·00 (F)
Total number of amputations and resections	102	45	57	0·89 (U)
Number of amputations and resections per study participant				0·89 (U)
one event	49 (14·2%)	25 (14·6%)	24 (13·8%)	
two events	16 (4·6%)	10 (5·8%)	6 (3·4%)	
three events	4 (1·2%)	0 (0%)	4 (2·3%)	
four events	1 (0·3%)	0 (0%)	1 (0·6%)	
five events	1 (0·3%)	0 (0%)	1 (0·6%)	
Study participants with minor amputation	69 (20·0%)	33 (19·3%)	36 (20·7%)	0·79 (F)
Study participants with major amputation	2 (0·6%)	2 (1·2%)	0 (0%)	0·25 (F)

Table 6: The table shows the number of study participants with amputations / resections and the number of amputations / resections performed for the ITT-population. Data show the number (N) of participants, the percentage with the 95% Confidence Interval (95%CI), or the number of events accompanied with the respective percentage values in total and for both treatment arms. F = Fisher's Exact Test; U = Mann-Whitney U-Test.

Overall, pain levels were very low and decreased further during the study treatment time. The values hardly differ between the treatment arms at any observation time point. A table with pain levels can be found in the appendix.

At baseline Quality of life (EQ5D) had significant limitations in both treatment arms. Patients reaching the end of treatment within 16 weeks showed improved EQ5D levels in the NPWT arm and in the SMWC arm. Similar results have been found for patients who reached the end of the maximum treatment time without successful end of therapy. At the follow-up time after 6-months all patients still show increased EQ5D levels in both treatment arms. A table with detailed results for the EQ5D is provided in the appendix.

Safety results

The number of study participants with AEs was significantly higher in the NPWT arm (96 (56·1%)) than in the SMWC arm (72 (41·4%)) (p=0·007) but only 16 (10· 2%) of the AEs in the NPWT arm were decided by the investigators to have a definite relation to the medical device (Table 7). The number of study participants with at least one AE documented to be serious (SAE) was not significantly different between the treatment arms (NPWT

N=63 (36,8%); SMWC N=58 (33,3%); p 0·50) (Table 7). None of the SAEs in the NWPT arm was documented as definitely or possibly related to the medical device by investigators. For 9 of 244 AEs (6·1%) in the NPWT arm and 6 of 96 AEs (6·3%) in the SMWC arm the outcome death was documented. arm.

Adverse events (AEs) and Serious adverse events (SAEs)	**Total N=345**	**NPWT N=171**	**SMWC N=174**	**p**
Study participants with at least one AE N (%)	168 (48·7%)	96 (56·1%)	72 (41·4%)	0·007 (F)
Study participants with one AE N	103	54	49	
Study participants with two or more AEs N	65	42	23	
Total number of AEs N	269	167	102	
AEs with relationship to the medical device				
$N_{available}$	257	157	100	
Yes	16 (6·2%)	16 (10· 2%)	0 (0%)	
Possible	13 (5·1%)	11 (7·0%)	2 (2·0%) *	
No	211 (82·1%)	117 (74·5%)	94 (94·0%)	
Not assessable	17 (6·6%)	13 (8·3%)	4 (4·0%)	
AEs with relationship to SMWC				
$N_{available}$	185	110	75	
Yes	2 (1·1%)	0 (0%)	2 (2·7%)	
Possible	5 (2·7%)	5 (4·5%)	0 (0%)	
No	163 (88·1%)	96 (87·3%)	67 (89·3%)	
Not assessable	15 (8·1%)	9 (8·2%)	6 (8·0%)	
AEs with relationship to the treatment procedure				
$N_{available}$	244	148	96	
Yes	10 (4·1%)	6 (4·1%)	4 (4·2%)	
Possible	17 (7·0%)	15 (10·1%)	2 (2·1%)	
No	191 (78·3%)	111 (75·0%)	80 (83·3%)	
Not assessable	26 (10·7%)	16 (10·8%)	10 (10·4%)	
Study participants with at least one SAE N (%)	121 (35·1%)	63 (36·8%)	58 (33·3%)	0·50 (F)

Study participants with one SAE N	90	45	45	
Study participants with two or more SAEs N	31	18	13	
Total number of SAEs N	163	87	76	
SAEs with relationship to the medical device				
$N_{available}$	161	85	76	
Yes	0 (0%)	0 (0%)	0 (0%)	
Possible	0 (0%)	0 (0%)	0 (0%)	
No	154 (95·7%)	79 (92·9%)	75 (98·7%)	
Not assessable	7 (4·3%)	6 (7·1%)	1 (1·3%)	
SAEs with relationship to SMWC				
$N_{available}$	121	64	57	
Yes	1 (0·8%)	0 (0%)	1 (1·8%)	
Possible	1 (0·8%)	1 (1·6%)	0 (0%)	
No	113 (93·4%)	57 (89·1%)	56 (98·2%)	
Not assessable	6 (5·0%)	6 (9·4%)	0 (0%)	
SAEs with relationship to the treatment procedure				
$N_{available}$	156	84	72	
Yes	4 (2·6%)	0 (0%)	4 (5·6%)	
Possible	2 (1·3%)	2 (2·4%)	0 (0%)	
No	140 (89·7%)	74 (88·1%)	66 (91·7%)	
Not assessable	10 (6·4%)	8 (9·5%)	2 (2·8%)	

Table 7: The table shows the number of study participants with AEs and SAEs and the number of AEs and SAEs for the ITT-population. Data show the number (N) and the percentage (%) in total and for both treatment arms. * No treatment change to NPWT has been documented. F = Fisher's Exact Test (alpha=0.05).

Secondary analyses and subgroups

The univariate analysis of predefined covariates potentially influencing wound closure in the ITT population showed that only the presence of an infection at the time of randomization was significantly associated with both the wound closure rate and time. The influencing factor "infection" was almost equally represented in both treatment arms (NPWT 35·1 [27·9 – 42·2] % N=60; SCWT 32·8 [25·8 – 39·7] % N= 57), so the treatment

comparison was not influenced by this confounder. Of the a priori defined factors potentially influencing wound closure nine factors needed to be excluded because the number of missing values was too high or they were never documented by the investigators. The covariate peripheral arterial occlusive disease had significant influence on the time until wound closure (p 0·026) and infection had a significant influence on the wound healing rate (p 0·012). However, both influencing factors were almost evenly distributed over both study arms by randomization. Thus, the comparison of the treatment arms was also not influenced by these confounders.

In the ITT population in 173 study participants the median wound surface area was smaller than 484 mm² and in 172 study participants wounds were bigger than 484 mm². In the NPWT arm 48·5% (N=83) of patients had small wounds and 51·5% (N=88) of patients had large wounds. The SMWC arm had 51·7% (N=90) small wounds and 48·3% (N=84) big wounds. The differences between the treatment arms were not significant.

An overview of the measures for small and big wounds and detailed results for this subgroup analysis can be found in the appendix.

In the subgroup of big wounds, wound closure rate was significantly higher in the NPWT arm within 16 weeks (p 0·08). Patients with big wounds have a lower risk of not achieving wound closure within 16 weeks when treated with NPWT (RR 0·91 [95%CI: 0·82-1·0]). In the subgroup of big wounds, a significantly faster wound closure was achieved in the NPWT arm (p 0·027) (Figure 3). Time until complete, sustained and verified wound closure was not significantly different between the treatment arms in the subgroup of small wounds (Figure 4).

In the subgroup of small wounds, the time to reach 95 % granulation tissue was significantly shorter for the patients treated with NPWT (p 0·005). Time until optimal wound bed preparation was shorter in the NPWT arm in the subgroup of big wounds, but did not significantly differ to the result of the SMWC arm (p 0·27). There are no relevant or significant differences in the overall number of patients with amputation or resection between the treatment arms in both subgroups. Both major amputations were performed in patients with big wounds treated with NPWT. Due to the low overall number of recurrences (N=16) we were not able to perform a subgroup analysis for this outcome parameter.

Results for the primary and secondary outcomes in the PP population

In the PP-population study participants treated with NPWT showed a 14·5 % higher wound closure rate within 16 weeks than those treated with SMWC (Appendix), but the difference was not significant (p 0·053). Wounds treated with NPWT had a lower risk of remaining open after 16 weeks (RR 0·82 [95%CI: 0·66-1·03]) than wounds treated with SMWC. Time to wound closure in the NPWT arm was significantly shorter (p=0·004) (Figure 5). After 6 months, wound closure rate in the SMWC-arm was higher than in the NPWT-arm, but the difference was not

significant (p 0·84). As in the ITT population, optimal wound bed preparation was achieved significantly faster in patients receiving NPWT (p<0·001). Patients receiving NPWT had a higher risk of recurrence than those in the control group (RR 1·50 [95%CI: 0·37-6·01]), however there was no significant difference between the treatment arms regarding the total number of recurrences (p 0.38) or the number of patients with recurrences (p 0·69). 9 patients in the NPWT group and 21 (21·4%) patients in the SMWC group had an amputation or resection (NPWT RR 1·07 [95%CI: 0·53-2·15]). Neither the number of patients with amputations or resections (NPWT 9 (20·5%) SMWC 21 (21·4%) p 0·83) nor the number of amputations or resections performed (NPWT 11 SMWC 28 p 0·86) differ significantly between the treatment arms. No major amputations were performed in the PP population. In the PP-population wound surface area started at smaller baseline levels and decreased faster than in the ITT-population whereas the measures were smaller in the NPWT arm than in the SMWC arm. Wound volume started higher in the NPWT arm and ended at similar levels for the treatment arms after decreasing continuously during the treatment period. This effect was stronger in the SMWC arm. Wound volume measures were lower in the PP-population than in the ITT-population. Wound tissues had a similar course over time like in the ITT population but showed higher values for granulation as well as lower values for fibrin and necrosis in the PP population. Like in the ITT population, pain levels were very low, showing no relevant difference between the treatment arms, and further decreased during the study treatment period. In the PP-population EQ5D values are higher than in the ITT population during screening, but still show that all patients have significant problems. In the NPWT arm QoL measures are similar to those of the SMWC arm for patients reaching end of maximum treatment time before end of therapy. EQ5D shows higher values for patients reaching the end of therapy during the study treatment time of 16 weeks. Detailed results for the PP population can be found in the appendix.

Additional results on treatment compliance and documentation quality

29 (17·0%) patients in the NPWT group had a temporary therapy change to SMWC (mean duration 20·5 ± 21·6 days). In the SMWC group, 17 (9·8%) patients had a temporary therapy change to NPWT (mean duration 28·9 ± 21·6 days). For only 2 of the 29 NPWT patients (6·9%) with a temporary therapy change to SMWC the wound closure was achieved within 16 weeks, whereas 16·2% (23 von 142) of the wounds of the NPWT patients without therapy change were completely closed.

A total of 57·3% (98 of 171) of the patients randomized to NPWT completed treatment before achieving a granulation surface of the wound of at least 95%. Fewer patients with this premature end of NPWT (4·7%, N=8) achieved a complete wound closure than patients with no premature end of therapy (9·9, N=17). Mean NPWT-

duration until premature end of therapy was 28.5 days (SD 24·1), while a mean granulation area of 59.6% (SD 30·5) was achieved.

For 131 patients (76· 6 %) in the NPWT arm less than the required three dressing changes per week were documented. 19 patients (14· 5 %) with this protocol violation achieved a complete wound closure. Six (15·4%) of the 39 NPWT patients who received at least 3 therapy changes per week achieved a complete wound closure.

In the electronic Case Report Forms (eCRF) a wound closure was documented for 96 patients (NPWT 56 of 171; SMWC 40 of 174), but only for 46 patients (NPWT 25; SMWC 21) all criteria for a complete, verified and sustained wound closure have been met. For the wound closure visit seven wound photographs (NPWT 7; SMWC 0) and for the wound closure confirmation visit four photographs (NPWT 3; SMWC 1) were missing. In addition, two of the existing wound photographs for the wound closure (NPWT 0; SMWC 2) and two photographs for the wound closure confirmation (NPWT 1, SMWC 3) were not assessable by the blinded observers due to serious quality issues. Furthermore 23 (NPWT 15; SMWC 8) existing and assessable wound photographs were not able to confirm the wound closure and 3 (NPWT 1; SMWC 2) photographs were not able to confirm the wound closure after 14 days.

Discussion

The DiaFu-study did not demonstrate significant superiority in wound closure rate or time to complete wound closure for either NPWT or SMWC. Wound closure rates were higher in the NPWT arm but did not significantly differ from those in the SMWC arm. Time to wound healing in the NPWT group was lower than in the SMWC arm while the difference between the treatment arms becomes statistically significant only in the PP population. Thus, with this study we were not able to confirm our hypothesis that wound closure can be achieved more often and faster with NPWT than with SMWC when used in German real-life clinical practice. Previous RCTs, which were the basis for sample size calculation, showed a higher rate and a significant superiority in healing when using NPWT on amputation and chronic wounds [16, 17], but the populations of these studies were different. Other than the DiaFu-study the studies of Armstrong and Blume excluded patients with Wagner stage four; active Charcot; uncontrolled hyperglycemia and therapy with glucocorticoids, immunosuppressants or chemotherapy; and required proof of adequate perfusion. The DiaFu-study, did not exclude patients with impaired perfusion, but required adequate therapy of the circulatory disorder according to clinical practice guidelines. However, baseline data show that the proportion of patients with critical limb ischemia in the DiaFu-study was low and did not differ significantly between the treatment arms. Additionally, patients with venous insufficiency were excluded from the Armstrong-study. The DiaFu study included more than twice as many patients as the Armstrong-study and patients were older than in both other studies. However, the probably most serious difference between the studies is that the DiaFu-study was performed in (German) real-life clinical practice including all factors that affect therapy. Our study is the first to show that temporary therapy changes and premature therapy cessation have a negative impact on reaching the patient relevant therapy outcome complete wound closure in study participants treated with NPWT. Optimal preparation of the wound bed (95% granulation tissue) was achieved significantly earlier when using NPWT in the ITT and the PP population, but the overall rate of wound closures was low. Wound bed preparation and granulation tissue formation are important prerequisites for wound healing, but are not a proof of treatment effectiveness and cannot serve as a basis for benefit assessment.

We were able to show that although significantly more AEs were documented in the NPWT arm only a small number of these events were related to the medical device according to the investigator`s assessment. Mortality rates were very low in both treatment arms and there was no significant difference between the treatment arms regarding amputations and resections performed during the study. Only two major amputations have been performed in patients with big wounds treated with NPWT. None of the treatments resulted in an additional impairment of the patients' quality of life during study treatment time or follow up. Time until complete wound

closure was significantly shorter with NPWT than with SMWC in the subgroup of big wounds, which indicates that NPWT has the potential to be a valuable treatment option for this kind of wounds.

In the DiaFu-study methods against bias have been implemented whenever possible in order to avoid bias that have been described by several systematic reviews [18-22], but shortcomings in documentation quality and missing compliance to therapy guidelines negatively impact the results.

Not addressing and analyzing all factors influencing the overall treatment outcome like targeted pressure relief, continuous infection control and adequate treatment of the underlying disease during the study treatment and observation period may be seen as a limitation of this health care research study. Study sites have been selected based on a self-disclosure by means of a qualification checklist and cross checks using quality reports. This ensured that all prerequisites were met for guideline-compliant patient care. Nevertheless, even in the application of NPWT there were deviations from the standards. Anyway, questioning the quality of investigators' treatment was not the main focus of this trial and evaluating the individual treatment quality within a single RCT is neither feasible nor effective.

In order to support the decision-making process of the German G-BA on general reimbursement of NPWT in German outpatient care the real-life clinical practice DiaFu-study included patients with chronic DFUs of neuropathic and angiopathic origin regardless of whether a simple wound cleansing, tissue debridement or even amputation was necessary prior to application of wound therapy targeted to achieve complete wound closure. The study was performed without excluding concomitant diseases negatively impacting wound healing; with therapy application in the discretion of the attending physician; and with evaluation of patient relevant outcome. Thus, results can easy be generalized and applied in clinical practice settings. Anyway, shortcomings in data quality negatively impacted the study results and statements about specific patient groups were not possible.

Conclusions

NPWT was not superior to SMWC when evaluated in German real-life clinical practice. Missing compliance with therapy guidelines and poor documentation quality led to restrictions in achieving the patient-relevant endpoint complete wound closure and prevents a clear proof of effectiveness. The question if NPWT is superior to SMWC for treating diabetic foot wounds remains unanswered due to the limitations of the DiaFu-study. An overall low number of wound closures indicate problems with the overall treatment quality. Despite all limitations NPWT showed a significant superiority in optimal wound bed preparation. This indicates that NPWT works according to its intended use and has at least a potential to be a valuable treatment option.

Furthermore, the results of the PP population suggest that without the negative impact of premature treatment cessation, temporary changes of the randomized therapy and partly incomplete documentation, NPWT may be more effective for treating diabetic foot wounds than SMWC.

In Germany, NPWT should be evaluated again after implementation of a sufficient, well-considered and widely-accepted concept for quality control. In a future health care research study, the treatment outcome before and after the implementation of these quality measures should be evaluated, for which the results of this trial may serve as a basis. Practitioners worldwide should review their processes with regard to the problems described here.

Ethics approval and consent to participate

Ethical approval of the main ethical committee (EC): Ethical Committee of the University of Witten-Herdecke, has been fully granted without any conditions. Due to performing the trial according to § 23b MPG (German Medical Device Act), participating study sites in Germany only received a consultation for the main clinical investigator according to professional law by the respective EC. All investigators have been fully approved by the respective ECs. An evaluation of the study's content by ECs of participating study sites in Germany was not applicable. All study participants gave written informed consent prior to randomization and any trial related procedure.

Data sharing

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Datasets are available in German language.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: The German statutory health insurance companies commissioned the Witten/Herdecke University (UW/H) to plan, conduct, analyze and publish the study. Dörthe Seidel is an employee of the UW/H. The study has been financed by the manufacturers KCI (Acelity) and Smith&Nephew. Dörthe Seidel received a consulting fee for the presentation of the study during an event organized by the manufacturer Hartmann. During study planning and conduct Edmund Neugebauer was an employee of the UW/H. He was the director of the IFOM.

The clinical investigators Martin Storck, Holger Lawall, Gernold Wozniak, Peter Maukner, Dirk Hochlenert, Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink received a case fee of 1000 € for each patient included in the DiaFu-study in order to compensate for the additional organizational and especially the documentation effort during trial conduct. Furthermore all investigators received compensation for travelling to the investigator meetings. The institutions of the investigators used integrated care contracts for NPWT during study conduct in order to provide best practice for the study participants during outpatient care.

Gernold Wozniak and Walter Wetzel-Roth are members of the scientific advisory board of the manufacturer Kinetic Concepts Incorporated (KCI) (now Acelity).

Funding

Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds, which provided integrated care contracts for all study participants and for up to 7000 patients with acute and chronic wounds in Germany; defined basic rules for study design based on the requirements of the German authorities; and provided a critical review of the study protocol and the final report. The study was funded by the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary support and information about the used material. The manufacturers had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

Authors' contributions

Dörthe Seidel was the principal coordinating investigator. She conceived the study, reviewed the scientific literature, and was responsible for study design, data analysis, data interpretation, writing and reviewing of the report. She is the lead author and takes overall responsibility for this report. She affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Martin Storck and Holger Lawall were study investigators and contributed to study design, data collection and interpretation, and reviewed the report.

Gernold Wozniak, Peter Maukner, Walter Wetzel-Roth and Dirk Hochlenert were study investigators and contributed to data collection and data interpretation and reviewed the report.

Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink were study investigators and contributed to data collection and reviewed the report.

Edmund Neugebauer contributed to study design and data interpretation and reviewed the report.

All authors approved the final version of the report.

Acknowledgements

The authors thank all investigators, nurses, patients and partners for supporting the study.

At least one patient was included in the following facilities: HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für Gefäßchirurgie Ludwig-Erhard-Straße 100 65199 Wiesbaden; Asklepios Westklinikum Hamburg Zentrum für Gefäßmedizin Suurheid 20 22559 Hamburg; Knappschaftskrankenhaus Bottrop Gefäßchirurgische Klinik

Osterfelderstraße 157 46242 Bottrop; Städtisches Klinikum Karlsruhe Klinik für Gefäß- und Thoraxchirurgie Moltkestraße 90 76133 Karlsruhe; Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Merheimer Straße 217 50733 Köln; Klinikum Döbeln Abt. für Gefäßchirurgie Sörmitzer Straße 10 04720 Döbeln; Klinikum Bielefeld Mitte Klinik für Allgemeine Innere Medizin Teutoburger Straße 50 33604 Bielefeld; Klinikum Frankfurt/Oder Klinik für Gefäßchirurgie Müllroser Chaussee 7 15236 Frankfurt/Oder; Weißeritztal-Kliniken GmbH Medizinische Klinik III Bürgerstraße 7 01705 Freital; Krankenhaus Porz am Rhein Klinik für Gefäßchirurgie Urbacher Weg 19 51149 Köln; St. Remigius Krankenhaus Opladen Innere Medizin An St. Remigius 26 51379 Leverkusen; Marien Hospital Dortmund-Hombruch Klinik für Innere Medizin/Diabetologie Gablonzstraße 9 44225 Dortmund; Zentrum für Chirurgie Klinik für Gefäß- und Endovascularchirurgie Theodor-Stern-Kai 7, Haus 23C/EG 60590 Frankfurt am Main; Facharzt für Chirurgie Thorax-Kardiovaskularchirurgie Hindenburgstraße 1 86807 Buchloe; Helfenstein Klinik Geisslingen Allgemein- und Viszeralchirurgie Eybstraße 16 73312 Geislingen/Steige; Paracelsus-Klinik am Silbersee Wundzentrum Hannover Oertzeweg 24 30851 Langenhagen; Klinikum Darmstadt Chirurgische Klinik III Grafenstraße 9 64283 Darmstadt; Ortenau Klinikum Offenburg-Ebertplatz Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ebertplatz 12 77654 Offenburg; Thüringen-Kliniken "Georgius Agricola" GmbH Klinik für Gefäßchirurgie Rainweg 68 07318 Saalfeld; Klinikum Dorothea Christiane Erxleben GmbH Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ditfurter Weg 24 06484 Quedlinburg; Franziskus-Krankenhaus Berlin Abt. für Innere Medizin Budapester Straße 15-19 10787 Berlin; Hegau-Bodensee Klinikum Radolfzell (HBK) Klinik für Innere Medizin Hausherrenstraße 12 78315 Radolfzell; Diabetologische Schwerpunktpraxis Dr. med. Hansjörg Mühlen & Partner Ruhrorter Straße 195 47119 Duisburg; Kliniken Maria Hilf Mönchengladbach Klinik für Gefäßchirurgie und Angiologie Sandradstraße 43 41061 Mönchengladbach; Städtisches Klinikum München/Bogenhausen Klinik für Endokrinologie, Diabetologie und Angiologie Englschalkingerstraße 77 81925 München; Gerhard Rothenaicher Facharzt für Chirurgie Cosimastraße 2 81927 München; Bürgerhospital Frankfurt am Main Interdisziplinäres Zentrum Diabetischer Fuß (DDG) Nibelungenallee 37- 41 60318 Frankfurt am Main; Gemeinschaftspraxis für Chirurgie und Gefäßmedizin Drs. Alter/Pourhassan/Heim Klosterstraße 12 46145 Oberhausen; Ev. KH Königin Elisabeth Herzberge gGmbH Abt. für Kardiologie, Angiologie und Diabetologie Herzbergstraße 79 10365 Berlin; Städtisches Klinikum Neunkirchen gGmbH Abt. für Gefäßchirurgie & Phlebologie Brunnenstraße 20 66538 Neunkirchen; Westküstenklinikum Heide Klinik für Viszeral- und Gefäßchirurgie Esmarchstraße 50 25746 Heide/Holstein; Chir. Praxisgemeinschaft am Bayenthalgürtel Praxis Dr. med. Gerald Engels Bayenthalgürtel 45 50968 Köln; Malteser Krankenhaus – St. Franziskus-Hospital Medizinische Klinik I, Abt. für Diabetologie Waldstraße 17 24939 Flensburg; St. Marienkrankenhaus Siegen gGmbH Klinik für Gastroenterologie Kampenstraße 51 57072 Siegen; Krankenhaus

Bietigheim Klinik für Innere Medizin, Kardiologie, Endokrinologie, Diabetologie und Internistische Intensivmedizin Riedstraße 12 74321 Bietigheim-Bissingen; Asklepios Kliniken Harburg Eißendorfer Pferdeweg 52 21075 Hamburg; Diabetologikum Ludwigshafen Diabetes-Schwerpunktpraxis Ludwigsplatz 9 67059 Ludwigshafen; Mariannen-Hospital Werl Abt. für Chirurgie Unnaer Straße 15 59457 Werl; Diabetes Klinik GmbH & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim; Institut für Diabetesforschung Münster GmbH Hohenzollernring 70 48145 Münster.

The study was initiated by a consortium of 19 statutory German health insurance funds represented by the AOK federal association (AOK-Bundesverband – AOK-BV), the association of alternative health insurance funds (Verband der Ersatzkrankenkassen – vdek) and the minors (Knappschaft). In order to guarantee outpatient care for all study participants without any restrictions, the contracting health insurance companies provided integrated care contracts for outpatient negative pressure wound therapy.

A project advisory board was implemented to coordinate all processes and project partners. The board comprised two representatives each from the statutory health insurance funds, the management company and the sponsor as well as one representative each from the participating medical device manufacturers (KCI and smith & nephew). Representing the contracting authority (statutory German health insurance funds) Dr. Gerhard Schillinger (AOK-BV) and Ute Leonhard (vdek) acted as contact persons for all aspects of the project.

The management company "Gesundheitsforen Leipzig" has been entirely responsible for the logistics of the study. Central tasks of the management company included the recruitment of study sites and patients, the development of the IT infrastructure including the documentation, communication and invoicing software as well as the processing of all payments.

The manufacturers Kinetic Concepts Incorporated (KCI) (Acelity) and smith & nephew provided the NPWT devices as well as support and training for the investigators and financed the study.

The Private University of Witten/Herdecke gGmbH acted as the Sponsor of the trial and the Institute for Research in Operative Medicine with its former director Prof. E.A.M. Neugebauer, the current interim head Prof. Rolf Lefering and the head of the division for clinical research Dörthe Seidel was responsible for the scientific conception, the evaluation as well as the reporting and publication of the study. Prof. Dr. Rolf Lefering was responsible for the statistical planning and analysis. PD Dr. Peter Krüger was responsible for the data management of the study. Special thanks are going to Stefan Bauer, who supported the data management as well as the statistical analysis and reporting.

We would like to thank Sophie Thorn, who checked the article as a native English speaker with regard to spelling and grammar.

List of figures:

References

1. World Health Organization, *Global report on diabetes.* 2016, WHO: http://www.who.int/diabetes/global-report/en/.
2. International Diabetes Federation, *IDF Diabetes Atlas*. 2015, IDF: www.diabetesatlas.org.
3. Yazdanpanah, L., M. Nasiri, and S. Adarvishi, *Literature review on the management of diabetic foot ulcer.* World J Diabetes, 2015. **6**(1): p. 37-53.
4. Leone, S., et al., *[Epidemiology of diabetic foot].* Infez Med, 2012. **20 Suppl 1**: p. 8-13.
5. Wu, L., et al., *Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews.* Cochrane Database Syst Rev, 2015(7): p. CD010471.
6. Norman, G., et al., *Dressings and topical agents for treating venous leg ulcers.* Cochrane Database Syst Rev, 2018. **6**: p. CD012583.
7. Wu, S.C., W. Marston, and D.G. Armstrong, *Wound care: the role of advanced wound-healing technologies.* J Am Podiatr Med Assoc, 2010. **100**(5): p. 385-94.
8. Fleischmann, W., et al., *[Vacuum sealing as treatment of soft tissue damage in open fractures].* Unfallchirurg, 1993. **96**(9): p. 488-92.
9. Argenta, L.C. and M.J. Morykwas, *Vacuum-assisted closure: a new method for wound control and treatment: clinical experience.* Ann Plast Surg, 1997. **38**(6): p. 563-76; discussion 577.
10. Morykwas, M.J., et al., *Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation.* Ann Plast Surg, 1997. **38**(6): p. 553-62.
11. Morykwas, M.J., et al., *Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine.* Ann Plast Surg, 2001. **47**(5): p. 547-51.
12. Gregor, S., et al., *Negative pressure wound therapy: a vacuum of evidence?* Arch Surg, 2008. **143**(2): p. 189-96.
13. Peinemann, F. and S. Sauerland, *Negative-pressure wound therapy: systematic review of randomized controlled trials.* Dtsch Arztebl Int, 2011. **108**(22): p. 381-9.
14. Ubbink Dirk, T., et al. *Topical negative pressure for treating chronic wounds*. Cochrane Database of Systematic Reviews, 2008. DOI: 10.1002/14651858.CD001898.pub2.
15. Vikatmaa, P., et al., *Negative pressure wound therapy: a systematic review on effectiveness and safety.* Eur J Vasc Endovasc Surg, 2008. **36**(4): p. 438-48.
16. Armstrong, D.G. and L.A. Lavery, *Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial.* Lancet, 2005. **366**(9498): p. 1704-10.
17. Blume, P.A., et al., *Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial.* Diabetes Care, 2008. **31**(4): p. 631-6.
18. Dumville, J.C., et al., *Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus.* Cochrane Database Syst Rev, 2013(10): p. CD010318.
19. Rhee, S.M., et al., *Negative Pressure Wound Therapy Technologies for Chronic Wound Care in the Home Setting*. 2014, Johns Hopkins University Evidence-based Practice Center: Rockville (MD).
20. Canadian Agency for Drugs and Technologies in Health, *Negative Pressure Wound Therapy for Managing Diabetic Foot Ulcers: A Review of the Clinical Effectiveness, Cost-effectiveness, and Guidelines*. 2014: Ottawa (ON).
21. Liu, S., et al., *Evaluation of negative-pressure wound therapy for patients with diabetic foot ulcers: systematic review and meta-analysis.* Ther Clin Risk Manag, 2017. **13**: p. 533-544.
22. Liu, Z., et al., *Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus.* Cochrane Database Syst Rev, 2018. **10**: p. CD010318.
23. Seidel, D., et al., *Negative pressure wound therapy versus standard wound care in chronic diabetic foot wounds: study protocol for a randomized controlled trial.* Trials, 2014. **15**: p. 334.
24. Bauer, H., et al. *Typ-2-Diabetes: Präventions- und Behandlungsstrategien für Fußkomplikationen*. Nationale Versorgungs Leitlinien, 2010.

25. Ruttermann, M., et al., *Local treatment of chronic wounds: in patients with peripheral vascular disease, chronic venous insufficiency, and diabetes.* Dtsch Arztebl Int, 2013. **110**(3): p. 25-31.
26. Dupont, W.D. and W.D. Plummer, Jr., *Power and sample size calculations. A review and computer program.* Control Clin Trials, 1990. **11**(2): p. 116-28.
27. Schaper, N.C., *Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies.* Diabetes Metab Res Rev, 2004. **20 Suppl 1**: p. S90-5.
28. Sanders LJ and Frykberg RG, *Diabetic neuropathic osteoarthropathy: the Charcot foot.*, in *The high risk foot in diabetes mellitus.*, F. RG, Editor. 1991, Churchill Livingstone: New York. p. 297-338.
29. Levin, M.E., *Preventing amputation in the patient with diabetes.* Diabetes Care, 1995. **18**(10): p. 1383-94.
30. Wagner, F.W., Jr., *The diabetic foot.* Orthopedics, 1987. **10**(1): p. 163-72.
31. Rutherford, R.B., et al., *Recommended standards for reports dealing with lower extremity ischemia: revised version.* J Vasc Surg, 1997. **26**(3): p. 517-38.
32. Widmer, L.K., et al., *[Venous diseases in 1800 employees. Basel Studies II].* Schweiz Med Wochenschr, 1967. **97**(4): p. 107-10.

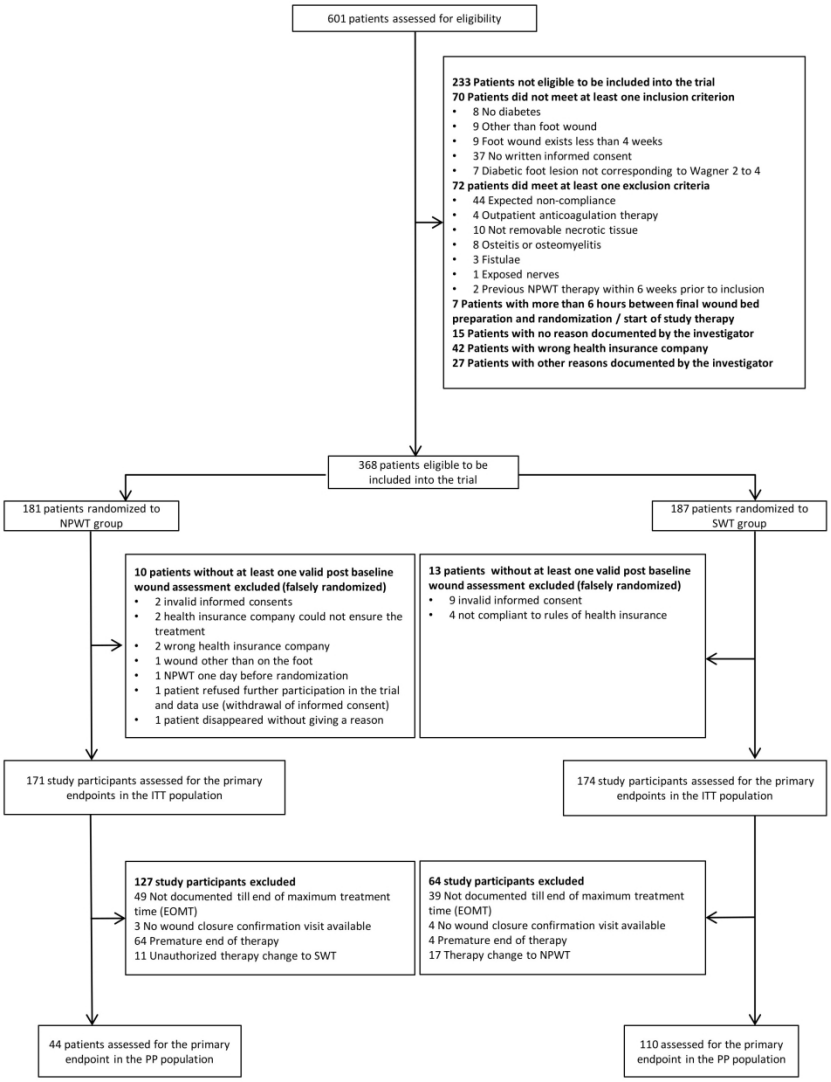


Figure 1: Trial profile (CONSORT Flow Diagram)

190x275mm (300 x 300 DPI)

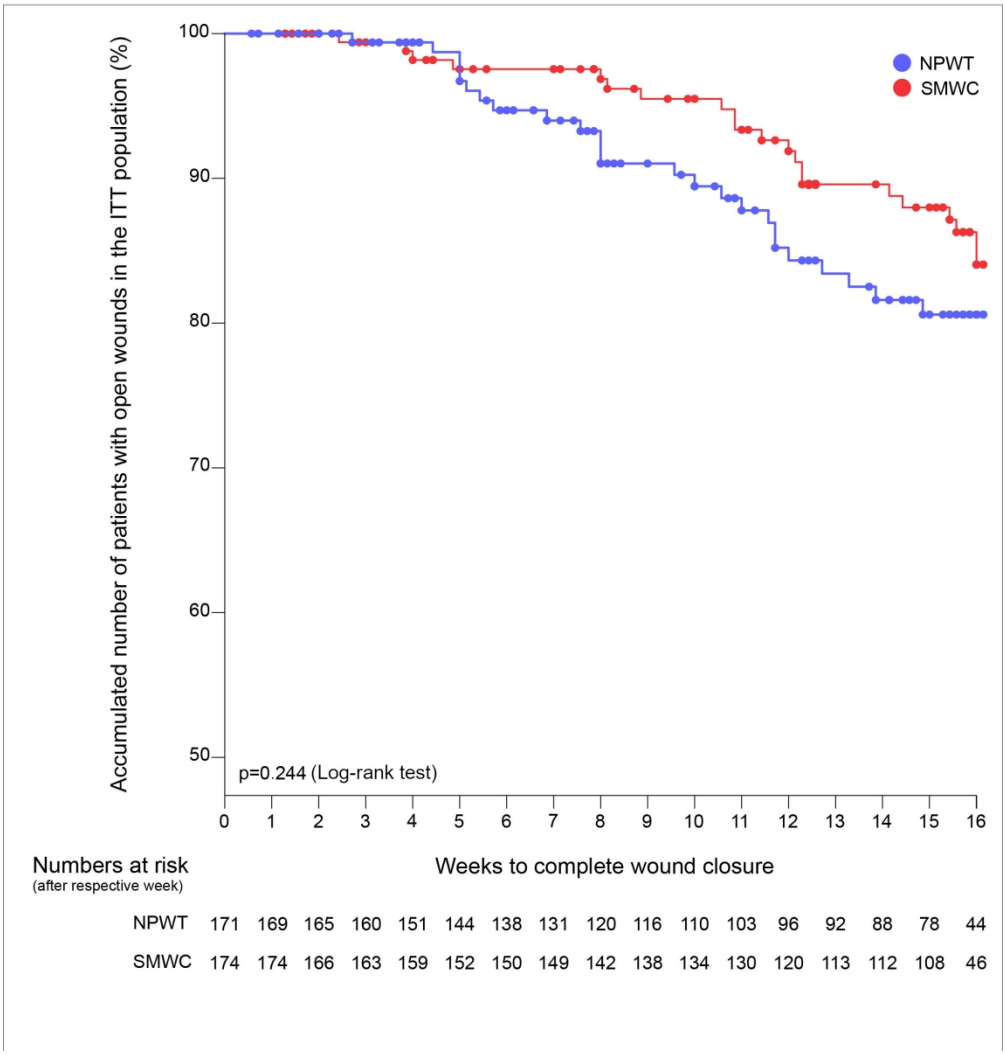


Figure 2: Time until complete, sustained and verified wound closure in the ITT population

189x198mm (300 x 300 DPI)

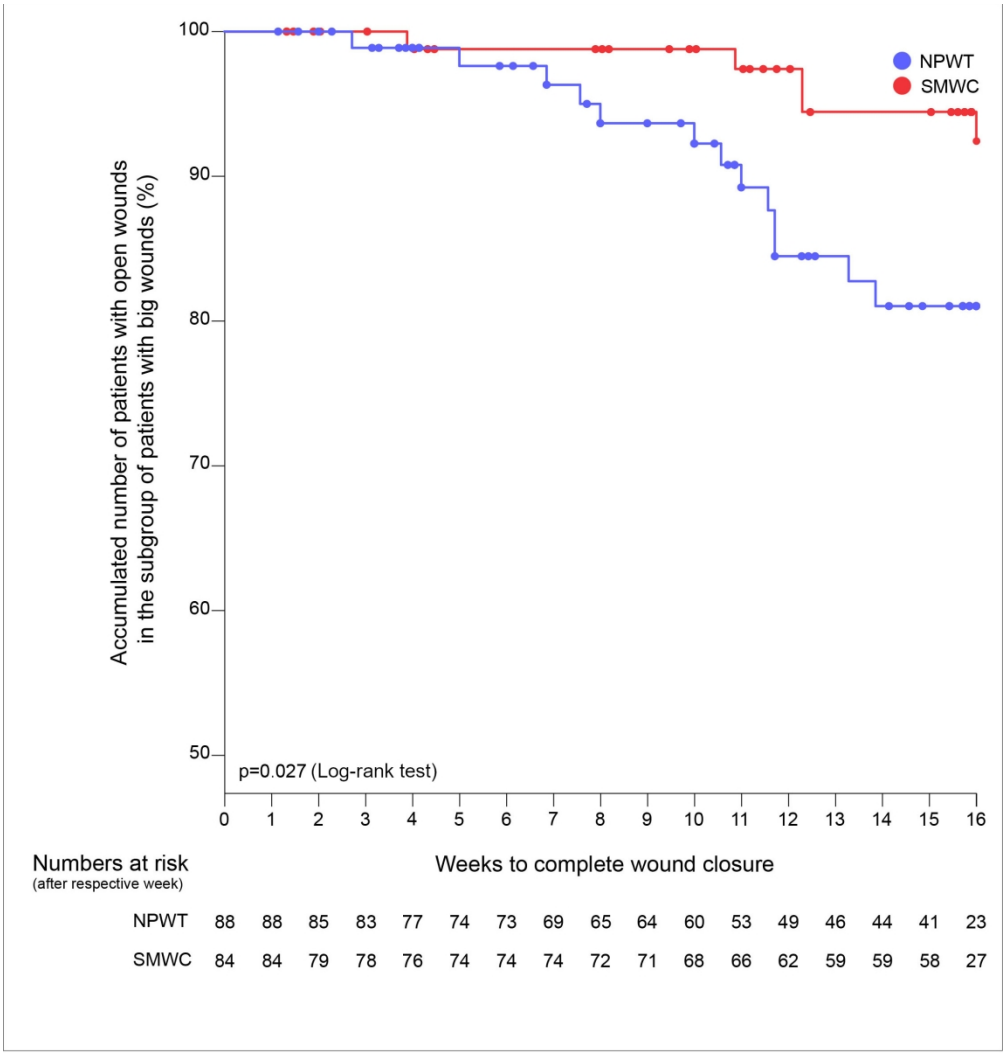


Figure 3: Time until complete, sustained and verified wound closure for the subgroup of big wounds

189x198mm (300 x 300 DPI)

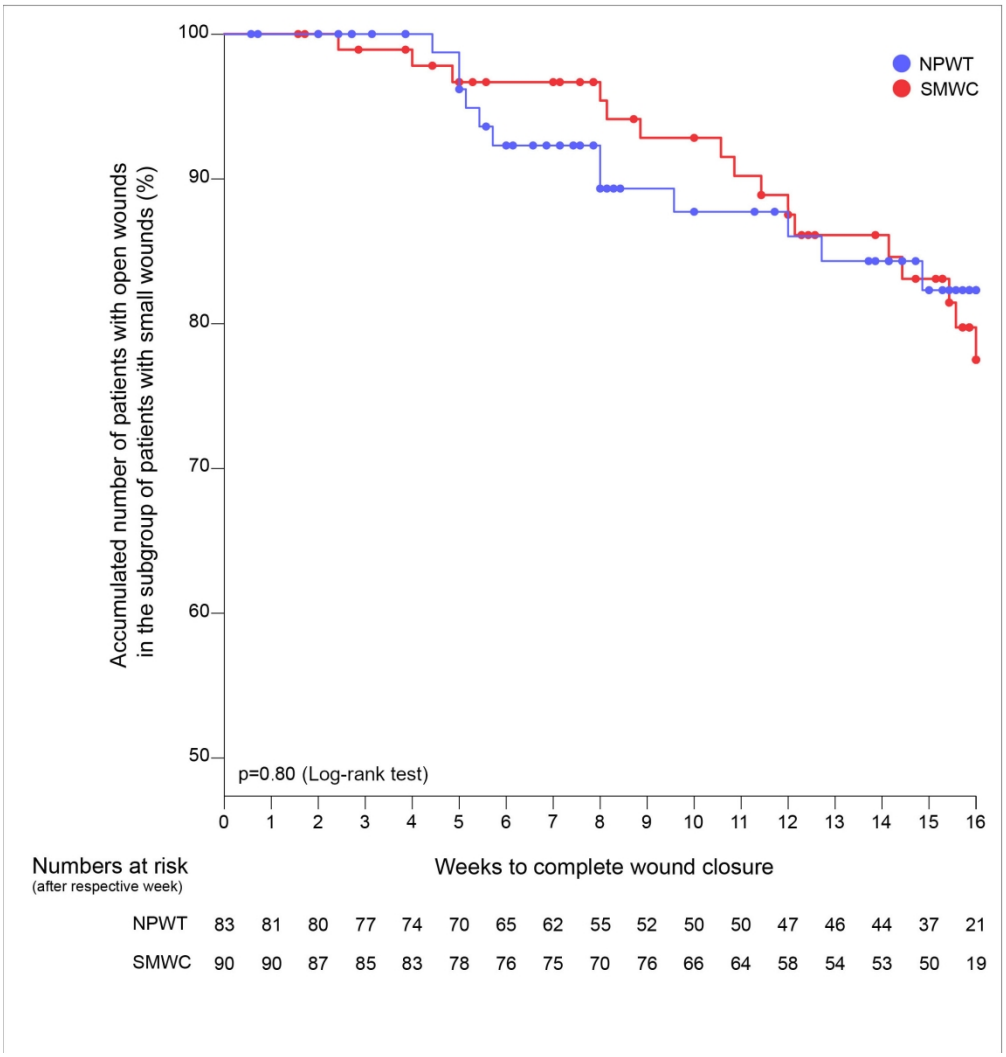


Figure 4: Time until complete, sustained and verified wound closure for the subgroup of small wounds

189x198mm (300 x 300 DPI)

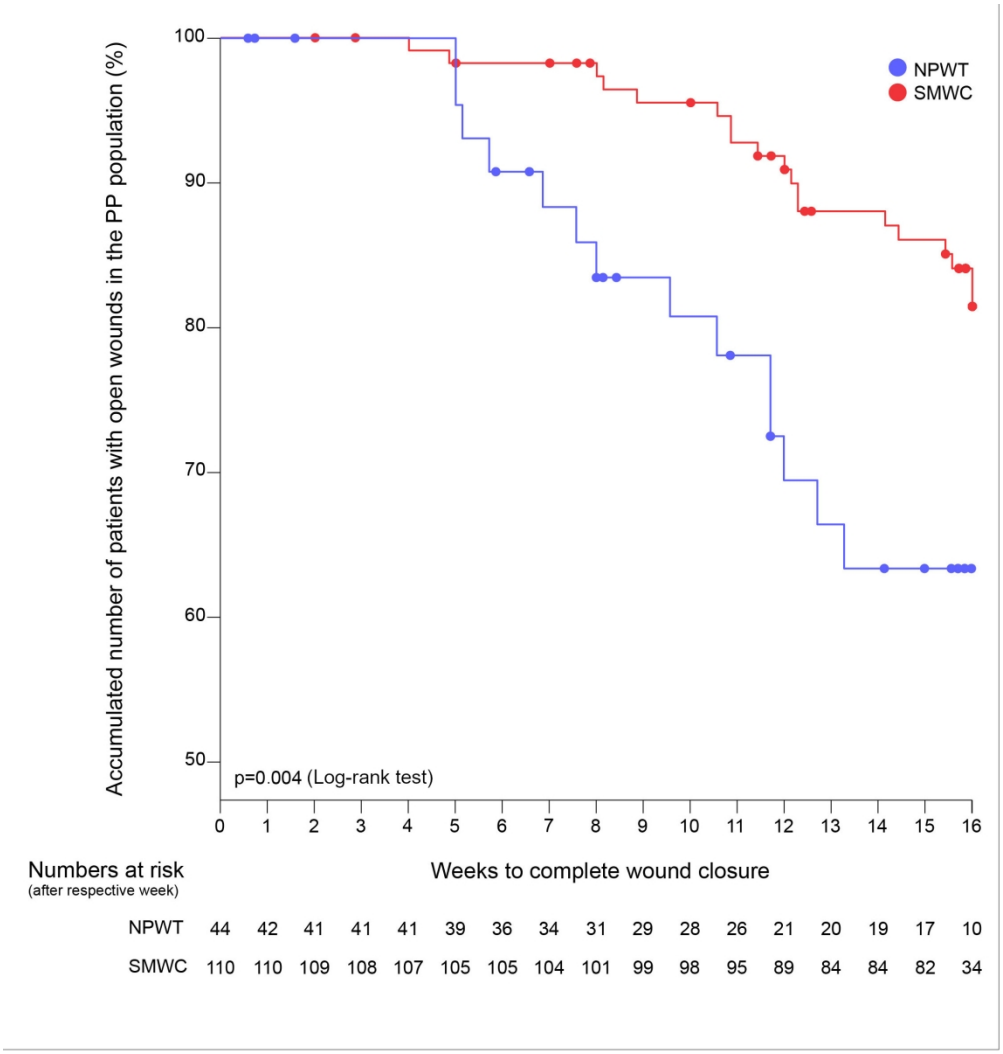


Figure 5: Time until complete, sustained and verified wound closure in the PP-population

189x198mm (300 x 300 DPI)

Supplementary Appendix

Table of contents:

List of investigators:

1. PD Dr. med. Achim Neufang	HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für Gefäßchirurgie Ludwig-Erhard-Straße 100 65199 Wiesbaden
2. Dr. med. Holger Lawall	Asklepios Westklinikum Hamburg Zentrum für Gefäßmedizin Suurheid 20 22559 Hamburg
3. Prof. Dr. med. Gernold Wozniak	Knappschaftskrankenhaus Bottrop Gefäßchirurgische Klinik Osterfelderstraße 157 46242 Bottrop
4. Prof. Dr. med. Martin Storck	Städtisches Klinikum Karlsruhe Klinik für Gefäß- und Thoraxchirurgie Moltkestraße 90 76133 Karlsruhe
5. Dr. med. Dirk Hochlenert	Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Merheimer Straße 217 50733 Köln
6. Dr. med. Gudrun Hetzel	Klinikum Döbeln Abt. für Gefäßchirurgie Sörmitzer Straße 10 04720 Döbeln
7. Dr. med. Karsten Jungheim	Klinikum Bielefeld Mitte Klinik für Allgemeine Innere Medizin Teutoburger Straße 50 33604 Bielefeld
8. Dr. med. Michael Petzold	Klinikum Frankfurt/Oder Klinik für Gefäßchirurgie

	Müllroser Chaussee 7 15236 Frankfurt/Oder
9. PD Dr. med. Matthias Weck	Weißeritztal-Kliniken GmbH Medizinische Klinik III Bürgerstraße 7 01705 Freital
10. Dr. med. Alexandra Zidek	Krankenhaus Porz am Rhein Klinik für Gefäßchirurgie Urbacher Weg 19 51149 Köln
11. Dr. med. Peter Mauckner	St. Remigius Krankenhaus Opladen Innere Medizin An St. Remigius 26 51379 Leverkusen
12. Dr. med. Klemens M. Sondern	Marien Hospital Dortmund-Hombruch Klinik für Innere Medizin/Diabetologie Gablonzstraße 9 44225 Dortmund
13. Prof. Dr. med. Thomas Schmitz-Rixen	Universitätsklinikum Frankfurt Zentrum für Chirurgie Klinik für Gefäß- und Endovascularchirurgie Theodor-Stern-Kai 7, Haus 23C/EG 60590 Frankfurt am Main
14. Dr. med. Walter Wetzel-Roth	Facharztpraxis für Chirurgie Hindenburgstraße 1 86807 Buchloe
15. Dr. med. Matthias Hahn	Helfenstein Klinik Geisslingen Allgemein- und Viszeralchirurgie Eybstraße 16 73312 Geislingen/Steige
16. Dr. med. Karsten Glockemann	Paracelsus-Klinik am Silbersee Wundzentrum Hannover Oertzeweg 24 30851 Langenhagen
17. PD Dr. med. Farzin Adili	Klinikum Darmstadt Chirurgische Klinik III Grafenstraße 9 64283 Darmstadt
18. Dr. med. Andreas Riemer	Ortenau Klinikum Offenburg-Ebertplatz Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ebertplatz 12

	77654 Offenburg
19. Dr. med. Thomas Krönert	Thüringen-Kliniken "Georgius Agricola" GmbH Klinik für Gefäßchirurgie Rainweg 68 07318 Saalfeld/Saale
20. Dr. med. Matthias Holfeld	Klinikum Dorothea Christiane Erxleben GmbH Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ditfurter Weg 24 06484 Quedlinburg
21. Prof. Dr. med. Jan Andre´ Schmidt-Lucke	Franziskus-Krankenhaus Berlin Abt. für Innere Medizin Budapester Straße 15-19 10787 Berlin
22. Dr. med. Wolf-Rüdiger Klare	Hegau-Bodensee Klinikum Radolfzell (HBK) Klinik für Innere Medizin Hausherrenstraße 12 78315 Radolfzell
23. Dr. med. Hansjörg Mühlen	Diabetologische Schwerpunktpraxis Dr. med. Hansjörg Mühlen & Partner Ruhrorter Straße 195 47119 Duisburg
24. Dr. med. Christian Reinhold	Kliniken Maria Hilf Mönchengladbach Klinik für Gefäßchirurgie und Angiologie Sandradstraße 43 41061 Mönchengladbach
25. Dr. med. Makarios Paschalidis	Städtisches Klinikum München/Bogenhausen Klinik für Endokrinologie, Diabetologie und Angiologie Englschalkingerstraße 77 81925 München
26. Gerhard Rothenaicher	Facharztpraxis für Chirurgie Cosimastraße 2 81927 München
27. Dr. med. Elke Anne Klug	Bürgerhospital Frankfurt am Main Interdisziplinäres Zentrum Diabetischer Fuß (DDG) Nibelungenallee 37- 41 60318 Frankfurt am Main
28. Dr. med. Siamak Pourhassan	Gemeinschaftspraxis für Chirurgie und Gefäßmedizin Drs. Alter / Pourhassan / Heim Klosterstraße 12 46145 Oberhausen

29. Dr. med. Jan Theil	Evangelisches Krankenhaus Königin Elisabeth Herzberge gGmbH Abt. für Kardiologie, Angiologie und Diabetologie Herzbergstraße 79 10365 Berlin
30. Dr. med. Martin Adolph	Städtisches Klinikum Neunkirchen gGmbH Abt. für Gefäßchirurgie & Phlebologie Brunnenstraße 20 66538 Neunkirchen
31. Dr. med. Frank von Feldmann	Westküstenklinikum Heide Klinik für Viszeral- und Gefäßchirurgie Esmarchstraße 50 25746 Heide/Holstein
32. Dr. med. Gerald Engels	Chir. Praxisgemeinschaft am Bayenthalgürtel Praxis Dr. med. Gerald Engels Bayenthalgürtel 45 50968 Köln
33. Dr. med. Joachim Oldenburg	Malteser Krankenhaus – St. Franziskus-Hospital Medizinische Klinik I Abt. für Diabetologie Waldstraße 17 24939 Flensburg
34. Dr. med. Philipp Kneppe	St. Marienkrankenhaus Siegen gGmbH Klinik für Gastroenterologie Kampenstraße 51 57072 Siegen
35. Dr. med. Steffen Hering	Krankenhaus Bietigheim Klinik für Innere Medizin, Kardiologie, Endokrinologie, Diabetologie und Internistische Intensivmedizin Riedstraße 12 74321 Bietigheim-Bissingen
36. Dr. med. Harald Daum	Asklepios Kliniken Harburg Eißendorfer Pferdeweg 52 21075 Hamburg
37. Dr. med. Lutz Stemler	Diabetologikum Ludwigshafen Diabetes-Schwerpunktpraxis Ludwigsplatz 9 67059 Ludwigshafen
38. Dr. med. Thomas Müller	Mariannen-Hospital Werl Abt. für Chirurgie Unnaer Straße 15 59457 Werl

39. Dr. med. Karl Zink	Diabetes Klinik GmbH & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim
40. Dr. med. Dirk Lammers	Institut für Diabetesforschung Münster GmbH Hohenzollernring 70 48145 Münster

Table S1: The table shows all study sites that have included at least one patient into the DiaFu-study.

Supplementary baseline characteristics for the ITT population

Baseline parameters (ITT population)	**Total N=345 (100 %)**	**NPWT N=171 (49·6%)**	**SMWC N=174 (50·4%)**
Alcohol	N=341	N=169	N=172
Occasionally	157 (46%)	83 (48·5%)	74 (42·3%)
Chronic	10 (2·9%)	3 (1·8%)	7 (4·0%)
No	174 (51%)	83 (48·5%)	91 (52%)
Smoking	N=342	N=169	N=173
No	49 (14·3%)	25 (14·6%)	24 (13·7%)
Yes	293 (85·7%)	144 (84·3%)	149 (85·1%)
Number of years Mean (SD)	34·8 (13·5)	36·5 (14·9)	33·1 (12·1)
Packs / day Mean	1·1	1·1	1·2
Drugs	N=341	N=169	N=172
Occasionally	1 (0·3%)	1 (0·6%)	0
Chronic	2 (0·6%)	0	2 (1·1%)
No	338 (97·7%)	168 (98·2%)	170 (97·1%)
Allergies	N=343	N=170	N=173
Yes	37 (10·7%)	16 (9·4%)	21 (12·0%)
No	306 (88·4%)	154 (90·1%)	152 (86·9%)
Subjective assessment of nutritional condition	N=342	N=169	N=173
Well-nourished	325 (94·2%)	162 (94·7%)	163 (93·7%)
Moderately malnourished or suspected malnutrition	11 (3·2%)	4 (2·3%)	7 (4%)

Malnourished	0 (0%)	0 (0%)	0 (0%)

Table S2: The table shows baseline characteristics of the ITT- population. Data are Number (N) and Percentage (%), or Mean and Standard Deviation (SD). "N=" is stating the number of patients with actual available information.

Supplementary baseline characteristics for the PP population

Demographic and baseline parameters (PP-Population)	**Total N=154 (100%)**	**NPWT N=44 (28·6%)**	**SMWC N=110 (71·4%)**
Sex	N=154	N=44	N=110
Male	113 (73·4%)	29 (65·9%)	84 (76·4%)
Female	41 (26·6%)	15 (34·1%)	26 (23·6%)
Age in years Mean (SD)	N=154 67·4 (10·6)	N=44 66·5 (11·0)	N=110 67·8 (10·4)
Height in cm Mean (SD)	N=153 173·8 (12·9)	N=43 173·5 (17·4)	N=110 174·0 (10·7)
Weight in kg Mean (SD)	N=150 95·4 (23·3)	N=42 96·2 (21·6)	N=108 95·1 (24·0)
Alcohol	N=153	N=44	N=109
Occasionally	71 (46·4%)	22 (50·0%)	49 (45·0%)
Chronic	3 (2·0%)	1 (2·3%)	2 (1·8%)
No	79 (51·6%)	21 (47·7%)	58 (53·2%)
Smoking	N=154	N=44	N=110
No	16 (10·4%)	2 (4·5%)	14 (12·7%)
Yes	138 (89·6%)	42 (95·5%)	96 (87·3%)
Number of years (Mean (SD))	37·0 (9·2)	42·0 (2·8)	36·3 (9·7)
Packs / day (Mean)	1·0	1·0	1·0
Drugs	N=153	N=44	N=109
Occasionally	0 (0%)	0 (0%)	0 (0%)
Chronic	1 (0·7%)	0 (0%)	1 (0·9%)
No	152 (99·3%)	44 (100%)	108 (99·1%)
Requiring dialysis	N=154	N=44	N=110
Yes	11 (7·1 %)	2 (4·5%)	9 (8·2%)
No	143 (92·9%)	42 (95·5%)	101 (91·8%)

Allergies	N=154	N=44	N=110
Yes	16 (10·4%)	6 (13·6%)	10 (9·1%)
No	138 (89·6%)	38 (86·4%)	100 (90·9%)
Subjective assessment of nutritional condition	N=150	N=43	N=107
Well-nourished	147 (98·0%)	42 (97·7%)	105 (98·1%)
Moderately malnourished or suspected malnutrition	3 (2·0%)	1 (2·3%)	2 (1·9%)
Malnourished	0 (0%)	0 (0%)	0 (0%)
Peripheral arterial occlusive disease (PAOD)	N=109 (70·8%)	N=29 (65·9%)	N=80 (72·7%)
without critical limb ischemia	103 (94·5%)	28 (96·6%)	75 (93·8%)
with critical limb ischemia	6 (5·5%)	1 (3·4%)	5 (6·3%)
Rutherford classification for chronic limb ischemia (Grade/Category)	N=109	N=29	N=80
0/0 Asymptomatic—no hemodynamically significant occlusive disease	13 (11·9%)	4 (13·8%)	9 (11·3%)
I/1 Mild claudication	13 (11·9%)	2 (6·9%)	11 (13·8%)
I/2 Moderate claudication	8 (7·3%)	0 (0·0%)	8 (10·0%)
I/3 Severe claudication	4 (3·7%)	1 (3·4%)	3 (3·8%)
II/4 Ischemic rest pain	1 (0·9%)	1 (3·4%)	0 (0%)
III/5 Minor tissue loss—non healing ulcer, focal gangrene with diffuse pedal ischemia	67 (61·5%)	21 (72·4%)	46 (57·5%)
III/6 Major tissue loss—extending above transmetatarsal level, functional foot no longer salvageable	3 (2·8%)	0 (0·0%)	3 (3·8%)
Revascularisation before study start	N=9 (5·8%)	N=1 (2·3%)	N=8 (7·3%)
Percutaneous transluminal angioplasty (PTA)	5 (55·6%)	0 (0·0%)	5 (62·5%)
PTA + Stent	0 (0%)	0 (0%)	0 (0%)
Veins-Bypass	1 (11·1%)	1 (100·0%)	0 (11·1%)
Polytetrafluoroethylene (PTFE) Bypass	1 (11·1%)	0 (0%)	1 (12·5%)
Thromboendarterectomy and patch plastic	2 (22·2%)	0 (0%)	2 (25·0%)
Revascularization with influence on the wound	9 of 9 (100%)	1 of 1 (100%)	0 of 8 (100%)
Sufficient revascularization result	9 of 9 (100%)	1 of 1 (100%)	8 of 8 (100%)
Insufficient revascularization result	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)
Revascularization result not assessable	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)

Table S3: Patient demographics and baseline characteristics of the Per-Protocol (PP) population. Data are N (%) and Mean (SD). "N=" is stating the number of patients with actual available information. Findings, diagnoses and procedures documented by the investigators are presented.

Supplementary result tables

	Wound surface NPWT		**Wound surface SMWC**	
Observation time point	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**
Randomization	1060 (1536) 550 (1236) N=171 (2)	687 (879) 321 (760) N=118 (10)	1141 (3247) 471 (1007) N=174 (0)	664 (1050) 316 (658) N=129 (13)
Week 1	847 (1489) 397 (801) N=171 (15)	643 (820) 329 (750) N=118 (32)	1085 (3234) 395 (867) N=174 (25)	713 (1065) 307 (749) N=129 (36)
Week 3	810 (1472) 314 (860) N=171 (24)	590 (742) 273 (633) N=118 (28)	1025 (3242) 390 (913) N=174 (22)	701 (1212) 266 (768) N=129 (35)
Week 5	717 (1379) 275 (769) N=171 (37)	607 (828) 231 (843) N=118 (42)	759 (1466) 267 (824) N=174 (41)	610 (1119) 219 (635) N=129 (38)
Week 8	636 (1322) 220 (712) N=171 (52)	495 (770) 182 (561) N=118 (48)	674 (1410) 186 (783) N=174 (42)	501 (937) 165 (481) N=129 (42)
Week 12	549 (858) 165 (964) N=171 (110)	457 (742) 134 (494) N=118 (88)	570 (940) 169 (632) N=174 (124)	493 (950) 133 (498) N=129 (104)
Week 16	440 (810) 79 (471) N=171 (80)	334 (649) 114 (363) N=118 (66)	493 (1095) 69 (415) N=174 (63)	351 (750) 77 (320) N=129 (56)

Table S4: Wound surface area at each observation time point in the ITTpopulation. Wound surface area at each observation time point until end of maximum study treatment time of 16 weeks is separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis. An elliptical wound surface area has been calculated from the documented width and length (eCRF) [(pi / 4) x length x width = area]. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Wound volume NPWT (mm^3)	Wound volume SMWC (mm^3)
Randomization	22498 (58930) 4710 (15048) N=171 (2)	21740 (74181) 4759 (12888) N=174 (0)
Week 1	13203 (28709) 2487 (6908) N=171 (15)	19979 (73143) 3533 (11407) N=174 (26)
Week 3	10708 (28521) 1884 (6857) N=171 (24)	16217 (67494) 2293 (8831) N=174 (23)
Week 5	7700 (19719) 1166 (5338) N=171 (37)	11286 (32566) 1365 (7539) N=174 (42)
Week 8	5592 (11535) 785 (4604) N=171 (78)	8772 (27674) 812 (5258) N=174 (67)
Week 12	5333 (12422) 565 (3913) N=171 (119)	6639 (16454) 625 (4083) N=174 (133)
Week 16	3880 (10534) 141 (1890) N=171 (83)	5465 (14874) 200 (1587) N=174 (64)

Table S5: Wound volume at each observation time point during the study treatment time of maximum 16 weeks in the ITT population. Wound volume (length x width x depth) was calculated from width, length and depth as documented in the eCRF. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	NPWT Granulation		NPWT Fibrin		NPWT Necrosis		SMWC Granulation		SMWC Fibrin		SMWC Necrosis	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.
Rando	34 (36) 20 (70) 171 (2)	22 (25) 12 (37) 118 (8)	21 (28) 10 (30) 170 (4)	71 (27) 79 (46) 118 (8)	3 (10) 0 (0) 169 (5)	7 (15) 0 (5) 118 (8)	34 (37) 20 (71) 174 (3)	24 (26) 14 (39) 129 (12)	22 (29) 10 (40) 174 (1)	69 (28) 79 (44) 129 (12)	2 (9) 0 (0) 172 (2)	7 (14) 0 (8) 129 (12)
Week 1	58 (35) 70 (70) 171 (16)	21 (25) 10 (36) 118 (32)	19 (22) 10 (30) 71 (19)	73 (27) 81 (47) 118 (32)	5 (13) 0 (2) 169 (23)	6 (12) 0 (5) 118 (32)	49 (35) 50 (70) 174 (28)	21 (25) 10 (36) 129 (36)	24 (27) 15 (31) 174 (27)	74 (26) 85 (40) 129 (36)	6 (15) 0 (5) 172 (30)	5 (9) 0 (5) 129 (36)
Week 3	67 (31) 80 (55) 171 (26)	16 (23) 5 (25) 118 (27)	18 (22) 10 (30) 171 (30)	80 (25) 91 (30) 118 (27)	5 (13) 0 (0) 169 (28)	4 (11) 0 (1) 118 (27)	57 (32) 60 (60) 174 (24)	21 (25) 10 (36) 129 (35)	25 (26) 20 (35) 174 (25)	77 (25) 85 (36) 129 (35)	5 (13) 0 (3) 172 (30)	3 (7) 0 (1) 129 (35)
Week 5	70 (30) 80 (45) 171 (36)	15 (22) 6 (21) 118 (43)	18 (24) 10 (25) 171 (38)	83 (22) 91 (26) 118 (43)	4 (13) 0 (0) 169 (42)	2 (8) 0 (1) 118 (43)	62 (31) 63 (50) 174 (44)	18 (26) 4 (32) 129 (36)	23 (25) 10 (39) 174 (47)	80 (26) 93 834) 129 (36)	4 (12) 0 (0) 172 (46)	3 (10) 0 (0) 129 (36)
Week 8	74 (30) 90 (40) 171 (53)	16 (23) 4 (27) 118 (48)	17 (24) 10 (20) 171 (56)	82 (24) 93 (33) 118 (48)	4 (13) 0 (0) 171 (59)	2 (6) 0 (0) 118 (48)	70 (29) 80 (40) 174 (44)	17 (24) 3 (33) 129 (43)	17 (21) 10 (20) 174 (49)	80 (25) 92 (36) 129 (43)	5 (13) 0 (0) 174 (52)	3 (11) 0 (0) 129 (43)
Week 12	75 (30) 90 (40) 171(115)	15 (23) 4 (22) 118 (89)	17 (25) 5 (20) 171(118)	83 (24) 96 (23) 118 (89)	4 (13) 0 (0) 171(119)	1 (5) 0 (0) 118 (89)	73 (29) 80 (38) 174(124)	16 (23) 3 (29) 129(102)	16 (20) 10 (20) 174(125)	82 (23) 93 (32) 129(102)	5 (13) 0 (0) 172(126)	2 (6) 0 (0) 129(102)
Week 16	77 (30) 90 (40) 171 (78)	13 (22) 1 (17) 118 (66)	14 (22) 2 (20) 171 (79)	86 (24) 98 (19) 118 (66)	3 (10) 0 (0) 171 (82)	1 (6) 0 (0) 118 (66)	76 (30) 90 (40) 174 (62)	17 (24) 4 (31) 129 (576	15 (24) 5 (20) 174 (65)	81 (24) 93 (35) 129 (56)	3 (13) 0 (0) 174 (66)	2 (6) 0 (0) 129 (56)

Table S6: Wound tissue composition at each observation time point during the study treatment time of maximum 16 week in the ITTpopulation. Wound tissue (granulation, fibrin, and necrosis) is separately shown for the data documented in the eCRF and for the data derived from the photo analysis using the Wound Healing Analyzing Tool (W.H.A.T.). Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Pain Total N=344	Pain NPWT N=171	Pain SMWC N=173
Screening	2·1 (2·4) 1 (4) N=344 (0)	2·1 (2·3) 1 (4) N=171 (0)	2·1 (2·4) 1 (4) N=173 (0)
Week 1	1·7 (2·2) 1 (3) N=344 (6)	1·6 (2·2) 0 (2) N=171 (1)	1·8 (2·2) 1 (3) N=173 (5)
Week 3	1·5 (2·0) 1 (2) N=344 (27)	1·3 (1·9) 0 (2) N=171 (11)	1·7 (2·1) 1 (3) N=173 (16)
Week 5	1·3 (1·9) 0 (2) N=344 (45)	1·2 (1·9) 0 (2) N=171 (21)	1·4 (2·0) 0 (2) N=173 (24)
Week 8	1·3 (1·9) 0 (2) N=344 (70)	1·2 (1·9) 0 (2) N=171 (38)	1·3 (1·9) 0 (2) N=173 (32)
Week 12	1·1 (1·8) 0 (2) N=344 (115)	1·2 (1·9) 0 (2) N=171 (64)	1·1 (1·8) 0 (2) N=173 (51)
Week 16	1·0 (1·7) 0 (1) N=344 (129)	1·0 (1·7) 0 (2) N=171 (76)	0·9 (1·7) 0 (1) N=173 (53)

Table S7: Pain in the course of the study treatment time of maximum 16 weeks in the ITT-population. Pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	EQ5D NPWT	EQ5D SMWC
Screening	0,53 (0,27) 0,53 (0,2) N=156 (2)	0,53 (0,24) 0,53 (0,18) N=159 (3)
End of therapy	0,67 (0,24) 0,77 (0,29) N=62 (2)	0,72 (0,17) 0,66 (0,35) N=13 (0)

End of maximum study treatment time	0,66 (0,22) 0,66 (0,28) N=63 (2)	0,61 (0,25) 0,63 (0,24) N=95 (2)
Follow up after 6 months	0,69 (0,26) 0,77 (0,35) N=93 (3)	0,67 (0,23) 0,63 (0,39) N=97 (2)

Table S8: Quality of life (EQ5D) in the course of the study treatment time of 16 week in the ITT-population. Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT-population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Adverse Events (AE)	**Total** **N=269**	**NPWT** **N=167**	**SMWC** **N=102**
Day of occurrence ($N_{available}$)	269	167	102
Mean (SD)	39·5 (28·9)	37·5 (28·6)	42·7 (29·2)
Median (IQR)	34·0 (42)	30·0 (40·0)	38·0 (50·0)
Duration in days ($N_{available}$)	254	157	97
Mean (SD)	21·9 (33·0)	19·7 (29·0)	25·3 (38·6)
Median (IQR)	11·0 (21)	10·0 (20·0)	13·0 (22·0)
Severity ($N_{available}$)	263	161	102
Mild	88 (33·5%)	64 (39·8%)	24 (23·5%)
Moderate	92 (35·0%)	54 (33·5%)	38 (37·3%)
Severe	83 (31·6%)	43 (26·7%)	40 (39·2%)
AE expected / unexpected ($N_{available}$)	259	159	100
Expected	79 (30·5%)	52 (32·7%)	27 (27·0%)
Unexpected	180 (69·5%)	107 (67·3%)	73 (73·0%)
Action taken ($N_{available}$)	240	146	94
No	46 (19·2%)	23 (15·8%)	23 (24·5%)
Yes	194 (80·8%)	123 (84·2%)	71 (75·5%)
Cessation of therapy	10 of 194 (5·2%)	10 of 123 (8·1%)	0 of 71 (0%)
Temporary interruption of therapy	30 of 194 (15·5%)	28 of 123 (22·8%)	2 of 71 (2·8%)
Adaptation of therapy / treatment	100 of 194 (51·5%)	52 of 123 (42·3%)	48 of 71 (67·6%)
Other	54 of 194 (27·8%)	33 of 123 (26·8%)	21 of 71 (29·6%)
Outcome ($N_{available}$)	244	148	96
Fixed without consequences	115 (47·1%)	72 (48·6%)	43 (44·8%)
Condition improved	58 (23·8%)	32 (21·6%)	26 (27·1%)
Fixed with consequences	34 (13·9%)	22 (14·9%)	12 (12·5%)
Not fixed	7 (2·9%)	4 (2·7%)	3 (3·1%)
Death	15 (6·1%)	9 (6·1%)	6 (6·3%)
Unknown	15 (6·1%)	9 (6·1%)	6 (6·3%)

Table S9: The table shows details on the adverse events (AEs) documented during the active study treatment time of 112 days after randomization. Data are Number (N) and Percentage (%), Mean and Standard Deviation (SD), and Median and Interquartile Range (IQR).

Wound surface area	**Small wounds**				**Big wounds**			
mm²	**Total N=173**	**NPWT N=83**	**SMWC N=90**	**p**	**Total N=172**	**NPWT N=88**	**SMWC N=84**	**p**
N (LOCF)	2	2	0	0·232	0	0	0	0·193
Mean (SD)	213 (136)	212 (138)	213 (135)		1995 (3377)	1860 (1805)	2135 (4474)	
Median (IQR)	188 (220)	176 (220)	196 (222)		1276 (1482)	1364 (1242)	1242 (1708)	
Min - Max	12-484	20-484	12-471		491-40773	520-13188	491-40773	

Table S10: Wound surface area for small and big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms, the number (N) of values substituted by the last observation carried forward (LOCF) method; mean (SD), median (IQR); and minimum (min) and maximum (max).

Wound closure rate Small wounds	**NPWT (N=171) N=83**	**SMWC (N=174) N=90**	**p**
Within 16 weeks maximum study treatment time	12 (14·5 %)	16 (17·8 %)	0·6
At follow up after 6 months	13 (15·7 %)	24 (26·7 %)	0·10

Table S11: Wound closure rates within the maximum study treatment time of 16 weeks and within the study observation time of 6 months for small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number of patients with wound closure (N) within 16 weeks and after 6 months as well the percentage (%) of patients achieving the endpoints within both treatment arms.

Wound closure rate Big wounds	**NPWT (N=171) N=88**	**SMWC (N=174) N=84**	**P**
Within 16 weeks maximum study treatment time	13 (14·8 %)	5 (6·0 %)	0·08
At follow up after 6 months	11 (12·5 %)	12 (14·3 %)	0·82

Table S12: Wound closure rates within the maximum study treatment time of 16 weeks and within the study observation time of 6 months for big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number of patients with wound closure (N) within 16 weeks and after 6 months as well the percentage (%) of patients achieving the endpoints within both treatment arms.

Time until min. 95 % granulation tissue for small wounds	**Total (N=100)**	**NPWT (N=52)**	**SMWC (N=48)**	**p**
Mean (SD)	38·6 (37·4)	28·5 (30·0)	49·5 (41·6)	0·005
Median (IQR)	26·5 (50·0)	20·0 (28·0)	48·0 (79·0)	
Min-Max	0-114	0-113	0-114	

Table S13: Time until optimal preparation of the wound bed (min. 95 % granulation tissue) for the subgroup of small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Time until min 95 % granulation tissue for big wounds	**Total (N=80)**	**NPWT (N=47)**	**SMWC (N=33)**	**p**
Mean (SD)	47·8 (40·8)	43·4 (37·9)	54·0 (44·6)	0·27
Median (IQR)	36·5 (70·0)	35·0 (61·0)	56·0 (105·0)	
Min-Max	0-127	0-127	0-115	

Table S14: Time until optimal preparation of the wound bed (min 95 % granulation tissue) for the subgroup of big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Amputations & Resections **Small wounds**	**Total** **N=173**	**NPWT** **N=83**	**SMWC** **N=90**	**p**
No. of patients with amputations or resections [N (%)]	35 (20·2%)	19 (22·9%)	16 (17·8%)	0·45 (F)
No. of performed amputations and resections [N]	50	22	28	0·51 (U)
No. of patients with minor amputations [N (%)]	35 (20·2%)	19 (22·9%)	16 (17·8%)	0·45 (F)
No. of patients with major amputations [N (%)]	0 (0%)	0 (0%)	0 (0%)	-

Table S15: Amputations and resections in the subgroup of small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

Amputations & Resections **Big wounds**	**Total** **N=172**	**NPWT** **N=88**	**SMWC** **N=84**	**p**
No. of patients with amputations or resections [N (%)]	36 (20·9%)	16 (18·2%)	20 (23·8%)	0·45 (F)
No. of performed amputations and resections [N]	52	45	57	0·41 (U)

No. of patients with minor amputations [N (%)]	34 (19·8%)	14 (15·9%)	20 (23·8%)	0·25 (F)
No. of patients with major amputations [N (%)]	2 (1·2%)	2 (2·3%)	0 (0%)	0·50 (F)

Table S16: Amputations and resections in the subgroup of big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

Wound closure rate	**Total N=154**	**NPWT N=44**	**SMWC N=110**	**p**
Wound closures [N (%)] within 16 weeks	33 (21·4 %)	14 (31·8%)	19 (17·3%)	0·053
Wound closures [N (%)] after 6 months	41 (26·6 %)	11 (25·0%)	30 (27·3%)	0·84

Table S17: Wound closure rate after 6 months and in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with wound closures within 16 weeks and after 6 months.

Time until min. 95 % granulation tissue	**Total (N=100)**	**NPWT (N=38)**	**SMWC (N=62)**	**p**
Mean (SD)	43·8 (42·3)	23·8 (31·7)	56·0 (43·5)	<0·001
Median (IQR)	30·0 (76)	8·5 (28·0)	56·0 (96·0)	
Min - Max	0 - 127	0 - 127	0 - 115	

Table S18: Time until optimal preparation of the wound for further treatment (min 95 % granulation tissue) in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Recurrences	**Total (N=154)**	**NPWT (N=44)**	**SMWC (N=110)**	**p**
No. of patients with recurrences [N (%)]	8 (5·2 %)	3 (8·1 %)	5 (5·3%)	0·69
No. of recurrences [N]	9	4	5	0·38

Table S19: Recurrences in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with recurrences.

Amputations & Resections	**Total (N=154)**	**NPWT (N=44)**	**SMWC (N=110)**	**p**
No. of patients with amputation or resection [N (%)]	30 (19·5%)	9 (20·5%)	21 (21·4%)	0·83
No. of amputations or resections [N]	39	11	28	0·86
No. of patients with Minor-Amputations [N (%)]	30 (18·9%)	9 (12·8%)	21 (21·4%)	0·83
No. of patients with Major-Amputations [N (%)]	0 (0%)	0 (0%)	0 (0%)	-

Table S20: Amputations and resections in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

	Wound surface NPWT		**Wound surface SMWC**	
Observation time point	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**	**Observation time point**	**Calculated from width and length (according to eCRF entry)**
Randomization	964 (1392) 345 (1426) N= 44 (1)	633 (795) 299 (705) N=41 (3)	878 (1266) 373 (889) N= 110 (0)	669 (1143) 294 (692) N=102 (9)
Week 1	525 (696) 224 (408) N= 44 (5)	524 (614) 318 (561) N=41 (8)	827 (1238) 306 (863) N= 110 (16)	706 (1138) 289 (775) N=102 (27)
Week 3	428 (635) 176 (378) N= 44 (6)	477 (737) 165 (424) N=41 (9)	803 (1306) 238 (867) N= 110 (7)	714 (1316) 259 (656) N=102 (26)
Week 5	355 (590) 100 (291) N= 44 (8)	418 (602) 165 (435) N=41 (15)	650 (1157) 161 (670) N= 110 (18)	607 (1212) 167 (545) N=102 (29)
Week 8	284 (528) 53 (217) N= 44 (8)	320 (530) 83 (264) N=41 (16)	569 (1072) 106 (443) N= 110 (17)	479 (990) 123 (397) N=102 (29)
Week 12	283 (580) 14 (130) N= 44 (24)	289 (537) 62 (175) N=41 (32)	528 (1024) 79 (419) N= 110 (71)	474 (1006) 111 (407) N=102 (80)
Week 16	190 (416) 0 (95) N= 44 (14)	179 (333) 30 (204) N=41 (25)	386 (1124) 31 (159) N= 110 (19)	319 (724) 65 (256) N=102 (42)

Table S21: Wound surface area at each observation time point during the study treatment time of maximum 16 weeks separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis using W.H.A.T. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	**Wound volume NPWT (mm^3)**	**Wound volume SMWC (mm^3)**

Randomization	33359 (95749) 5746 (17330) N=44 (1)	14742 (36523) 3905 (11189) N=110 (0)
Week 1	11606 (26991) 1824 (6113) N=44 (5)	13525 (34844) 2470 (9479) N=110 (16)
Week 3	8636 (24698) 777 (3199) N=44 (6)	11907 (32047) 1864 (8039) N=110 (7)
Week 5	5480 (13967) 271 (1790) N=44 (7)	8981 (25570) 1027 (4745) N=110 (18)
Week 8	3955 (9056) 192 (809) N=44 (16)	6899 (18607) 506 (3915) N=110 (29)
Week 12	6052 (16114) 71 (681) N=44 (25)	5964 (15930) 361 (1890) N=110 (77)
Week 16	3246 (11245) 0 (319) N=44 (15)	3396 (10783) 57 (609) N=110 (19)

Table S22: Wound volume (length x width x depth) for each observation time point during the study treatment time of maximum 16 weeks calculated from width· length and depth as documented in the eCRF. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	NPWT Granulation		NPWT Fibrin		NPWT Necrosis		SMWC Granulation		SMWC Fibrin		SMWC Necrosis	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.		eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF
Rando	32 (37)	23 (26)	18 (27)	68 (27)	2 (7)	9 (15)	38 (38)	26 (27)	21 (29)	67 (29)	1 (7)	7 (15)
	10 (68)	13 (37)	3 (28)	69 (45)	0 (0)	0 (15)	25 (80)	16 (42)	10 (33)	77 (56)	0 (0)	0 (8)
	44 (1)	41 (2)	44 (1)	41 (2)	44 (1)	41 (2)	110 (0)	102 (9)	110 (0)	102 (9)	108 (2)	102 (9)
Week 1	72 (37)	22 (26)	7 (13)	70 (28)	2 (7)	9 (15)	54 (35)	24 (27)	22 (24)	72 (27)	5 (14)	5 (9)
	90 (50)	9 (41)	0 (10)	75 (50)	0 (0)	0 (11)	63 (70)	13 (42)	13 (28)	78 (42)	0 (1)	0 (6)
	44 (5)	41 (8)	44 (6)	41 (8)	44 (7)	41 (8)	110 (16)	102 (27)	110 (16)	102 (27)	108 (19)	102 (27)
Week 3	77 (32)	16 (24)	11 (19)	79 (26)	1 (4)	6 (14)	61 (31)	24 (27)	25 (25)	75 (26)	4 (11)	3 (7)
	93 (34)	2 (29)	0 (20)	91 (37)	0 (0)	0 (1)	70 (50)	15 (42)	20 (35)	83 (41)	0 (0)	0 (1)
	44 (6)	41 (9)	44 (7)	41 (9)	44 (7)	41 (9)	110 (9)	102 (26)	110 (10)	102 (26)	108 (13)	102 (26)
Week 5	82 (29)	10 (16)	9 (19)	87 (17)	1 (4)	3 (9)	65 (29)	19 (27)	24 (24)	78 (27)	3 (9)	3 (11)
	95 (20)	4 (11)	2 (10)	93 (21)	0 (0)	0 (1)	73 (46)	4 (34)	13 (37)	93 (35)	0 (0)	0 (0)
	44 (7)	41 (16)	44 (8)	41 (16)	44 (9)	41 (16)	110 (19)	102 (27)	110 (22)	102 (27)	108 (22)	102 (27)
Week 8	85 (27)	15 (25)	6 (13)	82 (26)	2 (6)	3 (8)	74 (27)	20 (26)	18(21)	77 (27)	3 (10)	3 (12)
	100 (20)	1 (16)	0 (5)	96 (35)	0 (0)	0 (0)	80 (31)	3 (38)	10 (18)	91 (43)	0 (0)	0 (0)
	44 (9)	41 (16)	44 (10)	41 (16)	44 (9)	41 (16)	110 (18)	102 (30)	110 (21)	102 (30)	108 (25)	102 (30)
Week 12	86 (26)	13 (24)	6 (14)	85 (26)	2 (9)	2 (6)	77 (27)	18 (25)	16 (20)	80 (25)	3 (11)	2 (6)
	100 (18)	1 (13)	0 (4)	99 (20)	0 (0)	0 (0)	85 (29)	3 (36)	10 (20)	92 (36)	0 (0)	0 (0)
	44 (26)	41 (34)	44 (26)	41 (32)	44 (28)	41 (32)	110 (72)	101 (78)	110 (73)	102 (79)	108 (73)	102 (80)
Week 16	87 (25)	12 (22)	6 (14)	86 (24)	0·1 (1)	1 (6)	80 (30)	19 (25)	14 (24)	80 (26)	2 (11)	1 (5)
	100 (15)	0 (14)	0 (1)	100 (20)	0 (0)	0 (0)	95 (20)	5 (36)	0 (20)	92 (36)	0 (0)	0 (0)
	44 (14)	41 (25)	44 (16)	41 (25)	44 (15)	41 (25)	110 (18)	102 (42)	110 (21)	102 (42)	108 (24)	102 (42)

Table S23: Wound tissue (granulation, fibrin, necrosis) at each observation time point during the study treatment time of maximum 16 weeks separately shown for the data documented in the eCRF and for the data derived from the photo analysis using the wound healing analyzing too (W.H.A.T.). Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Pain Total N=344	Pain NPWT N=171
Screening	1·3 (2·1) 0 (2) N=44 (0)	1·8 (2·3) 1 (3) N=110 (0)
Week 1	0·7 (1·5) 0 (1) N=44 (0)	1·4 (2·1) 0 (3) N=110 (5)
Week 3	0·4 (0·7) 0 (1) N=44 (4)	1·3 (1·8) 0 (2) N=110 (3)
Week 5	0·3 (0·8) 0 (0) N=44 (2)	1·0 (1·6) 0 (2) N=110 (5)
Week 8	0·4 (1·1) 0 (0) N=44 (4)	0·9 (1·5) 0 (2) N=110 (9)
Week 12	0·3 (1·0) 0 (0) N=44 (11)	0·7 (1·3) 0 (1) N=110 (18)
Week 16	0·2 (0·7) 0 (0) N=44 (14)	0·5 (1·2) 0 (0) N=110 (13)

Table S24: Pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	EQ5D NPWT	EQ5D SMWC
Screening	0·61 (0·23) 0·63 (0·24) N=42 (1)	0·60 (0·20) 0·59 (0·25) N=100 (3)
End of therapy	0·65 (0·20) 0·78 (0·20) N=26 (2)	0·81 (0·14) 0·87 (0·26) N=8 (0)
End of maximum study treatment time	0·65 (0·25)	0·66 (0·21)

	0·66 (0·43) N=19 (0)	0·63 (0·28) N=73 (2)
Follow up after 6 months	0·75 (0·22) 0·78 (0·30) N=26 (0)	0·70 (0·23) 0·77 (0·34) N=73 (2)

Table S25: Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Supplementary Discussion

As direct blinding of patients and investigators was not possible due to the nature of the applied treatment methods, issues of blinding have been addressed using independent blinded outcome assessors and the W.H.A.T. for evaluating the wound photographs. For wound size and wound tissue, the values documented by the investigators reflect the expected course much better than the W.H.A.T. results. During study planning the W.H.A.T. (http://www.what-world.com/) was the only available validated instrument that was able to measure both wound size and wound tissue composition (granulation, fibrin, and necrosis). For the wound surface area, the difference between the clinical measurements and the W.H.A.T. results may have been caused by the different evaluation methods. An elliptical wound surface area was calculated by the investigators using length and width, but most wounds are not elliptical. The independent blinded assessors marked the wound margin on the photograph and the W.H.A.T. calculates the wound surface area automatically afterwards, thus if the wound photo is of good quality the W.H.A.T. is more precise. In addition, the depth of the wound cannot be assessed using a wound photo, thus wound volume has only been evaluated using the clinical measurements provided by the investigators. The values for granulation tissue and fibrin differ significantly between the clinical estimations and the W.H.A.T. results. This may be caused by the quality of the wound photography, the reliability and precision of both the clinical investigator and the W.H.A.T. system and the wound itself. Wounds with invisible, deeper areas cannot be detected without manipulation. Both circumstances possibly affect the results.

Supplementary Appendix

Table of contents:

List of investigators:

1. PD Dr. med. Achim Neufang	HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für Gefäßchirurgie Ludwig-Erhard-Straße 100 65199 Wiesbaden
2. Dr. med. Holger Lawall	Asklepios Westklinikum Hamburg Zentrum für Gefäßmedizin Suurheid 20 22559 Hamburg
3. Prof. Dr. med. Gernold Wozniak	Knappschaftskrankenhaus Bottrop Gefäßchirurgische Klinik Osterfelderstraße 157 46242 Bottrop
4. Prof. Dr. med. Martin Storck	Städtisches Klinikum Karlsruhe Klinik für Gefäß- und Thoraxchirurgie Moltkestraße 90 76133 Karlsruhe
5. Dr. med. Dirk Hochlenert	Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Merheimer Straße 217 50733 Köln
6. Dr. med. Gudrun Hetzel	Klinikum Döbeln Abt. für Gefäßchirurgie Sörmitzer Straße 10 04720 Döbeln
7. Dr. med. Karsten Jungheim	Klinikum Bielefeld Mitte Klinik für Allgemeine Innere Medizin Teutoburger Straße 50 33604 Bielefeld
8. Dr. med. Michael Petzold	Klinikum Frankfurt/Oder

	Klinik für Gefäßchirurgie Müllroser Chaussee 7 15236 Frankfurt/Oder
9. PD Dr. med. Matthias Weck	Weißeritztal-Kliniken GmbH Medizinische Klinik III Bürgerstraße 7 ~~tal~~01705 Freital
10. Dr. med. Alexandra Zidek	Krankenhaus Porz am Rhein Klinik für Gefäßchirurgie Urbacher Weg 19 51149 Köln
11. Dr. med. Peter Mauckner	St. Remigius Krankenhaus Opladen Innere Medizin An St. Remigius 26 51379 Leverkusen
12. Dr. med. Klemens M. Sondern	Marien Hospital Dortmund-Hombruch Klinik für Innere Medizin/Diabetologie Gablonzstraße 9 44225 Dortmund
13. Prof. Dr. med. Thomas Schmitz-Rixen	Universitätsklinikum Frankfurt Zentrum für Chirurgie Klinik für Gefäß- und Endovascularchirurgie Theodor-Stern-Kai 7, Haus 23C/EG 60590 Frankfurt am Main
14. Dr. med. Walter Wetzel-Roth	Facharztpraxis für Chirurgie Hindenburgstraße 1 86807 Buchloe
15. Dr. med. Matthias Hahn	Helfenstein Klinik Geisslingen Allgemein- und Viszeralchirurgie Eybstraße 16 73312 Geislingen/Steige
16. Dr. med. Karsten Glockemann	Paracelsus-Klinik am Silbersee Wundzentrum Hannover Oertzeweg 24 30851 Langenhagen
17. PD Dr. med. Farzin Adili	Klinikum Darmstadt Chirurgische Klinik III Grafenstraße 9 64283 Darmstadt
18. Dr. med. Andreas Riemer	Ortenau Klinikum Offenburg-Ebertplatz Klinik für Allgemein-, Viszeral- und Gefäßchirurgie

	Ebertplatz 12 77654 Offenburg
19. Dr. med. Thomas Krönert	Thüringen-Kliniken "Georgius Agricola" GmbH Klinik für Gefäßchirurgie Rainweg 68 ~~feld~~07318 Saalfeld/Saale
20. Dr. med. Matthias Holfeld	Klinikum Dorothea Christiane Erxleben GmbH Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ditfurter Weg 24 ~~linburg~~06484 Quedlinburg
21. Prof. Dr. med. Jan Andre´ Schmidt-Lucke	Franziskus-Krankenhaus Berlin Abt. für Innere Medizin Budapester Straße 15-19 10787 Berlin
22. Dr. med. Wolf-Rüdiger Klare	Hegau-Bodensee Klinikum Radolfzell (HBK) Klinik für Innere Medizin Hausherrenstraße 12 78315 Radolfzell
23. Dr. med. Hansjörg Mühlen	Diabetologische Schwerpunktpraxis Dr. med. Hansjörg Mühlen & Partner Ruhrorter Straße 195 47119 Duisburg
24. Dr. med. Christian Reinhold	Kliniken Maria Hilf Mönchengladbach Klinik für Gefäßchirurgie und Angiologie Sandradstraße 43 41061 Mönchengladbach
25. Dr. med. Makarios Paschalidis	Städtisches Klinikum München/Bogenhausen Klinik für Endokrinologie, Diabetologie und Angiologie Englschalkingerstraße 77 81925 München
26. Gerhard Rothenaicher	Facharztpraxis für Chirurgie Cosimastraße 2 81927 München
27. Dr. med. Elke Anne Klug	Bürgerhospital Frankfurt am Main Interdisziplinäres Zentrum Diabetischer Fuß (DDG) Nibelungenallee 37- 41 60318 Frankfurt am Main
28. Dr. med. Siamak Pourhassan	Gemeinschaftspraxis für Chirurgie und Gefäßmedizin Drs. Alter / Pourhassan / Heim Klosterstraße 12 46145 Oberhausen

29. Dr. med. Jan Theil	Evangelisches Krankenhaus Königin Elisabeth Herzberge gGmbH Abt. für Kardiologie, Angiologie und Diabetologie Herzbergstraße 79 10365 Berlin
30. Dr. med. Martin Adolph	Städtisches Klinikum Neunkirchen gGmbH Abt. für Gefäßchirurgie & Phlebologie Brunnenstraße 20 66538 Neunkirchen
31. Dr. med. Frank von Feldmann	Westküstenklinikum Heide Klinik für Viszeral- und Gefäßchirurgie Esmarchstraße 50 25746 Heide/Holstein
32. Dr. med. Gerald Engels	Chir. Praxisgemeinschaft am Bayenthalgürtel Praxis Dr. med. Gerald Engels Bayenthalgürtel 45 50968 Köln
33. Dr. med. Joachim Oldenburg	Malteser Krankenhaus – St. Franziskus-Hospital Medizinische Klinik I Abt. für Diabetologie Waldstraße 17 24939 Flensburg
34. Dr. med. Philipp Kneppe	St. Marienkrankenhaus Siegen gGmbH Klinik für Gastroenterologie Kampenstraße 51 57072 Siegen
35. Dr. med. Steffen Hering	Krankenhaus Bietigheim Klinik für Innere Medizin, Kardiologie, Endokrinologie, Diabetologie und Internistische Intensivmedizin Riedstraße 12 74321 Bietigheim-Bissingen
36. Dr. med. Harald Daum	Asklepios Kliniken Harburg Eißendorfer Pferdeweg 52 21075 Hamburg
37. Dr. med. Lutz Stemler	Diabetologikum Ludwigshafen Diabetes-Schwerpunktpraxis Ludwigsplatz 9 67059 Ludwigshafen
38. Dr. med. Thomas Müller	Mariannen-Hospital Werl Abt. für Chirurgie Unnaer Straße 15 59457 Werl

39. Dr. med. Karl Zink	Diabetes Klinik GmbH & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim
40. Dr. med. Dirk Lammers	Institut für Diabetesforschung Münster GmbH Hohenzollernring 70 48145 Münster

Table S1: The table shows all study sites that have included at least one patient into the DiaFu-study.

Supplementary baseline characteristics for the ITT population

Baseline parameters (ITT population)	**Total N=345 (100 %)**	**NPWT N=171 (49·6%)**	**SMWC N=174 (50·4%)**
Alcohol	N=341	N=169	N=172
Occasionally	157 (46%)	83 (48·5%)	74 (42·3%)
Chronic	10 (2·9%)	3 (1·8%)	7 (4·0%)
No	174 (51%)	83 (48·5%)	91 (52%)
Smoking	N=342	N=169	N=173
No	49 (14·3%)	25 (14·6%)	24 (13·7%)
Yes	293 (85·7%)	144 (84·3%)	149 (85·1%)
Number of years Mean (SD)	34·8 (13·5)	36·5 (14·9)	33·1 (12·1)
Packs / day Mean	1·1	1·1	1·2
Drugs	N=341	N=169	N=172
Occasionally	1 (0·3%)	1 (0·6%)	0
Chronic	2 (0·6%)	0	2 (1·1%)
No	338 (97·7%)	168 (98·2%)	170 (97·1%)
Allergies	N=343	N=170	N=173
Yes	37 (10·7%)	16 (9·4%)	21 (12·0%)
No	306 (88·4%)	154 (90·1%)	152 (86·9%)
Subjective assessment of nutritional condition	N=342	N=169	N=173
Well-nourished	325 (94·2%)	162 (94·7%)	163 (93·7%)
Moderately malnourished or suspected malnutrition	11 (3·2%)	4 (2·3%)	7 (4%)

Malnourished	0 (0%)	0 (0%)	0 (0%)

Table S2: The table shows baseline characteristics of the ITT- population. Data are Number (N) and Percentage (%), or Mean and Standard Deviation (SD). "N=" is stating the number of patients with actual available information.

~~**Supplementary Discussion**~~

~~As direct blinding of patients and investigators was not possible due to the nature of the applied treatment methods, issues of blinding have been addressed using independent blinded outcome assessors and the W.H.A.T. for evaluating the wound photographs. For wound size and wound tissue the values documented by the investigators reflect the expected course much better than the W.H.A.T. results. During study planning the W.H.A.T. (http://www.what-world.com/) was the only available validated instrument that was able to measure both wound size and wound tissue composition (granulation, fibrin, and necrosis). For the wound surface area, the difference between the clinical measurements and the W.H.A.T. results may have been caused by the different evaluation methods. An elliptical wound surface area was calculated by the investigators using length and width, but most wounds are not elliptical. The independent blinded assessors marked the wound margin on the photograph and the W.H.A.T. calculates the wound surface area automatically afterwards, thus if the wound photo is of good quality the W.H.A.T. is more precise. In addition, the depth of the wound cannot be assessed using a wound photo, thus wound volume has only been evaluated using the clinical measurements provided by the investigators. The values for granulation tissue and fibrin differ significantly between the clinical estimations and the W.H.A.T. results. This may be caused by the quality of the wound photography, the reliability and precision of both the clinical investigator and the W.H.A.T. system and the wound itself. Wounds with invisible, deeper areas cannot be detected without manipulation. Both circumstances possibly affect the results.~~

~~**Supplementary tables**~~

Supplementary baseline characteristics for the PP population

Demographic and baseline parameters (PP-Population)	**Total N=154 (100%)**	**NPWT N=44 (28·6%)**	**SMWC N=110 (71·4%)**
Sex	N=154	N=44	N=110
Male	113 (73·4%)	29 (65·9%)	84 (76·4%)
Female	41 (26·6%)	15 (34·1%)	26 (23·6%)
Age in years Mean (SD)	N=154 67·4 (10·6)	N=44 66·5 (11·0)	N=110 67·8 (10·4)
Height in cm Mean (SD)	N=153 173·8 (12·9)	N=43 173·5 (17·4)	N=110 174·0 (10·7)
Weight in kg Mean (SD)	N=150 95·4 (23·3)	N=42 96·2 (21·6)	N=108 95·1 (24·0)

Alcohol	N=153	N=44	N=109
Occasionally	71 (46·4%)	22 (50·0%)	49 (45·0%)
Chronic	3 (2·0%)	1 (2·3%)	2 (1·8%)
No	79 (51·6%)	21 (47·7%)	58 (53·2%)
Smoking	N=154	N=44	N=110
No	16 (10·4%)	2 (4·5%)	14 (12·7%)
Yes	138 (89·6%)	42 (95·5%)	96 (87·3%)
Number of years (Mean (SD))	37·0 (9·2)	42·0 (2·8)	36·3 (9·7)
Packs / day (Mean)	1·0	1·0	1·0
Drugs	N=153	N=44	N=109
Occasionally	0 (0%)	0 (0%)	0 (0%)
Chronic	1 (0·7%)	0 (0%)	1 (0·9%)
No	152 (99·3%)	44 (100%)	108 (99·1%)
Requiring dialysis	N=154	N=44	N=110
Yes	11 (7·1 %)	2 (4·5%)	9 (8·2%)
No	143 (92·9%)	42 (95·5%)	101 (91·8%)
Allergies	N=154	N=44	N=110
Yes	16 (10·4%)	6 (13·6%)	10 (9·1%)
No	138 (89·6%)	38 (86·4%)	100 (90·9%)
Subjective assessment of nutritional condition	N=150	N=43	N=107
Well-nourished	147 (98·0%)	42 (97·7%)	105 (98·1%)
Moderately malnourished or suspected malnutrition	3 (2·0%)	1 (2·3%)	2 (1·9%)
Malnourished	0 (0%)	0 (0%)	0 (0%)
Peripheral arterial occlusive disease (PAOD)	N=109 (70·8%)	N=29 (65·9%)	N=80 (72·7%)
without critical limb ischemia	103 (94·5%)	28 (96·6%)	75 (93·8%)
with critical limb ischemia	6 (5·5%)	1 (3·4%)	5 (6·3%)
Rutherford classification for chronic limb ischemia (Grade/Category)	N=109	N=29	N=80
0/0 Asymptomatic—no hemodynamically significant occlusive disease	13 (11·9%)	4 (13·8%)	9 (11·3%)
I/1 Mild claudication	13 (11·9%)	2 (6·9%)	11 (13·8%)
I/2 Moderate claudication	8 (7·3%)	0 (0·0%)	8 (10·0%)
I/3 Severe claudication	4 (3·7%)	1 (3·4%)	3 (3·8%)

II/4 Ischemic rest pain	1 (0·9%)	1 (3·4%)	0 (0%)
III/5 Minor tissue loss—non healing ulcer, focal gangrene with diffuse pedal ischemia	67 (61·5%)	21 (72·4%)	46 (57·5%)
III/6 Major tissue loss—extending above transmetatarsal level, functional foot no longer salvageable	3 (2·8%)	0 (0·0%)	3 (3·8%)
Revascularisation before study start	N=9 (5·8%)	N=1 (2·3%)	N=8 (7·3%)
Percutaneous transluminal angioplasty (PTA)	5 (55·6%)	0 (0·0%)	5 (62·5%)
PTA + Stent	0 (0%)	0 (0%)	0 (0%)
Veins-Bypass	1 (11·1%)	1 (100·0%)	0 (11·1%)
Polytetrafluoroethylene (PTFE) Bypass	1 (11·1%)	0 (0%)	1 (12·5%)
Thromboendarterectomy and patch plastic	2 (22·2%)	0 (0%)	2 (25·0%)
Revascularization with influence on the wound	9 of 9 (100%)	1 of 1 (100%)	0 of 8 (100%)
Sufficient revascularization result	9 of 9 (100%)	1 of 1 (100%)	8 of 8 (100%)
Insufficient revascularization result	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)
Revascularization result not assessable	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)

Table S3~~1~~: Patient demographics and baseline characteristics of the Per-Protocol (PP) population. Data are N (%) and Mean (SD). "N=" is stating the number of patients with actual available information. Findings, diagnoses and procedures documented by the investigators are presented.

Supplementary result tables

	Wound surface NPWT		**Wound surface SMWC**	
Observation time point	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**
Randomization	1060 (1536) 550 (1236) N=171 (2)	687 (879) 321 (760) N=118 (10)	1141 (3247) 471 (1007) N=174 (0)	664 (1050) 316 (658) N=129 (13)
Week 1	847 (1489) 397 (801) N=171 (15)	643 (820) 329 (750) N=118 (32)	1085 (3234) 395 (867) N=174 (25)	713 (1065) 307 (749) N=129 (36)
Week 3	810 (1472) 314 (860) N=171 (24)	590 (742) 273 (633) N=118 (28)	1025 (3242) 390 (913) N=174 (22)	701 (1212) 266 (768) N=129 (35)
Week 5	717 (1379)	607 (828)	759 (1466)	610 (1119)

	275 (769) N=171 (37)	231 (843) N=118 (42)	267 (824) N=174 (41)	219 (635) N=129 (38)
Week 8	636 (1322) 220 (712) N=171 (52)	495 (770) 182 (561) N=118 (48)	674 (1410) 186 (783) N=174 (42)	501 (937) 165 (481) N=129 (42)
Week 12	549 (858) 165 (964) N=171 (110)	457 (742) 134 (494) N=118 (88)	570 (940) 169 (632) N=174 (124)	493 (950) 133 (498) N=129 (104)
Week 16	440 (810) 79 (471) N=171 (80)	334 (649) 114 (363) N=118 (66)	493 (1095) 69 (415) N=174 (63)	351 (750) 77 (320) N=129 (56)

Table S42: Wound surface area at each observation time point in the ITT-population. Wound surface area at each observation time point until end of maximum study treatment time -of 16 weeks is separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis. An elliptical wound surface area has been calculated from the documented width and length (eCRF) [(pi / 4) x length x width = area]. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	**Wound volume NPWT (mm^3)**	**Wound volume SMWC (mm^3)**
Randomization	22498 (58930) 4710 (15048) N=171 (2)	21740 (74181) 4759 (12888) N=174 (0)
Week 1	13203 (28709) 2487 (6908) N=171 (15)	19979 (73143) 3533 (11407) N=174 (26)
Week 3	10708 (28521) 1884 (6857) N=171 (24)	16217 (67494) 2293 (8831) N=174 (23)
Week 5	7700 (19719) 1166 (5338) N=171 (37)	11286 (32566) 1365 (7539) N=174 (42)
Week 8	5592 (11535) 785 (4604) N=171 (78)	8772 (27674) 812 (5258) N=174 (67)
Week 12	5333 (12422) 565 (3913)	6639 (16454) 625 (4083)

	N=171 (119)	N=174 (133)
Week 16	3880 (10534) 141 (1890) N=171 (83)	5465 (14874) 200 (1587) N=174 (64)

Table S53: Wound volume at each observation time point during the study treatment time of maximum 16 weeks in the ITT-population. Wound volume (length x width x depth) -was calculated from width, length and depth as documented in the eCRF. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	NPWT Granulation		NPWT Fibrin		NPWT Necrosis		SMWC Granulation		SMWC Fibrin		SMWC Necrosis	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.
Rando	34 (36) 20 (70) 171 (2)	22 (25) 12 (37) 118 (8)	21 (28) 10 (30) 170 (4)	71 (27) 79 (46) 118 (8)	3 (10) 0 (0) 169 (5)	7 (15) 0 (5) 118 (8)	34 (37) 20 (71) 174 (3)	24 (26) 14 (39) 129 (12)	22 (29) 10 (40) 174 (1)	69 (28) 79 (44) 129 (12)	2 (9) 0 (0) 172 (2)	7 (14) 0 (8) 129 (12)
Week 1	58 (35) 70 (70) 171 (16)	21 (25) 10 (36) 118 (32)	19 (22) 10 (30) 71 (19)	73 (27) 81 (47) 118 (32)	5 (13) 0 (2) 169 (23)	6 (12) 0 (5) 118 (32)	49 (35) 50 (70) 174 (28)	21 (25) 10 (36) 129 (36)	24 (27) 15 (31) 174 (27)	74 (26) 85 (40) 129 (36)	6 (15) 0 (5) 172 (30)	5 (9) 0 (5) 129 (36)
Week 3	67 (31) 80 (55) 171 (26)	16 (23) 5 (25) 118 (27)	18 (22) 10 (30) 171 (30)	80 (25) 91 (30) 118 (27)	5 (13) 0 (0) 169 (28)	4 (11) 0 (1) 118 (27)	57 (32) 60 (60) 174 (24)	21 (25) 10 (36) 129 (35)	25 (26) 20 (35) 174 (25)	77 (25) 85 (36) 129 (35)	5 (13) 0 (3) 172 (30)	3 (7) 0 (1) 129 (35)
Week 5	70 (30) 80 (45) 171 (36)	15 (22) 6 (21) 118 (43)	18 (24) 10 (25) 171 (38)	83 (22) 91 (26) 118 (43)	4 (13) 0 (0) 169 (42)	2 (8) 0 (1) 118 (43)	62 (31) 63 (50) 174 (44)	18 (26) 4 (32) 129 (36)	23 (25) 10 (39) 174 (47)	80 (26) 93 834) 129 (36)	4 (12) 0 (0) 172 (46)	3 (10) 0 (0) 129 (36)
Week 8	74 (30) 90 (40) 171 (53)	16 (23) 4 (27) 118 (48)	17 (24) 10 (20) 171 (56)	82 (24) 93 (33) 118 (48)	4 (13) 0 (0) 171 (59)	2 (6) 0 (0) 118 (48)	70 (29) 80 (40) 174 (44)	17 (24) 3 (33) 129 (43)	17 (21) 10 (20) 174 (49)	80 (25) 92 (36) 129 (43)	5 (13) 0 (0) 174 (52)	3 (11) 0 (0) 129 (43)
Week 12	75 (30) 90 (40) 171(115)	15 (23) 4 (22) 118 (89)	17 (25) 5 (20) 171(118)	83 (24) 96 (23) 118 (89)	4 (13) 0 (0) 171(119)	1 (5) 0 (0) 118 (89)	73 (29) 80 (38) 174(124)	16 (23) 3 (29) 129(102)	16 (20) 10 (20) 174(125)	82 (23) 93 (32) 129(102)	5 (13) 0 (0) 172(126)	2 (6) 0 (0) 129(102)
Week 16	77 (30) 90 (40) 171 (78)	13 (22) 1 (17) 118 (66)	14 (22) 2 (20) 171 (79)	86 (24) 98 (19) 118 (66)	3 (10) 0 (0) 171 (82)	1 (6) 0 (0) 118 (66)	76 (30) 90 (40) 174 (62)	17 (24) 4 (31) 129 (576	15 (24) 5 (20) 174 (65)	81 (24) 93 (35) 129 (56)	3 (13) 0 (0) 174 (66)	2 (6) 0 (0) 129 (56)

Table ~~S4~~S6: Wound tissue composition at each observation time point during the study treatment time of maximum 16 week in the ITT-population. Wound tissue (granulation, fibrin, and necrosis) is separately shown for the data documented in the eCRF and for the data derived from the photo analysis using the Wound Healing Analyzing Tool (W.H.A.T.). Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Pain Total N=344	Pain NPWT N=171	Pain SMWC N=173
Screening	2·1 (2·4) 1 (4) N=344 (0)	2·1 (2·3) 1 (4) N=171 (0)	2·1 (2·4) 1 (4) N=173 (0)
Week 1	1·7 (2·2) 1 (3) N=344 (6)	1·6 (2·2) 0 (2) N=171 (1)	1·8 (2·2) 1 (3) N=173 (5)
Week 3	1·5 (2·0) 1 (2) N=344 (27)	1·3 (1·9) 0 (2) N=171 (11)	1·7 (2·1) 1 (3) N=173 (16)
Week 5	1·3 (1·9) 0 (2) N=344 (45)	1·2 (1·9) 0 (2) N=171 (21)	1·4 (2·0) 0 (2) N=173 (24)
Week 8	1·3 (1·9) 0 (2) N=344 (70)	1·2 (1·9) 0 (2) N=171 (38)	1·3 (1·9) 0 (2) N=173 (32)
Week 12	1·1 (1·8) 0 (2) N=344 (115)	1·2 (1·9) 0 (2) N=171 (64)	1·1 (1·8) 0 (2) N=173 (51)
Week 16	1·0 (1·7) 0 (1) N=344 (129)	1·0 (1·7) 0 (2) N=171 (76)	0·9 (1·7) 0 (1) N=173 (53)

Table ~~S5~~S7: Pain in the course of the study treatment time of maximum 16 weeks in the ITT-population. Pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	EQ5D NPWT	EQ5D SMWC
Screening	0,53 (0,27) 0,53 (0,2) N=156 (2)	0,53 (0,24) 0,53 (0,18) N=159 (3)
End of therapy	0,67 (0,24) 0,77 (0,29) N=62 (2)	0,72 (0,17) 0,66 (0,35) N=13 (0)

End of maximum study treatment time	0,66 (0,22) 0,66 (0,28) N=63 (2)	0,61 (0,25) 0,63 (0,24) N=95 (2)
Follow up after 6 months	0,69 (0,26) 0,77 (0,35) N=93 (3)	0,67 (0,23) 0,63 (0,39) N=97 (2)

Table ~~S6~~S8: Quality of life (EQ5D) in the course of the study treatment time of 16 week in the ITT-population. Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT-population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Adverse Events (AE)	**Total** **N=269**	**NPWT** **N=167**	**SMWC** **N=102**
Day of occurrence ($N_{available}$)	269	167	102
Mean (SD)	39·5 (28·9)	37·5 (28·6)	42·7 (29·2)
Median (IQR)	34·0 (42)	30·0 (40·0)	38·0 (50·0)
Duration in days ($N_{available}$)	254	157	97
Mean (SD)	21·9 (33·0)	19·7 (29·0)	25·3 (38·6)
Median (IQR)	11·0 (21)	10·0 (20·0)	13·0 (22·0)
Severity ($N_{available}$)	263	161	102
Mild	88 (33·5%)	64 (39·8%)	24 (23·5%)
Moderate	92 (35·0%)	54 (33·5%)	38 (37·3%)
Severe	83 (31·6%)	43 (26·7%)	40 (39·2%)
AE expected / unexpected ($N_{available}$)	259	159	100
Expected	79 (30·5%)	52 (32·7%)	27 (27·0%)
Unexpected	180 (69·5%)	107 (67·3%)	73 (73·0%)
Action taken ($N_{available}$)	240	146	94
No	46 (19·2%)	23 (15·8%)	23 (24·5%)
Yes	194 (80·8%)	123 (84·2%)	71 (75·5%)
Cessation of therapy	10 of 194 (5·2%)	10 of 123 (8·1%)	0 of 71 (0%)
Temporary interruption of therapy	30 of 194 (15·5%)	28 of 123 (22·8%)	2 of 71 (2·8%)
Adaptation of therapy / treatment	100 of 194 (51·5%)	52 of 123 (42·3%)	48 of 71 (67·6%)
Other	54 of 194 (27·8%)	33 of 123 (26·8%)	21 of 71 (29·6%)
Outcome ($N_{available}$)	244	148	96
Fixed without consequences	115 (47·1%)	72 (48·6%)	43 (44·8%)
Condition improved	58 (23·8%)	32 (21·6%)	26 (27·1%)
Fixed with consequences	34 (13·9%)	22 (14·9%)	12 (12·5%)
Not fixed	7 (2·9%)	4 (2·7%)	3 (3·1%)
Death	15 (6·1%)	9 (6·1%)	6 (6·3%)
Unknown	15 (6·1%)	9 (6·1%)	6 (6·3%)

Table S9: The table shows details on the adverse events (AEs) documented during the active study treatment time of 112 days after randomization. Data are Number (N) and Percentage (%), Mean and Standard Deviation (SD), and Median and Interquartile Range (IQR).

Wound surface area	**Small wounds**				**Big wounds**			
mm²	**Total N=173**	**NPWT N=83**	**SMWC N=90**	**p**	**Total N=172**	**NPWT N=88**	**SMWC N=84**	**p**
N (LOCF)	2	2	0	0·232	0	0	0	0·193
Mean (SD)	213 (136)	212 (138)	213 (135)		1995 (3377)	1860 (1805)	2135 (4474)	
Median (IQR)	188 (220)	176 (220)	196 (222)		1276 (1482)	1364 (1242)	1242 (1708)	
Min - Max	12-484	20-484	12-471		491-40773	520-13188	491-40773	

Table ~~S7~~S10: Wound surface area for small and big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms, the number (N) of values substituted by the last observation carried forward (LOCF) method; mean (SD), median (IQR); and minimum (min) and maximum (max).

Wound closure rate **Small wounds**	**NPWT (N=171)** **N=83**	**SMWC (N=174)** **N=90**	**p**
Within 16 weeks maximum study treatment time	12 (14·5 %)	16 (17·8 %)	0·6
At follow up after 6 months	13 (15·7 %)	24 (26·7 %)	0·10

Table S11~~8~~: Wound closure rates within the maximum study treatment time of 16 weeks and within the study observation time of 6 months for small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number of patients with wound closure (N) within 16 weeks and after 6 months as well the percentage (%) of patients achieving the endpoints within both treatment arms.

Wound closure rate **Big wounds**	**NPWT (N=171)** **N=88**	**SMWC (N=174)** **N=84**	**P**
Within 16 weeks maximum study treatment time	13 (14·8 %)	5 (6·0 %)	0·08
At follow up after 6 months	11 (12·5 %)	12 (14·3 %)	0·82

Table ~~S9~~S12: Wound closure rates within the maximum study treatment time of 16 weeks and within the study observation time of 6 months for big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number of patients with wound closure (N) within 16 weeks and after 6 months as well the percentage (%) of patients achieving the endpoints within both treatment arms.

Time until min. 95 % granulation tissue for small wounds	**Total (N=100)**	**NPWT (N=52)**	**SMWC (N=48)**	**p**

Mean (SD)	38·6 (37·4)	28·5 (30·0)	49·5 (41·6)	0·005
Median (IQR)	26·5 (50·0)	20·0 (28·0)	48·0 (79·0)	
Min-Max	0-114	0-113	0-114	

Table ~~S10~~S13: Time until optimal preparation of the wound bed (min. 95 % granulation tissue) for the subgroup of small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Time until min 95 % granulation tissue for big wounds	**Total (N=80)**	**NPWT (N=47)**	**SMWC (N=33)**	**p**
Mean (SD)	47·8 (40·8)	43·4 (37·9)	54·0 (44·6)	0·27
Median (IQR)	36·5 (70·0)	35·0 (61·0)	56·0 (105·0)	
Min-Max	0-127	0-127	0-115	

Table S-~~14~~11: Time until optimal preparation of the wound bed (min 95 % granulation tissue) for the subgroup of big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Amputations & Resections **Small wounds**	**Total** **N=173**	**NPWT** **N=83**	**SMWC** **N=90**	**p**
No. of patients with amputations or resections [N (%)]	35 (20·2%)	19 (22·9%)	16 (17·8%)	0·45 (F)
No. of performed amputations and resections [N]	50	22	28	0·51 (U)
No. of patients with minor amputations [N (%)]	35 (20·2%)	19 (22·9%)	16 (17·8%)	0·45 (F)
No. of patients with major amputations [N (%)]	0 (0%)	0 (0%)	0 (0%)	-

Table ~~S12~~S15: Amputations and resections in the subgroup of small wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

Amputations & Resections **Big wounds**	**Total** **N=172**	**NPWT** **N=88**	**SMWC** **N=84**	**p**
No. of patients with amputations or resections [N (%)]	36 (20·9%)	16 (18·2%)	20 (23·8%)	0·45 (F)
No. of performed amputations and resections [N]	52	45	57	0·41 (U)
No. of patients with minor amputations [N (%)]	34 (19·8%)	14 (15·9%)	20 (23·8%)	0·25 (F)
No. of patients with major amputations [N (%)]	2 (1·2%)	2 (2·3%)	0 (0%)	0·50 (F)

Table ~~S13~~S16: Amputations and resections in the subgroup of big wounds. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

Wound closure rate	**Total N=154**	**NPWT N=44**	**SMWC N=110**	**p**
Wound closures [N (%)] within 16 weeks	33 (21·4 %)	14 (31·8%)	19 (17·3%)	0·053
Wound closures [N (%)] after 6 months	41 (26·6 %)	11 (25·0%)	30 (27·3%)	0·84

Table ~~S14~~S17: Wound closure rate after 6 months and in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with wound closures within 16 weeks and after 6 months.

Time until min. 95 % granulation tissue	**Total (N=100)**	**NPWT (N=38)**	**SMWC (N=62)**	**p**
Mean (SD)	43·8 (42·3)	23·8 (31·7)	56·0 (43·5)	<0·001
Median (IQR)	30·0 (76)	8·5 (28·0)	56·0 (96·0)	
Min - Max	0 - 127	0 - 127	0 - 115	

Table ~~S15~~S18: Time until optimal preparation of the wound for further treatment (min 95 % granulation tissue) in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms; mean (SD); median (IQR); and minimum (min) and maximum (max).

Recurrences	**Total (N=154)**	**NPWT (N=44)**	**SMWC (N=110)**	**p**
No. of patients with recurrences [N (%)]	8 (5·2 %)	3 (8·1 %)	5 (5·3%)	0·69
No. of recurrences [N]	9	4	5	0·38

Table ~~S16~~S19: Recurrences in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with recurrences.

Amputations & Resections	**Total (N=154)**	**NPWT (N=44)**	**SMWC (N=110)**	**p**
No. of patients with amputation or resection [N (%)]	30 (19·5%)	9 (20·5%)	21 (21·4%)	0·83
No. of amputations or resections [N]	39	11	28	0·86
No. of patients with Minor-Amputations [N (%)]	30 (18·9%)	9 (12·8%)	21 (21·4%)	0·83
No. of patients with Major-Amputations [N (%)]	0 (0%)	0 (0%)	0 (0%)	-

Table ~~S17~~S20: Amputations and resections in the PP-population. Data show the number (N) of participants available for the analysis in total and for both treatment arms and the number (N) and the percentage (%) of patients with amputations or resections and minor and major amputations.

	Wound surface NPWT		Wound surface SMWC	
Observation time point	**Calculated from width and length (according to eCRF entry)**	**Results of the photo analysis**	**Observation time point**	**Calculated from width and length (according to eCRF entry)**
Randomization	964 (1392) 345 (1426) N= 44 (1)	633 (795) 299 (705) N=41 (3)	878 (1266) 373 (889) N= 110 (0)	669 (1143) 294 (692) N=102 (9)
Week 1	525 (696) 224 (408) N= 44 (5)	524 (614) 318 (561) N=41 (8)	827 (1238) 306 (863) N= 110 (16)	706 (1138) 289 (775) N=102 (27)
Week 3	428 (635) 176 (378) N= 44 (6)	477 (737) 165 (424) N=41 (9)	803 (1306) 238 (867) N= 110 (7)	714 (1316) 259 (656) N=102 (26)
Week 5	355 (590) 100 (291) N= 44 (8)	418 (602) 165 (435) N=41 (15)	650 (1157) 161 (670) N= 110 (18)	607 (1212) 167 (545) N=102 (29)
Week 8	284 (528) 53 (217) N= 44 (8)	320 (530) 83 (264) N=41 (16)	569 (1072) 106 (443) N= 110 (17)	479 (990) 123 (397) N=102 (29)
Week 12	283 (580) 14 (130) N= 44 (24)	289 (537) 62 (175) N=41 (32)	528 (1024) 79 (419) N= 110 (71)	474 (1006) 111 (407) N=102 (80)
Week 16	190 (416) 0 (95) N= 44 (14)	179 (333) 30 (204) N=41 (25)	386 (1124) 31 (159) N= 110 (19)	319 (724) 65 (256) N=102 (42)

Table S~~18~~21: Wound surface area at each observation time point during the study treatment time of maximum 16 weeks separately shown for the calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis using W.H.A.T. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	**Wound volume NPWT (mm^3)**	**Wound volume SMWC (mm^3)**
Randomization	33359 (95749) 5746 (17330) N=44 (1)	14742 (36523) 3905 (11189) N=110 (0)

Week 1	11606 (26991) 1824 (6113) N=44 (5)	13525 (34844) 2470 (9479) N=110 (16)
Week 3	8636 (24698) 777 (3199) N=44 (6)	11907 (32047) 1864 (8039) N=110 (7)
Week 5	5480 (13967) 271 (1790) N=44 (7)	8981 (25570) 1027 (4745) N=110 (18)
Week 8	3955 (9056) 192 (809) N=44 (16)	6899 (18607) 506 (3915) N=110 (29)
Week 12	6052 (16114) 71 (681) N=44 (25)	5964 (15930) 361 (1890) N=110 (77)
Week 16	3246 (11245) 0 (319) N=44 (15)	3396 (10783) 57 (609) N=110 (19)

Table S2219: Wound volume (length x width x depth) for each observation time point during the study treatment time of maximum 16 weeks calculated from width· length and depth as documented in the eCRF. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	NPWT Granulation		NPWT Fibrin		NPWT Necrosis		SMWC Granulation		SMWC Fibrin		SMWC Necrosis	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.		eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF
Rando	32 (37)	23 (26)	18 (27)	68 (27)	2 (7)	9 (15)	38 (38)	26 (27)	21 (29)	67 (29)	1 (7)	7 (15)
	10 (68)	13 (37)	3 (28)	69 (45)	0 (0)	0 (15)	25 (80)	16 (42)	10 (33)	77 (56)	0 (0)	0 (8)
	44 (1)	41 (2)	44 (1)	41 (2)	44 (1)	41 (2)	110 (0)	102 (9)	110 (0)	102 (9)	108 (2)	102 (9)
Week 1	72 (37)	22 (26)	7 (13)	70 (28)	2 (7)	9 (15)	54 (35)	24 (27)	22 (24)	72 (27)	5 (14)	5 (9)
	90 (50)	9 (41)	0 (10)	75 (50)	0 (0)	0 (11)	63 (70)	13 (42)	13 (28)	78 (42)	0 (1)	0 (6)
	44 (5)	41 (8)	44 (6)	41 (8)	44 (7)	41 (8)	110 (16)	102 (27)	110 (16)	102 (27)	108 (19)	102 (27)
Week 3	77 (32)	16 (24)	11 (19)	79 (26)	1 (4)	6 (14)	61 (31)	24 (27)	25 (25)	75 (26)	4 (11)	3 (7)
	93 (34)	2 (29)	0 (20)	91 (37)	0 (0)	0 (1)	70 (50)	15 (42)	20 (35)	83 (41)	0 (0)	0 (1)
	44 (6)	41 (9)	44 (7)	41 (9)	44 (7)	41 (9)	110 (9)	102 (26)	110 (10)	102 (26)	108 (13)	102 (26)
Week 5	82 (29)	10 (16)	9 (19)	87 (17)	1 (4)	3 (9)	65 (29)	19 (27)	24 (24)	78 (27)	3 (9)	3 (11)
	95 (20)	4 (11)	2 (10)	93 (21)	0 (0)	0 (1)	73 (46)	4 (34)	13 (37)	93 (35)	0 (0)	0 (0)
	44 (7)	41 (16)	44 (8)	41 (16)	44 (9)	41 (16)	110 (19)	102 (27)	110 (22)	102 (27)	108 (22)	102 (27)
Week 8	85 (27)	15 (25)	6 (13)	82 (26)	2 (6)	3 (8)	74 (27)	20 (26)	18(21)	77 (27)	3 (10)	3 (12)
	100 (20)	1 (16)	0 (5)	96 (35)	0 (0)	0 (0)	80 (31)	3 (38)	10 (18)	91 (43)	0 (0)	0 (0)
	44 (9)	41 (16)	44 (10)	41 (16)	44 (9)	41 (16)	110 (18)	102 (30)	110 (21)	102 (30)	108 (25)	102 (30)
Week 12	86 (26)	13 (24)	6 (14)	85 (26)	2 (9)	2 (6)	77 (27)	18 (25)	16 (20)	80 (25)	3 (11)	2 (6)
	100 (18)	1 (13)	0 (4)	99 (20)	0 (0)	0 (0)	85 (29)	3 (36)	10 (20)	92 (36)	0 (0)	0 (0)
	44 (26)	41 (34)	44 (26)	41 (32)	44 (28)	41 (32)	110 (72)	101 (78)	110 (73)	102 (79)	108 (73)	102 (80)
Week 16	87 (25)	12 (22)	6 (14)	86 (24)	0·1 (1)	1 (6)	80 (30)	19 (25)	14 (24)	80 (26)	2 (11)	1 (5)
	100 (15)	0 (14)	0 (1)	100 (20)	0 (0)	0 (0)	95 (20)	5 (36)	0 (20)	92 (36)	0 (0)	0 (0)
	44 (14)	41 (25)	44 (16)	41 (25)	44 (15)	41 (25)	110 (18)	102 (42)	110 (21)	102 (42)	108 (24)	102 (42)

Table S2320: Wound tissue (granulation, fibrin, necrosis) at each observation time point during the study treatment time of maximum 16 weeks separately shown for the data documented in the eCRF and for the data derived from the photo analysis using the wound healing analyzing too (W.H.A.T.). Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	Pain Total N=344	Pain NPWT N=171
Screening	1·3 (2·1) 0 (2) N=44 (0)	1·8 (2·3) 1 (3) N=110 (0)
Week 1	0·7 (1·5) 0 (1) N=44 (0)	1·4 (2·1) 0 (3) N=110 (5)
Week 3	0·4 (0·7) 0 (1) N=44 (4)	1·3 (1·8) 0 (2) N=110 (3)
Week 5	0·3 (0·8) 0 (0) N=44 (2)	1·0 (1·6) 0 (2) N=110 (5)
Week 8	0·4 (1·1) 0 (0) N=44 (4)	0·9 (1·5) 0 (2) N=110 (9)
Week 12	0·3 (1·0) 0 (0) N=44 (11)	0·7 (1·3) 0 (1) N=110 (18)
Week 16	0·2 (0·7) 0 (0) N=44 (14)	0·5 (1·2) 0 (0) N=110 (13)

Table S2421: Pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Observation time point	EQ5D NPWT	EQ5D SMWC
Screening	0·61 (0·23) 0·63 (0·24) N=42 (1)	0·60 (0·20) 0·59 (0·25) N=100 (3)
End of therapy	0·65 (0·20) 0·78 (0·20) N=26 (2)	0·81 (0·14) 0·87 (0·26) N=8 (0)
End of maximum study treatment time	0·65 (0·25)	0·66 (0·21)

	0·66 (0·43) N=19 (0)	0·63 (0·28) N=73 (2)
Follow up after 6 months	0·75 (0·22) 0·78 (0·30) N=26 (0)	0·70 (0·23) 0·77 (0·34) N=73 (2)

Table S2522: Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).

Supplementary Discussion

As direct blinding of patients and investigators was not possible due to the nature of the applied treatment methods, issues of blinding have been addressed using independent blinded outcome assessors and the W.H.A.T. for evaluating the wound photographs. For wound size and wound tissue, the values documented by the investigators reflect the expected course much better than the W.H.A.T. results. During study planning the W.H.A.T. (http://www.what-world.com/) was the only available validated instrument that was able to measure both wound size and wound tissue composition (granulation, fibrin, and necrosis). For the wound surface area, the difference between the clinical measurements and the W.H.A.T. results may have been caused by the different evaluation methods. An elliptical wound surface area was calculated by the investigators using length and width, but most wounds are not elliptical. The independent blinded assessors marked the wound margin on the photograph and the W.H.A.T. calculates the wound surface area automatically afterwards, thus if the wound photo is of good quality the W.H.A.T. is more precise. In addition, the depth of the wound cannot be assessed using a wound photo, thus wound volume has only been evaluated using the clinical measurements provided by the investigators. The values for granulation tissue and fibrin differ significantly between the clinical estimations and the W.H.A.T. results. This may be caused by the quality of the wound photography, the reliability and precision of both the clinical investigator and the W.H.A.T. system and the wound itself. Wounds with invisible, deeper areas cannot be detected without manipulation. Both circumstances possibly affect the results.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6,8,9
Participants	4a	Eligibility criteria for participants	6,7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7,8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8,9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	9,10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12 Fig. 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig. 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12,13,14Tab. 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig. 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14-20
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	14-20
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	18-19
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	19-20
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3,21-22
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	21
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10-11

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Negative Pressure Wound Therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026345.R3
Article Type:	Original research
Date Submitted by the Author:	15-Jan-2020
Complete List of Authors:	Seidel, Dörthe; Universitat Witten/Herdecke, Institut für Forschung in der Operativen Medizin (IFOM) Storck, Martin; Stadtisches Klinikum Karlsruhe gGmbH, Klinik für Gefäß- und Thoraxchirurgie Lawall, Holger; Praxis für Herzkreislauferkrankungen; Max-Grundig Klinik Wozniak, Gernold; Knappschaftskrankenhaus Bottrop GmbH, Gefäßchirurgische Klinik Mauckner, Peter; St. Remigius Krankenhaus Opladen, Innere Medizin Hochlenert, Dirk; Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Wetzel-Roth, Walter; Chirurgische Praxis Wetzel-Roth Sondern, Klemens; Marien Hospital Dortmund-Hombruch, Klinik für Innere Medizin/Diabetologie Hahn, Matthias; Helfenstein Klinik, Allgemein- und Viszeralchirurgie Rothenaicher, Gerhard; Chirurgische Praxis Rothenaicher Krönert, Thomas; Thüringen-Kliniken "Georgius Agricola" GmbH, Klinik für Gefäßchirurgie Zink, Karl; Diabetes Klinik Neugebauer, Edmund; Universitat Witten/Herdecke Department fur Humanmedizin; Medizinische Hochschule Brandenburg -Theodor Fontane
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Surgery, Evidence based practice, Dermatology
Keywords:	negative pressure wound therapy, wound healing, benefit assessment, wound treatment, Diabetic foot < DIABETES & ENDOCRINOLOGY, wound care

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Negative Pressure Wound Therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT

Dörthe Seidel, Martin Storck, Holger Lawall, Gernold Wozniak, Peter Mauckner, Dirk Hochlenert, Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert, Karl Zink, Edmund Neugebauer

Institut für Forschung in der Operativen Medizin (IFOM), University of Witten/Herdecke, Köln, Germany (D Seidel MD), Doerthe.Seidel@uni-wh.de

Klinik für Gefäß- und Thoraxchirurgie, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany (Prof M Storck MD), Martin.Storck@klinikum-karlsruhe.de

Praxis für Herzkreislauferkrankungen, Ettlingen und Max-Grundig Klinik Bühlerhöhe, Germany (Dr med H Lawall MD), holger.lawall@gmail.com

Gefäßchirurgische Klinik, Knappschaftskrankenhaus, Bottrop, Germany (Prof G Wozniak MD), gernold.wozniak@kk-bottrop.de

Innere Medizin, St. Remigius Krankenhaus Opladen, Leverkusen, Germany (Dr med P Mauckner MD), peter-mauckner@live.de

Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock, Köln, Germany (Dr med D Hochlenert MD), dirk.hochlenert@web.de

Chirurgische Praxis Wetzel-Roth, Buchloe, Germany (Dr med W Wetzel-Roth MD), info@wetzel-roth.de

Klinik für Innere Medizin/Diabetologie, Marien Hospital Dortmund-Hombruch, Dortmund, Germany (Dr med Sondern MD), klemens.sondern@marien-hospital-dortmund.de

Allgemein- und Viszeralchirurgie, Helfenstein Klinik, Geisslingen, Germany (Dr med M Hahn, MD), matthias.hahn@af-k.de

Chirurgische Praxis Rothenaicher, München, Germany (G Rothenaicher MD), rothenaicher@arcor.de

Klinik für Gefäßchirurgie, Thüringen-Kliniken "Georgius Agricola" GmbH, Saalfeld, Germany (Dr med T Krönert MD), tkroenert@thueringen-kliniken.de

Diabetes Klinik, Bad Mergentheim, Germany (Dr med K Zink MD), zink@diabetes-zentrum.de

University of Witten/Herdecke, Köln, Germany (Prof E Neugebauer), Edmund.Neugebauer@uni-wh.de

Correspondence to:

Dörthe Seidel*

Institut für Forschung in der Operativen Medizin (IFOM)

University of Witten/Herdecke

Ostmerheimerstraße 200 Haus 38

Köln (Cologne)

51109 Germany

Doerthe.Seidel@uni-wh.de

Abstract

Objectives

The aim of the DiaFu-study was to evaluate effectiveness and safety of Negative Pressure Wound Therapy (NPWT) in patients with diabetic foot wounds in clinical practice.

Design

In this controlled clinical superiority trial with blinded outcome assessment patients were randomized in a 1:1 ratio stratified by study site and ulcer severity grade using a web-based-tool.

Setting

This German-national study was conducted in 40 surgical and internal medicine in- and outpatient facilities specialized in diabetes foot care.

Participants

368 patients were randomized and 345 participants were included in the modified ITT population. Adult patients suffering from a diabetic foot ulcer at least for 4 weeks and without contraindication for NPWT were allowed to be included.

Interventions

NPWT was compared with Standard Moist Wound Care (SMWC) according to local standards and guidelines.

Primary and secondary outcome measures

Primary outcome was wound closure within 16 weeks. Secondary outcomes were wound- and treatment-related adverse events (AEs), amputations, time until optimal wound bed preparation, wound size and wound tissue composition, pain, and quality of life within 16 weeks, and recurrences and wound closure within 6 months.

Results

In the ITT population, neither the wound closure rate (Difference: N=4 (2.5% [95%CI -4.7 - 9.7]; p=0.53) nor the time to wound closure (p=0.244) was significantly different between the treatment arms. 191 participants (NPWT 127; SMWC 64) had missing endpoint documentations, premature therapy ends or unauthorized treatment changes. 96 patients in the NPWT-arm and 72 patients in the SMWC-arm had at least one AE (p=0.007), but only 11 AEs were possibly related to NPWT.

Conclusions

NPWT was not superior to SMWC in diabetic foot wounds in German clinical practice. Overall wound closure rate was low. Documentation deficits and deviations from treatment guidelines negatively impacted the outcome wound closure.

Trial registration

Clinical Trials.gov: NCT01480362

Strengths and limitations of this study

- The DiaFu study included patients with diabetic foot ulcers both with peripheral neuropathy and peripheral arterial occlusive disease, which corresponds to the typical mixed patient population in real-life clinical practice. This allows a general statement on effectiveness and safety of NPWT in the typical medical care situation, but including patients with peripheral artery occlusive disease and clinical signs of inflammation (suspected infection) had a potentially negative effect on the treatment outcome wound closure.
- The study does not provide any information on the effectiveness of NPWT in specific patient groups.
- In this health services research study, hospitals and outpatient facilities were selected by means of a qualification checklist and clinical investigators were obliged to provide patients with the best clinical practice in compliance with all relevant diagnostic and treatment guidelines, but there was no active monitoring of the implementation of these guidelines.
- To ensure the best quality of local wound treatment and to achieve optimal baseline conditions, the study sites were trained for both NPWT and SMWC, but treatment application was at the discretion of the clinical investigators.
- A high number of missing endpoint documentations, premature termination of NPWT and unauthorized therapy changes negatively impacted the treatment outcome wound closure and may have led to bias in the results.

Background

More than 400 million people worldwide suffer from diabetes [1, 2] and about 15% of all these patients will develop a diabetic foot ulcer (DFU) during their lifetime [3, 4]. Approximately 50-70% of all lower limb amputations are due to diabetes [4]. DFUs represent complex chronic wounds with a major impact on patients` morbidity, mortality and quality of life. Beside an optimal diabetes and infection control, pressure relieving strategies and restoring pulsatile blood flow, effective local wound care is part of the holistic approach necessary to optimally treat patients with DFUs. Only a few modern moist wound dressings and topical agents have been convincingly shown to achieve higher wound closure rates compared with traditional wet gauze dressings in patients with diabetic foot wounds [5]. Also, for other ulcer types there is an uncertainty which dressings and topical agents are most effective for treatment [6]. Negative pressure wound therapy (NPWT) is an innovative treatment option and one of the most commonly used and well-established technologies with the aim to promote

wound healing [7]. The first use of vacuum sealing was described in 1993 by Fleischmann et al. [8] and the commercially available product was developed later in the 1990s [9, 10]. Positive effects of NPWT on wound healing have been suggested in various basic studies [10, 11]. At the time of planning the DiaFu-study, the clinical evidence largely consisted of clinician perception, case reports and series, small cohort studies, and weakly-powered or low-quality randomized trials that documented broad use of NPWT in various clinical settings and constituted a substantial number of publications but an overall small amount of evidence [12-15]. Two randomized controlled trials (RCTs) performed by Armstrong 2005 [16] and Blume 2008 [17] provided a solid basis for planning a study.

In the recent years, a specific review for the use of NPWT in diabetic foot wounds performed by Dumville et al in 2013 [18], an assessment in the home setting by Rhee at al. in 2014 [19] and a health technology assessment particularly issued for the evaluation of NPWT for managing diabetic foot ulcers [20] in 2014, as well as the most recent work of Liu et al in 2017 [21, 22] all concluded that although NPWT may have a positive effect, the trials that have been performed have methodological flaws and sufficient, unbiased evidence of whether wounds heal better or worse with NPWT than with conventional treatment is still missing.

In Germany, the issue of evidence for efficacy and safety of NPWT in acute and chronic wounds was first addressed in 2002 when the German Federal Joint Committee (German: Gemeinsamer Bundesausschuss [G-BA]) needed to decide whether NPWT could be reimbursed without restrictions in outpatient care.

Finally, in 2007 taking into account all available evidence the G-BA decided that the benefits of the treatment method NPWT should be evaluated in a so-called model project. This included the conduct of clinical studies for which the G-BA defined basic requirements. This essentially concerned the formulation of a study hypothesis that supports G-BA's overall question if NPWT can be reimbursed in German outpatient care without any limitation; the selection of a comparator that represents the current treatment standard in Germany; and implementation of all measures to ensure a sufficient certainty of the results.

Following the announcement of the G-BA, the German statutory health insurance funds initiated an overall project through a European tender. The DFU has been chosen to be the representative for chronic wounds in a RCT comparing NPWT and standard moist wound care (SMWC) in clinical practice.

Methods

Aim of the study

The aim of the DiaFu-study was to evaluate whether the effectiveness and safety of NPWT is superior to SMWC in German real-life clinical practice.

Study Design

The DiaFu-study was a multicenter, randomized controlled clinical superiority trial with blinded assessment of wound closure, wound size and wound tissue qualities using photographs. This German national study was conducted both in hospital departments and outpatient facilities with a special qualification for diabetic foot care. Study sites were selected based on their qualifications and experiences using a pre-study qualification checklist and annual quality reports of the respective institution (if available). Study treatment was allowed to be started both in in- and outpatient care and should be continued outpatient whenever possible. Ethical approval of the Lead Ethical Committee of the University of Witten/Herdecke has been fully granted without any conditions. More detailed information on the study design can be found in the study protocol publication that is available open access [23].

Patient and Public Involvement

Patients were not involved in the design, recruitment or conduct of the study. The results of this study will not be disseminated directly to study participants.

Participants

Following a pragmatic approach with the aim to include a patient population best representing real-life clinical practice, in- and exclusion criteria were selected based on manufacturers' contraindications and FDA warnings, the necessity to exclude patients in need of protection and who are unable to give their consent, and the intention to avoid general study-related and treatment specific influences on the results.

Adult patients (age >18 years) with at least 4-week-old chronic diabetic foot ulcers corresponding to Wagner 2 to 4 were screened for study participation by the local investigators. Before inclusion, the study protocol required either a debridement or, if necessary, an amputation of foot parts, or a thorough wound cleansing, depending on the individual needs of the patients. Thus, chronic diabetic foot wounds after adequate wound pretreatment as well as post-surgical amputation wounds below the upper ankle joint were eligible for inclusion. The initially planned minimum ulcer age of 6 weeks was reduced to 4 weeks during the course of the study. As in clinical practice, the assessment of patients' suitability for a specific wound therapy with the aim of complete wound closure and due to randomization for both study treatment arms (NPWT and SMWC) was at the discretion of the treating physicians (clinical investigators of the study). Particular attention was to be paid to the diagnosis and therapy of concomitant diseases.

Patients estimated to be at risk of non-compliance with study requirements, with wounds with necrotic tissue present that could not be removed by debridement or amputation, with exposed blood vessels within or directly surrounding the wound not possible to be sufficiently covered or with an increased risk of bleeding with hemodynamic consequences (mainly relevant for posterior tibial artery dorsalis pedis artery), and outpatients receiving anticoagulation therapy or suffering from a high-grade impaired clotting function with a heightened risk of bleeding with hemodynamic consequences were excluded from the DiaFu-study. The use of NPWT devices on the study wound within six weeks prior to study start represented an exclusion criterion in order to demonstrate a clear therapeutic effect of each treatment arm.

Written informed consent was obtained from every participant after being informed about all aspects of the trial and before randomization and any trial-related procedure. As the statutory health insurance funds provided integrated care contracts for outpatient NPWT, it was only possible to include patients in the study who were members of a participating health insurance fund.

Randomization and masking

Patients were randomly allocated to the treatment arms in a 1:1 ratio using a computer-generated list located on a centralized web-based tool. The randomization list consisted of permuted blocks of variable length (4, 6) which were randomly arranged. Patients were stratified by study site and by Wagner-Armstrong stage within each site (<Wagner-Armstrong stage 2C and ≥ Wagner-Armstrong stage 2C). The randomization lists were generated with the help of a self-created Java program and integrated into the study database. Each registered investigator received individual access to the randomization tool via the study website, but without knowledge of future treatment assignment, which provided adequate allocation concealment. The investigators were responsible for adequately implementing the assigned therapy. Due to the physical differences between the treatment regimens it was not possible to blind either participant or physician to the treatment assignment. Verification of complete wound closure was performed by independent, blinded assessment of wound photographs. Determination of wound size and percentage wound tissue quality was also performed by central, blinded outcome assessors based on the wound photographs using the Wound Healing Analyzing Tool (W.H.A.T.). The determination of sufficient wound bed conditioning and the indication for surgical closure was carried out by the treating physician, as in clinical practice. The treating physician was not blinded to treatment allocation.

Procedures

Basic data were collected for all patients considered for study participation during screening and have been updated during the randomization visit. Patients received an extensive examination of overall health status, specific diabetes associated disorders, and relevant influence factors on wound healing during screening with an update at the randomization visit. Neuropathy and vascular diagnostics were performed according to the German National Health Care Guidelines for Type 2 Diabetes Foot Complications [24]. After anamnesis and general diagnostics (physical examination) this care guideline recommends the following further vascular diagnostics: ankle-arm index (ABI, "Ankle-Brachial-Index") and additional assessment of the Doppler frequency spectrum (due to the possible falsifying of the results by Media sclerosis) and, if necessary, additional hydrostatic toe pressure measurement (pole test) or a transcutaneous oxygen partial pressure measurement (tcPO2); duplex sonography to determine the extent and distribution pattern of PADK (including the lower leg arteries if necessary). In case of inconclusive findings contrast-agent-enhanced MR angiography (MRA) and intra-arterial digital subtraction angiography (DSA) were considered. No detailed examination results of the vascular diagnostics but the final diagnosis of peripheral artery occlusive disease (PAOD) and critical limb ischemia (CLI) were to be documented in the eCRF by the clinical investigators. Infection diagnosis comprised clinical evaluation and laboratory testing. In case of suspected diabetic foot osteomyelitis (DFO) a probe to bone test and a stepwise approach to imaging modalities were applied in order to confirm the clinical diagnosis and to determine the best treatment regimen for the study participants.

Before randomization and start of study treatment all patients underwent one or more of the following no longer than six hours before randomization: amputation, debridement or thorough wound cleansing. Study therapy was allowed to be started either in-hospital or as outpatient and was intended to be continued in outpatient care whenever possible.

In the intervention arm commercially available CE-marked NPWT devices of the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew were used in the discretion of the clinical investigator according to clinical routine and manufacturer's instructions [23]. Intermittent and continuous NPWT was allowed to be used with the negative pressure to be adapted as recommended for the dressing applied (V.A.C.-Granufoam®black or Silver®; V.A.C.-White Foam®; Renassys™ –F/P; Renassys™ –G) and adapted to the wound needs. Recommendations for use can be found on the manufacturers' websites. As part of the European tender for the overall project, the German statutory health insurance funds awarded lots for the provision of the medical products by the respective manufacturers. Germany was divided into 4 supply areas. During the award procedure, Smith & Nephew received 1 lot and KCI 3 lots. Thus, devices and consumables of Smith& Nephew were used for the north

and northern east region of Germany and for the rest of Germany the therapy systems of KCI were used. Within the study, NPWT was required to be used for wound bed preparation in order to achieve at least 95% granulation of the wound area. After optimal preparation of the wound, complete closure could be achieved either by secondary intention with dressings or by surgical closure with subsequent removal of the suture.

Control therapy was defined as any SMWC according to local clinical standards and guidelines [25, 26]. Healthcare providers were obligated to provide patients with best practice. In the control arm it was permitted to apply any local wound treatment standard used in the respective study site that did not have an experimental status or was NPWT. To ensure the best quality of local wound treatment, the study sites were trained for both the intervention arm by the manufacturers and the control arm by the German Society for Wound Healing and Wound Treatment which provided parts of its curriculum and experienced instructors.

The maximum study treatment time was 16 weeks after randomization. Study visits needed to be performed at week one, three, five, 12 and 16, and in the event of end of treatment, hospital discharge, wound closure and for wound closure confirmation after a minimum of 14 days. Study participants were followed up until 6 months after randomization. The initially planned follow-up period of 12 months was reduced to 6 months in the course of the study. The amendment to the study protocol was endorsed by the Ethics Committee and immediately communicated to all participating study sites.

Outcomes

The primary outcome was wound closure (100% epithelialization of the wound, no drainage, no suture material and no need for wound dressing or adjuvants) within the maximum study treatment period of 16 weeks. Wound closure could be achieved both by healing by secondary intention and by delayed primary closure and needed to sustain for a minimum of 14 days. Complete closure of the wound needed to be confirmed by independent blinded observers using wound photographs.

Secondary outcomes were wound closure after six months; time until optimal preparation of the wound bed (a minimum of 95% granulation), amputations and resections, wound size and wound tissue composition, pain and quality of life within 16 weeks, and recurrence within six months. The initial planned secondary endpoint time until wound closure within 6 months was abandoned during the course of the study. It was found that a time-to-event survey was not possible outside the active study treatment period. This was mostly due to the fact that after this 16-week period weekly study visits were no longer an obligation and further patient care was no longer bound to the study site.

Minor and major amputations were considered separately, whereas the disarticulation at the midtarsal joint (Chopart's amputation) was considered still to be minor. Wound size and wound tissue composition (percentage of granulation tissue, fibrin and necrosis) were monitored at each study visit. Quality of life (QoL) was measured using the questionnaire Euro Quol 5D (EQ5D) at inclusion, end of the maximum treatment time or end of the therapy and at the six-month follow-up visit. At each study visit participants were asked to provide their assessment of wound-associated pain on a numerical rating scale (0 to 10). The incidence of serious adverse events (SAEs) within six months and the incidence of device-related and wound-related adverse events occurring within 16 weeks or until wound closure confirmation were safety endpoints of this trial.

Statistical analysis

Sample size calculation was performed using the expected difference between wound closure rates in both treatment arms based on information extracted from previously published studies by Armstrong and Lavery [16] and Blume [17]. We assumed a complete wound closure rate of 45% for NPWT and 30% in the SMWC group, resulting in a minimum difference of 15% after a treatment time of 16 weeks. Based on a type one error of $\alpha = 0.05$ and a type two error of $\beta = 0.2$ (corresponding to a power of 80%) a total sample size of 162 patients per group was calculated. The computer program of Dupont and Plummer was used for sample size calculation [27].

We performed all analyses based on a modified intention-to-treat (ITT) population that includes all randomized participants who have a valid baseline and at least one valid post baseline wound assessment. As a secondary approach a per-protocol (PP) analysis has been performed excluding patients with any serious protocol deviations, like temporary changes from SMWC to NPWT, permanent wound treatment changes or without valid documentation until wound closure confirmation or end of maximum treatment time (EOMT). Safety data are presented on an ‘as treated’ basis. Subgroup analysis is presented for small vs big wound subpopulations. There was no interim analysis.

The superiority hypothesis was tested in parallel for wound closure rate and time to wound closure within16 weeks. Incidence of complete wound closure was analyzed using a chi-squared test (Fisher's exact test) comparing the two treatment arms. Time to complete wound closure was compared between the two treatment arms using a Log-rank test. The method of Bonferroni-Holm was used for adjustment of the α-error for parallel confirmatory testing of both primary endpoints. Missing values have been incorporated as censored values.

During study planning, the following concomitant diseases and therapeutic measures with a possible influence on the primary study outcome wound closure (confounders) were identified: presence of neuropathy (sensation loss according to the PEDIS classification system [28]); presence of diabetic neuropathic osteoarthropathy (DNOAP)

(anatomical classification according to Sanders [29] and progression stages according to Levin [30]), Wagner [31] grading of the ulcer; presence of peripheral arterial occlusive disease (Rutherford classification for chronic limb ischemia [32]), chronic venous insufficiency (CVI) (Widmer I-III [33]), presence of extreme foot deformities and malpositions of toes, foot or the entire limb; untreated or therapy-refractory inflammation in the wound area; chronic anemia; heel necrosis; presence of a lymphedema; infection; heightened glycated hemoglobin (HbA1c) level; dialysis; application of hyperbaric oxygen (HBO) or normothermal therapy, application of recombinant or autologous growth factors to the study wound, and application of skin or dermal substitutes and with living cells that produce growth factors. These covariates thought to influence wound closure were analyzed for their effect on the two primary endpoints. Covariates were excluded from the analysis if the number of missing values was too high. First, the relevant covariates were tested by means of a univariate analysis with regard to their effect on wound closure rate and time without consideration of the treatment arms. If there was a significant influence, the frequency of occurrence in the treatment arms was analyzed. Secondary, multivariate analyses were performed for both primary endpoints, taking into account treatment assignment and including all relevant covariates. The multivariate analysis of the primary endpoint wound closure rate was performed with binary logistic regression to describe the influence of the independent covariates (regressors) on the dependent dichotomous variable wound closure. The multivariate analysis of the primary endpoint time to wound closure was performed using a COX regression model.

Safety and secondary endpoints were analyzed using conventional univariate testing.

Within a priori planned subgroup analysis the ITT population was divided into a group of small wounds and a group of big wounds based on the wound surface area documented during the randomization visit. Wounds smaller than or equal to the total median wound surface (483 mm²) were assigned to the subgroup "small wounds". Patients with wound surface areas larger than the median value were assigned to the subgroup "large wounds". Since no citable scientific definition of a large wound was available at the time of study planning and the clinical experts involved could not make a decision, the median of all wounds was chosen as the criterion for the division into the two subgroups. Confirmatory analysis of primary and secondary endpoints was repeated for the subgroups.

Missing values for the following outcome parameters were replaced using the Last Observation Carried Forward (LOCF) method: wound closure rate, wound size and wound tissue quality, recurrence and amputation. The outcome parameters time to wound closure and time until optimal preparation of the wound bed did not require data replacement, since missing values are included in the analysis as right-censored values. If the wound closure was not confirmed to be closed after a minimum of 14 days, the wound wass considered as an unsustained wound closure. All missing quality of life values (EQ-5D) were replaced with the overall quality of life assessment (visual

analogue scale), if available. If there was no quality of life assessment, there was no replacement. For missing values of the demographic and baseline characteristics, which are necessary for the estimation of the regression coefficients, no replacement was performed. IBM SPSS Statistics (version 23) was used for all analyses.

This study is registered with ClinicalTrials.gov. Number NCT01480362 and in the German Clinical Trial Registry, number DRKS00003347.

A data monitoring committee was formed to oversee overall study performance and safety.

Role of the funding source

Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds, which provided integrated care contracts for all study participants and for up to 7000 patients with acute and chronic wounds in Germany; defined basic rules for study design based on the requirements of the German authorities; and provided a critical review of the study protocol and the final report. The study was funded by the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary support and information about the used material. The manufacturers had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

Results

Between Dec 23, 2011 and August 12, 2014 386 patients were enrolled and randomly assigned to receive NPWT (181) or SMWC (187) in the DiaFu-study (**Error! Reference source not found.**) in overall 40 study sites, which recruited minimum 1 patient and maximum 76 patients. 13 clinical investigators randomized more than 10 patients. 23 study sites enrolled only between 1 and 4 patients. Most of these study sites refused further study participation due lack of time and staff for adequately performing the documentation. In the further course of the trial research nurses have been hired by the independent scientific institute overseeing the trial in order to support the documentation in the study sites whenever needed.

Demographics and relevant baseline characteristics of the DFU are presented in Table 1 and Supplement Table 1. Baseline characteristics of the patients in the NPWT-and the SMWC-arm are similar in the ITT population without any relevant difference between the treatment arms.

Demographics of the study population and baseline parameters of the DFU of the ITT population	Total N=345 (100 %)	NPWT N=171 (49.6%)	SMWC N=174 (50.4%)
Male	267 of 345 (77.4%)	133 of 171 (77.8%)	134 of 174 (77.0%)
Female	78 of 345 (22.6%)	38 of 171(22.2%)	40 of 174 (23.0%)
Age (years) (N=345) Mean (SD)	67.8 (11.9)	67.6 of 171(12.3)	68.1 (11.5)
Height (N=340) (in cm) Mean (SD)	174.1 (12.4)	173.4 (14.6)	174.8 (9.9)
Weight (N=335) (in kg) Mean (SD)	93.3 (22)	92.7 (21.5)	93.8 (22.6)
Localization of the ulcer			
Regio calcanea	39 (11.3%)	17 (9.9%)	22 (12.6%)
Dorsum pedis	20 (5.8%)	13 (7.6%)	7 (4%)
Planta pedis	56 (16.2%)	30 (17.5%)	26 (14.9%)
Metatarsalia	147 (42.6%)	73 (42.7%)	74 (42.5%)
Phalanges distales	64 (18.6%)	31 (18.1%)	33 (19%)
Phalanges mediales	28 (8.1%)	14 (8.2%)	14 (8%)
Phalanges proximales	40 (11.6%)	21 (12.3%)	19 (10.9%)
Hallux	42 (12.2%)	24 (14%)	18 (10.3%)
Digitus pedis II	22 (6.4%)	10 (5.8%)	12 (6.9%)
Digitus pedis III	14 (4.1%)	7 (4.1%)	7 (4%)
Digitus pedis IV	20 (5.8%)	7 (4.1%)	13 (7.5%)
Digitus minimus	25 (7.2%)	12 (7%)	13 (7.5%)
Type of ulcer			
Primary ulcer	279 of 342 (80.9%)	136 of 170 (79.5%)	143 of 172 (82.2%)
Recurrence	63 of 342 (18.3%)	34 of 170 (19.9%)	29 of 172 (16.7%)
Duration of ulcer (days)			
N	335	168	167
Mean (SD)	189.7 (360.2)	217.1 (458.1)	162.1 (220)
Median	83 (136)	81 (140)	85 (132)
Min – Max	0 – 4468	0 – 4468	0 – 1826
Wound surface area at randomization (mm^2)			
Mean (SD)	1101 (2543)	1060 (1536)	1141 (3247)
Median (IQR)	491 (1079)	550 (1217)	471 (1007)
Min-Max	12 – 40773	20 – 13188	12 – 40773
Wound surface area at randomization for small wounds (mm^2)			

N	173	83	90
Mean (SD)	213 (136)	212 (138)	213 (135)
Median (IQR)	188 (220)	176 (220)	196 (222)
Min-Max	12-484	20-484	12-471
Wound surface area at randomization for large wounds (mm²)			
N	172	88	84
Mean (SD)	1995 (3377)	1860 (1805)	2135 (4474)
Median (IQR)	1276 (1482)	1364 (1242)	1242 (1708)
Min-Max	491-40773	520-13188	491-40773

Table 1: The table shows patient demographics and baseline characteristics of the ITT population. Data are Number (N) and Percentage (%), Mean and Standard Deviation (SD), Median and Interquartile Range (IQR), and Minimum – Maximum [Min – Max]. "N=" is stating the number of patients with actual available information. Based on the median wound surface area of all included patients, the wounds were divided into an a priori planned subgroup of large (Median wound surface area ≤484 mm² and a subgroup of small wounds (Median wound surface area >484 mm²).

The baseline of the identified factors possibly influencing wound closure is shown in Table 2.

Confounders at baseline in the ITT population	**Total N=345**	**NPWT N=171.**	**SMWC N=174.**
Presence of neuropathy (sensation loss according to the PEDIS classification system)	250 of 334 (72.5%)	125 of 166 (73.1%)	125 of 168 (71.8%)
Presence of a diabetic neuropathic osteoarthropathy (DNOAP)	61 (17.7%)	30 (17.5%)	31 (17.8%)
Wagner grading of the ulcer			
1 - Superficial ulcer of skin or subcutaneous tissue	6 (1.7%)	2 (1.2%)	4 (2.3%)
2 - Ulcers extend into tendon, bone, or capsule	225 (65.2%)	110 (64.3%)	115 (66.1%)
3 - Deep ulcer with osteomyelitis, or abscess	85 (24.6%)	45 (26.3%)	40 (23%)
4 - Gangrene of toes or forefoot	26 (7.5%)	13 (7.6%)	13 (7.5%)
5 - Midfoot or hindfoot gangrene	3 (0.9%)	1 (0.6%)	2 (1.1%)
Peripheral arterial occlusive disease (PAOD)	244 of 345 (70.7%)	121 of 171 (70.8%)	123 of 174 (70.7%)
PAOD with critical limb ischemia (persistent pain at rest with regular analgesia for a period of 2 weeks while nerve function is maintained or the occurrence of ulceration or gangrene of the foot or toes with a systolic blood pressure of the	26 of 243 (10.7%)	15 of 121 (12.4%)	11 of 122 (9.0%)

ankle below 50 mmHg or a systolic toe pressure below 30 mmHg or $tcPO_2$ < 20 mmHg)			
No chronic venous insufficiency (CVI)	259 of 302 (75.1%)	132 of 150 (77.2%)	127 of 152 (73%)
CVI Widmer I	25 of 302 (7.2%)	11 of 150 (6.4%)	14 of 152 (8%)
CVI Widmer II	12 of 302 (3.5%)	3 of 150 (1.8%)	9 of 152 (5.2%)
CVI Widmer III	6 of 302 (1.7%)	4 of 150 (2.3%)	2 of 152 (1.1%)
Presence of extreme foot deformities and malpositions of toes, foot or the entire limb	59 of 342 (17.1%)	26 of 170 (15.2%)	33 of 172 (19%)
Untreated or therapy-refractory inflammation in the wound area	15 of 343 (4.3%)	7 of 170 (4.1%)	8 of 173 (4.6%)
Presence of a heel necrosis	23 of 342 (6.7%)	10 of 168 (5.8%)	13 of 174 (7.5%)
No lymphedema	282 of 340 (81.7%)	139 of 167 (81.3%)	143 of 173 (82.2%)
Primary lymphedema	12 of 340 (3.5%)	5 of 167 (2.9%)	7 of 173 (4%)
Secondary lymphedema	46 of 340 (13.3%)	23 of 167 (13.5%)	23 of 173 (13.2%)
Clinical signs of inflammation (suspected infection)	159 of 344 (46.1%)	83 of 170 (48.5%)	76 of 174 (43.7%)
Local wound swab as part of the clinical routine	248 of 343 (71.9%)	126 of 170 (73.7%)	122 of 173 (70.1%)
Detection of germs within the local wound swab	205 of 247 (59.4%)	104 of 125 (60.8%)	101 of 122 (58%)
Hemoglobin			
N	177 of 345	86 of 171	91 of 174
Mean (SD)	9.5 (3,2)	9.6 (3.1)	9.4 (3.3)
Hemoglobin A1c (HbA1c)			
N	32 of 345	13 of 171	19 of 174
Mean (SD)	15.6 (18,3)	16.8 (16,7)	14.7 (19.6)
Requiring dialysis	29 of 343 (8.4 %)	15 of 170 (8.8%)	14 of 173 (8.0%)
Application of skin or dermal substitutes and with living cells that produce growth factors	0 of 341 (0%)	0 of 169 (0%)	0 of 172 (0%)

Table 2: The table shows the baseline of the identified factors possibly influencing wound closure in the ITT population. Findings, diagnoses and procedures documented by the investigators are presented. Data are Number (N), Percentage (%), Mean and Standard Deviation (SD), and Minimum – Maximum [Min – Max].

Details on revascularization performed before study start are shown in Table 3.

Revascularization before study start in the ITT population	**Total N=345**	**NPWT N=171.**	**SMWC N=174.**
Performed revascularization before study start	23 of 345 (6.7%)	9 of 171 (5.3%)	14 of 174 (8.0%)

Percutaneous transluminal angioplasty (PTA)	13 of 23 (57%)	6 of 9 (67%)	7 of 9 (50%)
PTA + Stent	1 of 23 (4%)	0 of 9 (0%)	1 of 9 (7%)
Veins-Bypass	5 of 23 (22%)	2 of 9 (22%)	3 of 9 (21%)
Polytetrafluoroethylene (PTFE) Bypass	1 of 23 (4%)	0 of 9 (0%)	1 of 9 (7%)
Thromboendarterectomy and patch plastic	2 of 23 (9%)	0 of 9 (0%)	2 of 9 (14%)
Revascularization with influence on the wound	22 of 23 (96%)	9 of 9 (100%)	13 of 14 (93.9%)
Sufficient revascularization result*	20 of 23 (88%)	7 of 9 (78%)	13 of 14 (93%)
Insufficient revascularization result	2 of 23 (9%)	1 of 9 (11%)	1 of 14 (7%)
Revascularization result not assessable	1 of 23 (4%)	1 of 9 (11%)	0 of 14 (0%)

Table 3: The table shows revascularizations performed in the ITT population before study start. Data are N (%). * Sufficient revascularization result was defined as successful recanalization of the tibial artery in which the foot lesion is located or, if it is technically impossible to recanalize the respective artery, achievement of an unhindered inflow into at least one of the tibial vessels. The evaluation of the revascularization result was in the discretion of the attending physician.

Results for the primary outcome wound closure in the ITT population

In the ITT population, there was no significant difference between the treatment arms for either wound closure rate (Table 4) or time to complete wound closure (p=0.244, Log-Rank test; Figure 2) within 16 weeks. Beginning in week five the number of study participants with open wounds in the NPWT-arm was lower than in the SMWC-arm (Figure 2). However, after 16 weeks, the difference between the treatment arms was only 2.5% [-4.7 - 9.7] (Table 4). Wounds treated with NPWT were approximately at the same risk of remaining open as wounds treated with SMWC (RR 0.97 [95% CI: 0.89-1.06]).

Wound closure rate in the ITT population	**Total N=345**	**NPWT N=171**	**SMWC N=174**	**Difference p***
Patients with complete, sustained and confirmed wound closure within 16 weeks				
N	46 of 345	25 of 171 14.6%	21 of 174 12.1%	4
%	13.3 %	[9.5 –21.6]	[7.5 – 18.4]	2.5%
[95% CI]	[9.8 – 17.8]			[-4.7 - 9.7]
				0.53

Patients with recurrence of the diabetic foot wound after complete, sustained and confirmed closure within 6 months				
N	1 of 46	1 of 25	0 of 21	1
%	2.2%	4%	0%	4%
[95% CI]	[0,1 – 12,1]	[0,1 – 22,3]	[0,0 – 14,3]	[-3.7 – 11.7]
				1.00

Table 4: The table shows the number of patients with wound closure (wound closure rate) and the number of patients with recurrences (recurrence rate) in the ITT population. Data show the number (N) of participants available for the analysis in total and for both treatment arms. Wound closures within the maximum study treatment time of 16 weeks and recurrences during the Follow up of 6 months are shown with the number (N), the percentage (%) of patients, and the 95% Confidence Interval (CI). *F=Fisher's Exact Test.

Since the cumulative number of patients with open wounds was more than 70% after 16 weeks, we could not calculate medians for the time to wound closure.

Results for the secondary outcomes in the ITT population

Only one recurrence of the foot wound after complete, sustained and confirmed closure was documented for one study participant in the NPWT arm (Table 4). Study participants treated with NPWT were at higher risk for a recurrence than participants treated with SMWC 0.96 [0.87-1.04].

After 6 months the number of study participants with closed wounds was higher in the SMWC- than in the NPWT-arm (36 of 174 [20.7 %] vs 24 of 171 [14. 0 %]), but the difference was not significant (p 0.12).

The time until optimal preparation of the wound for further treatment to achieve a complete epithelization (min 95 % granulation tissue) was significantly shorter for patients treated with NPWT (p 0.021) (Table 5).

Time until optimal preparation of the wound bed (min 95 % granulation tissue) within 16 weeks (days) in the ITT population $N_{available\ values}$	**Total N=183**	**NPWT N=100**	**SMWC N=83**	**Mean difference [95% CI] p***
Mean (SD)	42.7 (39.0)	35.6 (34.6)	51.4 (42.6)	15.8
Median (IQR)	31 (64)	22.0 (48.0)	49.0 (53.6)	[4.6 - 27.0]
Min - Max	0 - 127	0 - 127	0 - 115	**0.008**

Table 5: The table shows time until optimal preparation of the wound for further treatment (min 95 % granulation tissue for the ITT population. Data show the number (N) of participants available for the analysis in total and for both treatment arms. Time until optimal preparation of the wound is described with Mean and Standard Deviation (SD); Median and Inter Quartile Range (IQR); and Minimum (Min) and Maximum (Max). *Student's t-test

In the ITT population, wound surface area and wound volume were similar at baseline (Table 1) and decreased continuously during the study treatment time of 16 weeks in both treatment arms (Supplement Tables 2 and 3). The values are largely scattered. Measurements derived from the blinded photo analysis using the Wound Healing Analyzing Tool (W.H.A.T.) were smaller than the values documented by the clinical investigators.

Wound tissue composition (Supplement Table 4) was similar in both treatment arms at baseline. Granulation tissue values increased during the study treatment period of 16 weeks and fibrin values decreased, with clinically documented values showing only minor differences between treatment arms. The values for necrotic tissue were very low and did not differ relevantly between the treatment arms. The results of the W.H.A.T. evaluation for granulation and fibrin deviate markedly from the values documented by the clinical investigators.

Patients treated with NPWT were approximately at the same risk of undergoing an amputation or resection like patients treated with SMWC (RR: 0.99 [95%CI: 0.65-1.50]) (Table 6).

Amputations and resections in the ITT population	**Total N=345**	**NPWT N=171**	**SMWC N=174**	**Difference p**
Study participants with amputation or resection				
N	71	35	36	1
%	20.6%	20.5%	20.7%	0.2 %
[95% CI]	[16.3 – 24,8]	[14,4 – 26,5]	[14.7 – 26,7]	[-19.0 - 18.6]
				1.00 (F)
Total number of amputations and resections	102	45	57	12
				0.89 (U)
Number of amputations and resections per study participant				
One event N (%)	49 (14.2%)	25 (14.6%)	24 (13.8%)	1 (0.8%)
Two events N (%)	16 (4.6%)	10 (5.8%)	6 (3.4%)	4 (2.4%)
Three events N (%)	4 (1.2%)	0 (0%)	4 (2.3%)	4 (2.3%)
Four events N (%)			1 (0.6%)	1 (0.6%)

Five events N (%)	1 (0.3%) 1 (0.3%)	0 (0%) 0 (0%)	1 (0.6%)	1 (0.6%) 0.89 (U)
Study participants with minor amputation	69 (20.0%)	33 (19.3%)	36 (20.7%)	3 (1.4%) 0.79 (F)
Study participants with major amputation	2 (0.6%)	2 (1.2%)	0 (0%)	2 (1.2%) 0.25 (F)

Table 6: The table shows the number of study participants with amputations / resections and the number of amputations / resections performed for the ITT-population. Data show the number (N) of participants, the percentage with the 95% Confidence Interval (95% CI), or the number of events accompanied with the respective percentage values in total and for both treatment arms. F = Fisher's Exact Test; U = Mann-Whitney U-Test.

Overall, pain levels were very low and decreased further during the study treatment time (Supplement Table 5). The values hardly differ between the treatment arms at any observation time point.

At baseline, Quality of life (EQ5D) was significantly limited in both treatment arms (Supplement Table 6). EQ5D levels were improved in both study participants reaching end of therapy as well as end of maximum treatment time. On follow-up after 6-months, all patients still showed increased EQ5D levels in both treatment arms.

Safety results

The number of study participants with AEs was significantly higher in the NPWT arm (96 (56.1%)) than in the SMWC arm (72 (41.4%)) (p=0.007) but only 16 (10.2%) of the AEs in the NPWT arm were decided by the investigators to have a definite relation to the medical device (Table 7). The number of study participants with at least one AE documented to be serious (SAE) was not significantly different between the treatment arms (NPWT N=63 (36.8%); SMWC N=58 (33.3%); p=0.50) (Table 7). None of the SAEs in the NWPT-arm was documented as definitely or possibly related to the medical device by the investigators. 9 of 171 (5.3%) study participants in the NPWT arm and 6 of 174 (3.5%) study participants in the SMWC-arm died during the study.

Adverse events (AEs) and Serious adverse events (SAEs)	**Total N=345**	**NPWT N=171**	**SMWC N=174**	**Difference**
Study participants with at least one AE N (%) [95% CI]	168 (48.7%) [43,4 -54,0]	96 (56.1%) [48,7 – 63,6]	72 (41.4%) [34,1 – 48,7]	24 (14.7%) [4.3 – 25.1] p=0.007 (F)

Study participants with one AE N	103	54	49	5
Study participants with two or more AEs N	65	42	23	19
Total number of AEs N	269	167	102	65
AEs with relationship to the medical device $N_{available}$	257	157	100	57
Yes	16 (6.2%)	16 (10. 2%)	0 (0%)	16 (10.2%)
Possible	13 (5.1%)	11 (7.0%)	2 (2.0%) *	9 (5%)
No	211 (82.1%)	117 (74.5%)	94 (94.0%)	23 (19.5%)
Not assessable	17 (6.6%)	13 (8.3%)	4 (4.0%)	9 (4.3%)
AEs with relationship to SMWC $N_{available}$	185	110	75	35
Yes	2 (1.1%)	0 (0%)	2 (2.7%)	2 (2.7%)
Possible	5 (2.7%)	5 (4.5%)	0 (0%)	5 (4.5%)
No	163 (88.1%)	96 (87.3%)	67 (89.3%)	29 (2%)
Not assessable	15 (8.1%)	9 (8.2%)	6 (8.0%)	3 (0.2%)
AEs with relationship to the treatment procedure $N_{available}$	244	148	96	52
Yes	10 (4.1%)	6 (4.1%)	4 (4.2%)	2 (0.1%)
Possible	17 (7.0%)	15 (10.1%)	2 (2.1%)	13 (8%)
No	191 (78.3%)	111 (75.0%)	80 (83.3%)	31 (8.3%)
Not assessable	26 (10.7%)	16 (10.8%)	10 (10.4%)	6 (0.4%)
Study participants with at least one SAE N (%) [95% CI]	121 (35.1%) [30,0 – 40,1]	63 (36.8%) [29,6 – 44,1]	58 (33.3%) [26,3 – 40,3]	5 (3.5%) [-6.6 – 13.6] p=0.50 (F)
Study participants with one SAE N	90	45	45	0
Study participants with two or more SAEs N	31	18	13	5
Total number of SAEs N	163	87	76	11

SAEs with relationship to the medical device				
$N_{available}$	161	85	76	9
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Possible	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No	154 (95.7%)	79 (92.9%)	75 (98.7%)	4 (5.8%)
Not assessable	7 (4.3%)	6 (7.1%)	1 (1.3%)	5 (5.8%)
SAEs with relationship to SMWC				
$N_{available}$	121	64	57	7
Yes	1 (0.8%)	0 (0%)	1 (1.8%)	1 (1.8%)
Possible	1 (0.8%)	1 (1.6%)	0 (0%)	1 (1.6%)
No	113 (93.4%)	57 (89.1%)	56 (98.2%)	1 (9.1%)
Not assessable	6 (5.0%)	6 (9.4%)	0 (0%)	6 (9.4%)
SAEs with relationship to the treatment procedure				
$N_{available}$	156	84	72	12
Yes	4 (2.6%)	0 (0%)	4 (5.6%)	4 (5.6%)
Possible	2 (1.3%)	2 (2.4%)	0 (0%)	2 (2.4%)
No	140 (89.7%)	74 (88.1%)	66 (91.7%)	8 (10.6%)
Not assessable	10 (6.4%)	8 (9.5%)	2 (2.8%)	6 (6.7%)

Table 7: The table shows the number of study participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) and the number of AEs and SAEs for the ITT-population. Data show the number (N) and the percentage (%) in total and for both treatment arms. * No treatment change to NPWT has been documented. F = Fisher's Exact Test (alpha=0.05).

Secondary analyses and subgroups

Of the factors with possible influence on the outcomes identified during study planning, the covariate peripheral arterial occlusive disease was found to have significant influence on the endpoint time until wound closure (p 0.026, Log Rank Test). The covariate clinical signs of inflammation (suspected infection) had a significant influence on the wound closure rate (p 0.012, Chi-square test) in the univariate analysis of the primary endpoints. However, both covariates were almost equally represented in both treatment arms. Thus, the comparison of the treatment arms was not influenced by these confounders. Furthermore, the covariate suspected infection was found to be significantly associated with both wound closure rate (Logistic regression; p=0.027) and time until wound closure (Cox-regression; p=0.037) in the multivariate confounder analysis. Wound closure was significantly less likely in wounds with suspected infection (Odds ratio 0.38).

In the subgroup of large wounds (wound surface area at randomization shown in Table 1), wound closure rate within 16 weeks was significantly higher in the NPWT-arm (13 of 88 (14.8 [7.4 – 22.2] %)) than in the SMWC-arm (5 of 84 (6.0 [0.9 – 11.0] %) (Difference: N=8 (8.8 [-0.2 - 17.8] %), p=0.08). Study participants with large wounds had a lower risk of not achieving wound closure within 16 weeks when treated with NPWT (RR 0.91 [95% CI: 0.82-1.0]) and achieved wound closure significantly faster in the NPWT-arm than in the SMWC-arm (p 0.027) (Figure 3). The only recurrence occurred in the subgroup of large wounds. Both major amputations were performed in study participants with large wounds treated with NPWT.

In the subgroup of small wounds (wound surface area at randomization shown in Table 1), the time to reach 95 % granulation tissue was significantly shorter for the patients treated with NPWT than for those treated with SMWC (p 0.005), but wound closure rate and time until wound closure within 16 weeks were not significantly different between the treatment arms (Figure 4). Further details of the subgroup analyses are presented in the Supplement Tables 7 and 8.

Results for the primary and secondary outcomes in the PP population

Demographics, relevant baseline characteristics and the results of the revascularization before study start of the PP population are presented in Supplement Table 9. In the PP population, 14 of 44 study participants (31.8% [95%CI 18.1 -45.6]) treated with NPWT and 19 of 110 participants (17.3% [95%CI 10.2 – 24.3]) .treated with SMWC achieved complete, sustained and verified wound closure within 16 weeks, but the difference was not significant (5 (14.5% [95%CI -1.0 – 30.0]; p 0.053). Wounds treated with NPWT had a lower risk of remaining open after 16 weeks (RR 0.82 [95%CI: 0.66-1.03]) than wounds treated with SMWC. Time to wound closure in the NPWT arm was significantly shorter than in the SMWC-arm (p=0.004) (Figure 5). After 6 months, wound closure rate in the SMWC-arm (30 of 110 (27.3% [95%CI 18.9 – 35.6]) was higher than in the NPWT-arm11 of 44 (25.0% [95%CI 12.2 – 37.8]), but the difference was not significant (N=19 (2.3% [-13.0 – 17.6]); p 0.84). As in the ITT population, optimal wound bed preparation was achieved significantly faster in patients receiving NPWT (p<0.001). No recurrences occurred after complete, sustained and confirmed wound closure in the PP population. Neither the number of patients with amputations or resections nor the number of amputations or resections performed .differed significantly between the treatment arms. No major amputations were performed in the PP population. Further details on the results for the PP population are presented in the Supplement Tables 10 – 16.

Treatment compliance

29 (17.0%) patients in the NPWT-armhad a temporary therapy change to SMWC (mean duration 20.5 ± 21.6 days). In the SMWC group, 17 (9.8%) patients had a temporary therapy change to NPWT (mean duration 28.9 ± 21.6 days). For only 2 of the 29 NPWT patients (6.9%) with a temporary therapy change to SMWC the wound closure was achieved within 16 weeks, whereas 16.2% (23 von 142) of the wounds of the NPWT patients without therapy change were completely closed.

A total of 57.3% (98 of 171) of the patients randomized to NPWT completed treatment before achieving a granulation surface of the wound of at least 95%. Fewer patients with this premature end of NPWT (4.7%, N=8) achieved a complete wound closure than patients with no premature end of therapy (9.9, N=17). Mean NPWT-duration until premature end of therapy was 28.5 days (SD 24.1), while a mean granulation area of 59.6% (SD 30. 5) was achieved. For 131 patients (76. 6 %) in the NPWT arm less than the required three dressing changes per week were documented. 19 patients (14. 5 %) with this protocol violation achieved a complete wound closure. Six (15.4%) of the 39 NPWT patients who received at least 3 therapy changes per week achieved a complete wound closure.

Documentation quality

In the NPWT-arm 52 study participants and in the SMWC-arm 43 participants were excluded from the PP population due to missing documentation until the end of maximum treatment time or at wound closure confirmation (Figure 1). In the electronic Case Report Forms (eCRF) a wound closure was documented for 96 patients (NPWT 56 of 171; SMWC 40 of 174), but only for 46 participants (NPWT 25; SMWC 21) all criteria for a complete, verified and sustained wound closure have been met. For the wound closure visit seven wound photographs (NPWT 7; SMWC 0) and for the wound closure confirmation visit four photographs (NPWT 3; SMWC 1) were missing. In addition, two of the existing wound photographs for wound closure (NPWT 0; SMWC 2) and two photographs for wound closure confirmation (NPWT 1; SMWC 3) were not assessable by the blinded observers due to serious quality issues. Furthermore 23 (NPWT 15; SMWC 8) existing and assessable wound photographs were not able to confirm the wound closure and 3 (NPWT 1; SMWC 2) photographs were not able to confirm the wound closure after 14 days.

Discussion

The DiaFu-study did not demonstrate significant superiority in wound closure rate or time to complete wound closure for neither NPWT nor SMWC. Wound closure rates were higher in the NPWT arm but did not significantly differ from those in the SMWC arm. Time to wound healing in the NPWT group was lower than in the SMWC

arm while the difference between the treatment arms becomes statistically significant only in the PP population. Thus, with this study we were not able to confirm our hypothesis that wound closure can be achieved more often and faster with NPWT than with SMWC when used in German real-life clinical practice. Previous RCTs, which were the basis for sample size calculation, showed a higher rate and a significant superiority in healing when using NPWT on amputation and chronic wounds [16, 17], but the populations of these studies were different. Other than the Armstrong-study, the DiaFu-study did not exclude patients with venous insufficiency and included more than twice as many patients. The studies of Armstrong and Blume excluded patients with Wagner stage four; active Charcot; uncontrolled hyperglycemia and therapy with glucocorticoids, immunosuppressants or chemotherapy; and required proof of adequate perfusion. The DiaFu-study, did not exclude patients with impaired perfusion, but required adequate therapy of the circulatory disorder according to clinical practice guidelines. In the DiaFu-study, we were able to show that the presence of PAOD at randomization had a significant influence on the time to wound closure but not on the overall wound closure rate within the maximum study treatment time. The number of patients with critical limb ischemia at baseline was low and differed only slightly between the treatment arms. As in clinical practice, in the DiaFu-study adequate treatment of concomitant diseases was mandatory. Invasive therapy of POAD could be performed before initiation of wound therapy as well as during the study treatment period, if the wound needed pretreatment as a basis for the revascularization procedure or if new or recurrent critical ischemia. The presence of clinical signs of inflammation (suspected infection) at randomization had a significant effect on both, time to wound closure and wound closure rate within 16 weeks. Both covariates were equally represented in the treatment arms, thus the differences in time until wound closure and wound closure rate were not affected by these confounders.

However, the probably most serious factors negatively influencing treatment and outcome are documentation deficiencies and deviations from treatment guidelines. Temporary therapy changes and premature therapy cessation negatively impacted the patient relevant treatment outcome wound closure in study participants treated with NPWT. Missing study visits resulting in low numbers of complete endpoint documentations strongly affected the proof of the outcome wound closure in both, the NPWT- and the SMWC-arm.

Optimal preparation of the wound bed (95% granulation tissue) was achieved significantly earlier when using NPWT in the ITT and the PP population, but the overall rate of wound closures was low. Wound bed preparation and granulation tissue formation are important prerequisites for wound healing, but are not a proof of treatment effectiveness and cannot serve as a basis for benefit assessment.

Although significantly more AEs were documented in the NPWT-arm only a small number of these events were related to the medical device according to the investigator`s assessment. Mortality rates were very low in both

treatment arms and there was no significant difference between the treatment arms regarding amputations and resections performed during the study. Only two major amputations have been performed in patients with big wounds treated with NPWT. None of the treatments resulted in an additional impairment of the patients' quality of life during study treatment time or follow up. Time until complete wound closure was significantly shorter with NPWT than with SMWC in the subgroup of big wounds, which indicates that NPWT has the potential to be a valuable treatment option for this kind of wounds.

In the DiaFu-study methods against bias have been implemented whenever possible in order to avoid bias that have been described by several systematic reviews [18-22], but blinding of study participants as well as attending physicians and nurses was not possible due to the nature of NPWT..

Not addressing and analyzing all factors influencing the overall treatment outcome like targeted pressure relief, continuous infection control and adequate treatment of the underlying disease during the study treatment and observation period may be seen as a limitation of this health care research study. Study sites have been selected based on a self-disclosure by means of a qualification checklist and cross checks using quality reports. This ensured that all prerequisites were met for guideline-compliant patient care. Nevertheless, even in the application of NPWT there were deviations from the standards.

In order to support the decision-making process of the German G-BA on general reimbursement of NPWT in German outpatient care the real-life clinical practice DiaFu-study included patients with chronic DFUs of neuropathic and angiopathic origin regardless of whether a simple wound cleansing, tissue debridement or even amputation was necessary prior to application of wound therapy targeted to achieve complete wound closure. The study was performed without excluding concomitant diseases negatively impacting wound healing; with therapy application in the discretion of the attending physician; and with evaluation of patient relevant outcome. Thus, results can easy be generalized and applied in clinical practice settings. Anyway, shortcomings in data quality negatively impacted the study results and statements about specific patient groups were not possible. A high number of study participants needed to be excluded from the PP population (NPWT 127 of 171 (74%), SMWC arm 64 of 174 (37%). For most of these participants, documentation was lacking until the end of the maximum treatment period (Total=88, NPWT=49, SMWC=39) (Figure 1). In the primary analysis based on the ITT population it was assumed that these patients did not achieve wound closure within 16 weeks study treatment and observation time (using the las observation carried forward (LOCF) method, the open wound status was ”carried forward” until the end of the maximum treatment period. This may have led to a false negative bias in the outcome wound closure in the ITT population. Due to the high loss of patients and the difference in the number of participants excluded from the treatment arms, the validity of the PP analysis is very limited.

Conclusions

NPWT was not superior to SMWC when evaluated in German real-life clinical practice. Missing compliance with therapy guidelines and poor documentation quality led to restrictions in achieving the patient-relevant endpoint complete wound closure and prevents a clear proof of effectiveness. The question if NPWT is superior to SMWC for treating diabetic foot wounds remains unanswered due to the limitations of the DiaFu-study. Although the study protocol required adequate monitoring and therapy of the concomitant diseases, the presence of POAD and infection at randomization had a significant influence on the outcome wound closure. Despite all limitations NPWT showed a significant superiority in optimal wound bed preparation. This indicates that NPWT works according to its intended use and has a potential to be a valuable treatment option. The results of the PP population suggest that without the negative impact of premature treatment cessation, temporary changes of the randomized therapy and partly incomplete documentation, NPWT may be more effective for treating diabetic foot wounds than SMWC. In Germany, NPWT should be evaluated again after implementation of a sufficient, well-considered and widely-accepted concept for quality control. In a future health care research study, the treatment outcome before and after the implementation of these quality measures should be evaluated, for which the results of this trial may serve as a basis.

Ethics approval and consent to participate

Ethical approval of the main ethical committee (EC): Ethical Committee of the University of Witten-Herdecke, has been fully granted without any conditions. Due to performing the trial according to § 23b MPG (German Medical Device Act), participating study sites in Germany only received a consultation for the main clinical investigator according to professional law by the respective EC. All investigators have been fully approved by the respective ECs. An evaluation of the study's content by ECs of participating study sites in Germany was not applicable. All study participants gave written informed consent prior to randomization and any trial related procedure.

Data sharing

The datasets analyzed for the results presented in this article are available from the corresponding author on reasonable request. Datasets are available in German language.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: The German statutory health insurance companies commissioned the Witten/Herdecke University (UW/H) to plan, conduct, analyze and publish the study. Dörthe Seidel is an employee of the UW/H. The study has been financed by the manufacturers KCI (Acelity) and Smith&Nephew. Dörthe Seidel received a consulting fee for the presentation of the study during an event organized by the manufacturer Hartmann. During study planning and conduct Edmund Neugebauer was an employee of the UW/H. He was the director of the IFOM.

The clinical investigators Martin Storck, Holger Lawall, Gernold Wozniak, Peter Maukner, Dirk Hochlenert, Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink received a case fee of 1000 € for each patient included in the DiaFu-study in order to compensate for the additional organizational and especially the documentation effort during trial conduct. Furthermore all investigators received compensation for travelling to the investigator meetings. The institutions of the investigators used integrated care contracts for NPWT during study conduct in order to provide best practice for the study participants during outpatient care.

Gernold Wozniak and Walter Wetzel-Roth are members of the scientific advisory board of the manufacturer Kinetic Concepts Incorporated (KCI) (now Acelity).

Funding

Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds, which provided integrated care contracts for all study participants and for up to 7000 patients with acute and chronic wounds in Germany; defined basic rules for study design based on the requirements of the German authorities; and provided a critical review of the study protocol and the final report. The study was funded by the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary support and information about the used material. The manufacturers had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

Authors' contributions

Dörthe Seidel was the principal coordinating investigator. She conceived the study, reviewed the scientific literature, and was responsible for study design, data analysis, data interpretation, writing and reviewing of the report. She is the lead author and takes overall responsibility for this report. She affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Martin Storck and Holger Lawall were study investigators and contributed to study design, data collection and interpretation, and reviewed the report.

Gernold Wozniak, Peter Maukner, Walter Wetzel-Roth and Dirk Hochlenert were study investigators and contributed to data collection and data interpretation and reviewed the report.

Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink were study investigators and contributed to data collection and reviewed the report.

Edmund Neugebauer contributed to study design and data interpretation and reviewed the report.

All authors approved the final version of the report.

Acknowledgements

The authors thank all investigators, nurses, patients and partners for supporting the study.

At least one patient was included in the following facilities: HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für Gefäßchirurgie Ludwig-Erhard-Straße 100 65199 Wiesbaden; Asklepios Westklinikum Hamburg Zentrum für Gefäßmedizin Suurheid 20 22559 Hamburg; Knappschaftskrankenhaus Bottrop Gefäßchirurgische Klinik

Osterfelderstraße 157 46242 Bottrop; Städtisches Klinikum Karlsruhe Klinik für Gefäß- und Thoraxchirurgie Moltkestraße 90 76133 Karlsruhe; Gemeinschaftspraxis Schlotmann-Hochlenert-Zavaleta-Haberstock Merheimer Straße 217 50733 Köln; Klinikum Döbeln Abt. für Gefäßchirurgie Sörmitzer Straße 10 04720 Döbeln; Klinikum Bielefeld Mitte Klinik für Allgemeine Innere Medizin Teutoburger Straße 50 33604 Bielefeld; Klinikum Frankfurt/Oder Klinik für Gefäßchirurgie Müllroser Chaussee 7 15236 Frankfurt/Oder; Weißeritztal-Kliniken GmbH Medizinische Klinik III Bürgerstraße 7 01705 Freital; Krankenhaus Porz am Rhein Klinik für Gefäßchirurgie Urbacher Weg 19 51149 Köln; St. Remigius Krankenhaus Opladen Innere Medizin An St. Remigius 26 51379 Leverkusen; Marien Hospital Dortmund-Hombruch Klinik für Innere Medizin/Diabetologie Gablonzstraße 9 44225 Dortmund; Zentrum für Chirurgie Klinik für Gefäß- und Endovascularchirurgie Theodor-Stern-Kai 7, Haus 23C/EG 60590 Frankfurt am Main; Facharzt für Chirurgie Thorax-Kardiovaskularchirurgie Hindenburgstraße 1 86807 Buchloe; Helfenstein Klinik Geisslingen Allgemein- und Viszeralchirurgie Eybstraße 16 73312 Geislingen/Steige; Paracelsus-Klinik am Silbersee Wundzentrum Hannover Oertzeweg 24 30851 Langenhagen; Klinikum Darmstadt Chirurgische Klinik III Grafenstraße 9 64283 Darmstadt; Ortenau Klinikum Offenburg-Ebertplatz Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ebertplatz 12 77654 Offenburg; Thüringen-Kliniken "Georgius Agricola" GmbH Klinik für Gefäßchirurgie Rainweg 68 07318 Saalfeld; Klinikum Dorothea Christiane Erxleben GmbH Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ditfurter Weg 24 06484 Quedlinburg; Franziskus-Krankenhaus Berlin Abt. für Innere Medizin Budapester Straße 15-19 10787 Berlin; Hegau-Bodensee Klinikum Radolfzell (HBK) Klinik für Innere Medizin Hausherrenstraße 12 78315 Radolfzell; Diabetologische Schwerpunktpraxis Dr. med. Hansjörg Mühlen & Partner Ruhrorter Straße 195 47119 Duisburg; Kliniken Maria Hilf Mönchengladbach Klinik für Gefäßchirurgie und Angiologie Sandradstraße 43 41061 Mönchengladbach; Städtisches Klinikum München/Bogenhausen Klinik für Endokrinologie, Diabetologie und Angiologie Englschalkingerstraße 77 81925 München; Gerhard Rothenaicher Facharzt für Chirurgie Cosimastraße 2 81927 München; Bürgerhospital Frankfurt am Main Interdisziplinäres Zentrum Diabetischer Fuß (DDG) Nibelungenallee 37- 41 60318 Frankfurt am Main; Gemeinschaftspraxis für Chirurgie und Gefäßmedizin Drs. Alter/Pourhassan/Heim Klosterstraße 12 46145 Oberhausen; Ev. KH Königin Elisabeth Herzberge gGmbH Abt. für Kardiologie, Angiologie und Diabetologie Herzbergstraße 79 10365 Berlin; Städtisches Klinikum Neunkirchen gGmbH Abt. für Gefäßchirurgie & Phlebologie Brunnenstraße 20 66538 Neunkirchen; Westküstenklinikum Heide Klinik für Viszeral- und Gefäßchirurgie Esmarchstraße 50 25746 Heide/Holstein; Chir. Praxisgemeinschaft am Bayenthalgürtel Praxis Dr. med. Gerald Engels Bayenthalgürtel 45 50968 Köln; Malteser Krankenhaus – St. Franziskus-Hospital Medizinische Klinik I, Abt. für Diabetologie Waldstraße 17 24939 Flensburg; St. Marienkrankenhaus Siegen gGmbH Klinik für Gastroenterologie Kampenstraße 51 57072 Siegen; Krankenhaus

Bietigheim Klinik für Innere Medizin, Kardiologie, Endokrinologie, Diabetologie und Internistische Intensivmedizin Riedstraße 12 74321 Bietigheim-Bissingen; Asklepios Kliniken Harburg Eißendorfer Pferdeweg 52 21075 Hamburg; Diabetologikum Ludwigshafen Diabetes-Schwerpunktpraxis Ludwigsplatz 9 67059 Ludwigshafen; Mariannen-Hospital Werl Abt. für Chirurgie Unnaer Straße 15 59457 Werl; Diabetes Klinik GmbH & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim; Institut für Diabetesforschung Münster GmbH Hohenzollernring 70 48145 Münster.

The study was initiated by a consortium of 19 statutory German health insurance funds represented by the AOK federal association (AOK-Bundesverband – AOK-BV), the association of alternative health insurance funds (Verband der Ersatzkrankenkassen – vdek) and the minors (Knappschaft). In order to guarantee outpatient care for all study participants without any restrictions, the contracting health insurance companies provided integrated care contracts for outpatient negative pressure wound therapy.

A project advisory board was implemented to coordinate all processes and project partners. The board comprised two representatives each from the statutory health insurance funds, the management company and the sponsor as well as one representative each from the participating medical device manufacturers (KCI and smith & nephew). Representing the contracting authority (statutory German health insurance funds) Dr. Gerhard Schillinger (AOK-BV) and Ute Leonhard (vdek) acted as contact persons for all aspects of the project.

The management company "Gesundheitsforen Leipzig" has been entirely responsible for the logistics of the study. Central tasks of the management company included the recruitment of study sites and patients, the development of the IT infrastructure including the documentation, communication and invoicing software as well as the processing of all payments.

The manufacturers Kinetic Concepts Incorporated (KCI) (Acelity) and smith & nephew provided the NPWT devices as well as support and training for the investigators and financed the study.

The Private University of Witten/Herdecke gGmbH acted as the Sponsor of the trial and the Institute for Research in Operative Medicine with its former director Prof. E.A.M. Neugebauer, the current interim head Prof. Rolf Lefering and the head of the division for clinical research Dörthe Seidel was responsible for the scientific conception, the evaluation as well as the reporting and publication of the study. Prof. Dr. Rolf Lefering was responsible for the statistical planning and analysis. PD Dr. Peter Krüger was responsible for the data management of the study. Special thanks are going to Stefan Bauer, who supported the data management as well as the statistical analysis and reporting.

We would like to thank Sophie Thorn, who checked the article as a native English speaker with regard to spelling and grammar.

List of figures:

References

1. World Health Organization, *Global report on diabetes.* 2016, WHO: http://www.who.int/diabetes/global-report/en/.
2. International Diabetes Federation, *IDF Diabetes Atlas*. 2015, IDF: www.diabetesatlas.org.
3. Yazdanpanah, L., M. Nasiri, and S. Adarvishi, *Literature review on the management of diabetic foot ulcer.* World J Diabetes, 2015. **6**(1): p. 37-53.
4. Leone, S., et al., *[Epidemiology of diabetic foot].* Infez Med, 2012. **20 Suppl 1**: p. 8-13.
5. Wu, L., et al., *Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews.* Cochrane Database Syst Rev, 2015(7): p. CD010471.
6. Norman, G., et al., *Dressings and topical agents for treating venous leg ulcers.* Cochrane Database Syst Rev, 2018. **6**: p. CD012583.
7. Wu, S.C., W. Marston, and D.G. Armstrong, *Wound care: the role of advanced wound-healing technologies.* J Am Podiatr Med Assoc, 2010. **100**(5): p. 385-94.
8. Fleischmann, W., et al., *[Vacuum sealing as treatment of soft tissue damage in open fractures].* Unfallchirurg, 1993. **96**(9): p. 488-92.
9. Argenta, L.C. and M.J. Morykwas, *Vacuum-assisted closure: a new method for wound control and treatment: clinical experience.* Ann Plast Surg, 1997. **38**(6): p. 563-76; discussion 577.
10. Morykwas, M.J., et al., *Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation.* Ann Plast Surg, 1997. **38**(6): p. 553-62.
11. Morykwas, M.J., et al., *Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine.* Ann Plast Surg, 2001. **47**(5): p. 547-51.
12. Gregor, S., et al., *Negative pressure wound therapy: a vacuum of evidence?* Arch Surg, 2008. **143**(2): p. 189-96.
13. Peinemann, F. and S. Sauerland, *Negative-pressure wound therapy: systematic review of randomized controlled trials.* Dtsch Arztebl Int, 2011. **108**(22): p. 381-9.
14. Ubbink Dirk, T., et al. *Topical negative pressure for treating chronic wounds*. Cochrane Database of Systematic Reviews, 2008. DOI: 10.1002/14651858.CD001898.pub2.
15. Vikatmaa, P., et al., *Negative pressure wound therapy: a systematic review on effectiveness and safety.* Eur J Vasc Endovasc Surg, 2008. **36**(4): p. 438-48.
16. Armstrong, D.G. and L.A. Lavery, *Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial.* Lancet, 2005. **366**(9498): p. 1704-10.
17. Blume, P.A., et al., *Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial.* Diabetes Care, 2008. **31**(4): p. 631-6.
18. Dumville, J.C., et al., *Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus.* Cochrane Database Syst Rev, 2013(10): p. CD010318.
19. Rhee, S.M., et al., *Negative Pressure Wound Therapy Technologies for Chronic Wound Care in the Home Setting*. 2014, Johns Hopkins University Evidence-based Practice Center: Rockville (MD).

20. Canadian Agency for Drugs and Technologies in Health, *Negative Pressure Wound Therapy for Managing Diabetic Foot Ulcers: A Review of the Clinical Effectiveness, Cost-effectiveness, and Guidelines*. 2014: Ottawa (ON).
21. Liu, S., et al., *Evaluation of negative-pressure wound therapy for patients with diabetic foot ulcers: systematic review and meta-analysis.* Ther Clin Risk Manag, 2017. **13**: p. 533-544.
22. Liu, Z., et al., *Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus.* Cochrane Database Syst Rev, 2018. **10**: p. CD010318.
23. Seidel, D., et al., *Negative pressure wound therapy versus standard wound care in chronic diabetic foot wounds: study protocol for a randomized controlled trial.* Trials, 2014. **15**: p. 334.
24. Ärztliches Zentrum für Qualität in der Medizin (Gemeinsame Einrichtung von Bundesärztekammer und Kassenärztlicher Bundesvereinigung) im Auftrag von BÄK, K., AWMF, *Nationale VersorgungsLeitlinie (NVL) Typ-2-Diabetes Präventions- und Behandlungsstrategien für Fußkomplikationen*. 2010, Bundesärztekammer (BÄK) Arbeitsgemeinschaft der Deutschen Ärztekammern http://www.baek.de; Kassenärztliche Bundesvereinigung (KBV); http://www.kbv.de; Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) http://www.awmf-online.de: Berlin, Germany.
25. Bauer, H., et al. *Typ-2-Diabetes: Präventions- und Behandlungsstrategien für Fußkomplikationen*. Nationale Versorgungs Leitlinien, 2010.
26. Ruttermann, M., et al., *Local treatment of chronic wounds: in patients with peripheral vascular disease, chronic venous insufficiency, and diabetes.* Dtsch Arztebl Int, 2013. **110**(3): p. 25-31.
27. Dupont, W.D. and W.D. Plummer, Jr., *Power and sample size calculations. A review and computer program.* Control Clin Trials, 1990. **11**(2): p. 116-28.
28. Schaper, N.C., *Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies.* Diabetes Metab Res Rev, 2004. **20 Suppl 1**: p. S90-5.
29. Sanders LJ and Frykberg RG, *Diabetic neuropathic osteoarthropathy: the Charcot foot.*, in *The high risk foot in diabetes mellitus.*, F. RG, Editor. 1991, Churchill Livingstone: New York. p. 297-338.
30. Levin, M.E., *Preventing amputation in the patient with diabetes.* Diabetes Care, 1995. **18**(10): p. 1383-94.
31. Wagner, F.W., Jr., *The diabetic foot.* Orthopedics, 1987. **10**(1): p. 163-72.
32. Rutherford, R.B., et al., *Recommended standards for reports dealing with lower extremity ischemia: revised version.* J Vasc Surg, 1997. **26**(3): p. 517-38.
33. Widmer, L.K., et al., *[Venous diseases in 1800 employees. Basel Studies II].* Schweiz Med Wochenschr, 1967. **97**(4): p. 107-10.

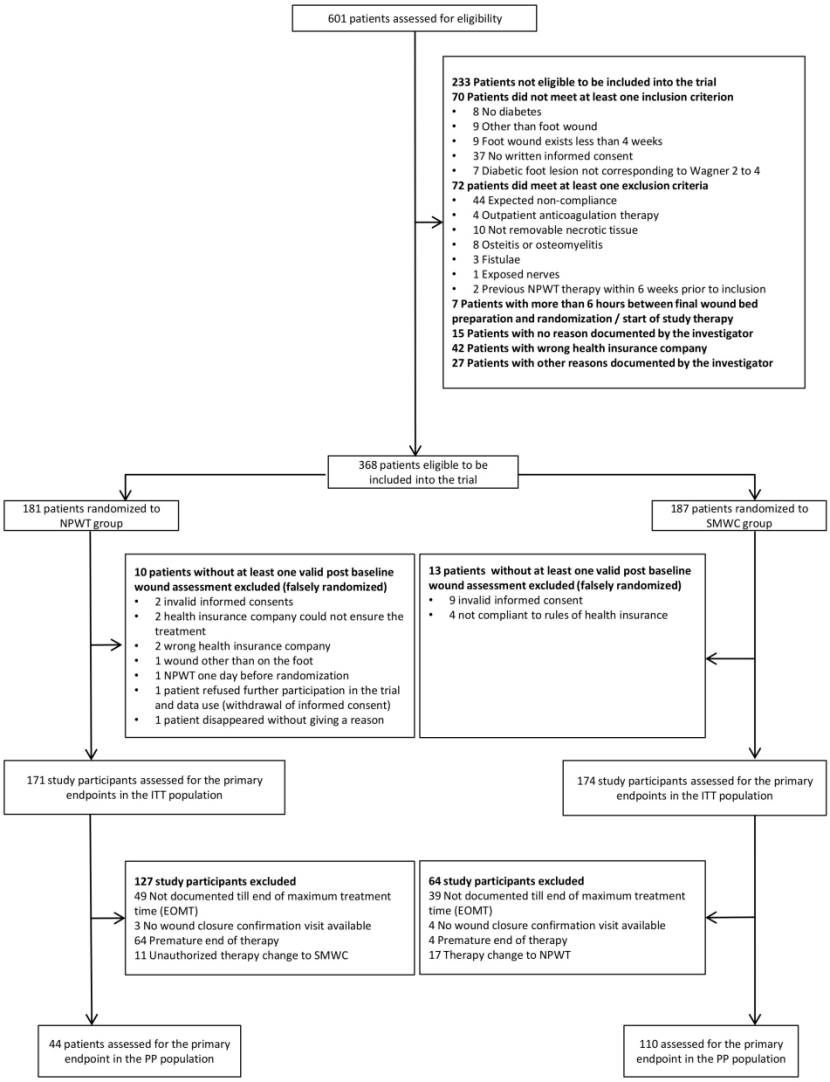


Figure 1: Trial profile (CONSORT)

190x275mm (300 x 300 DPI)

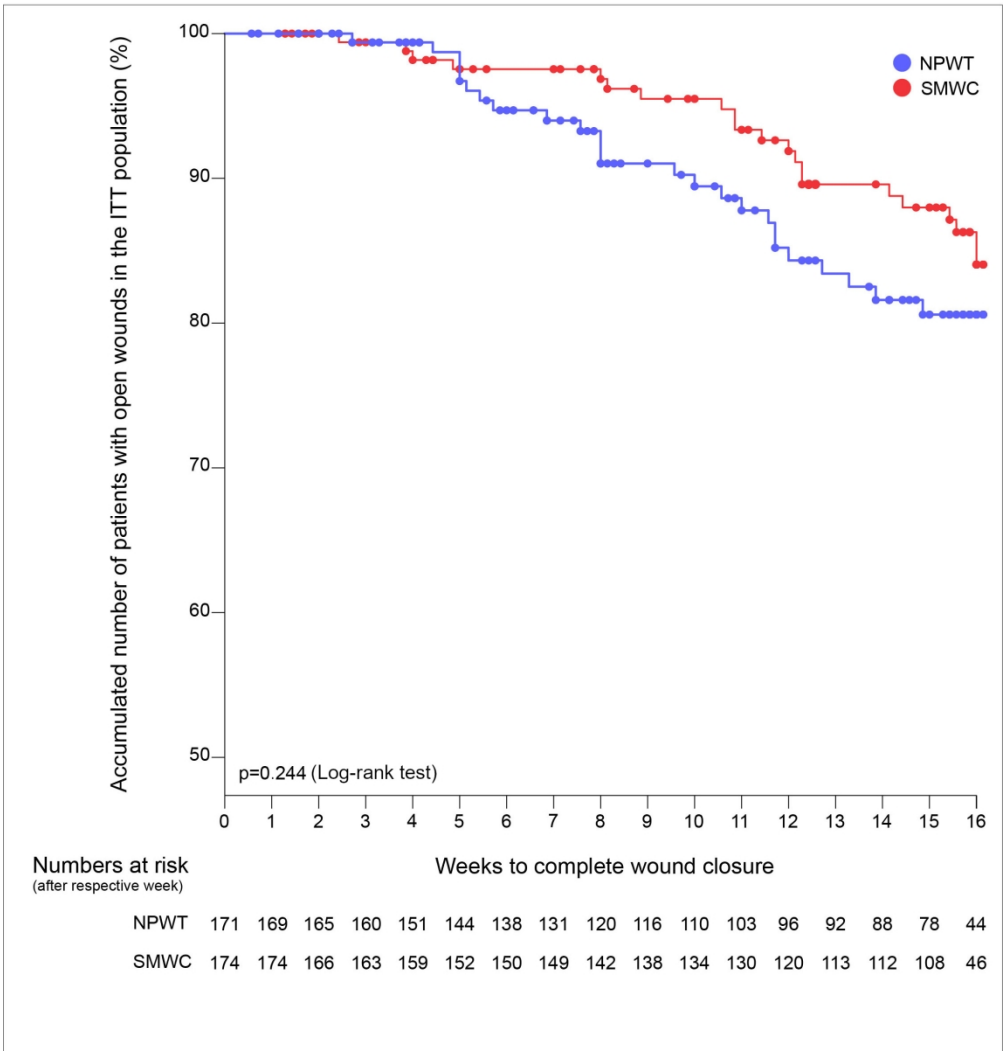


Figure 2: Time until complete, sustained and verified wound closure in the ITT population

189x198mm (300 x 300 DPI)

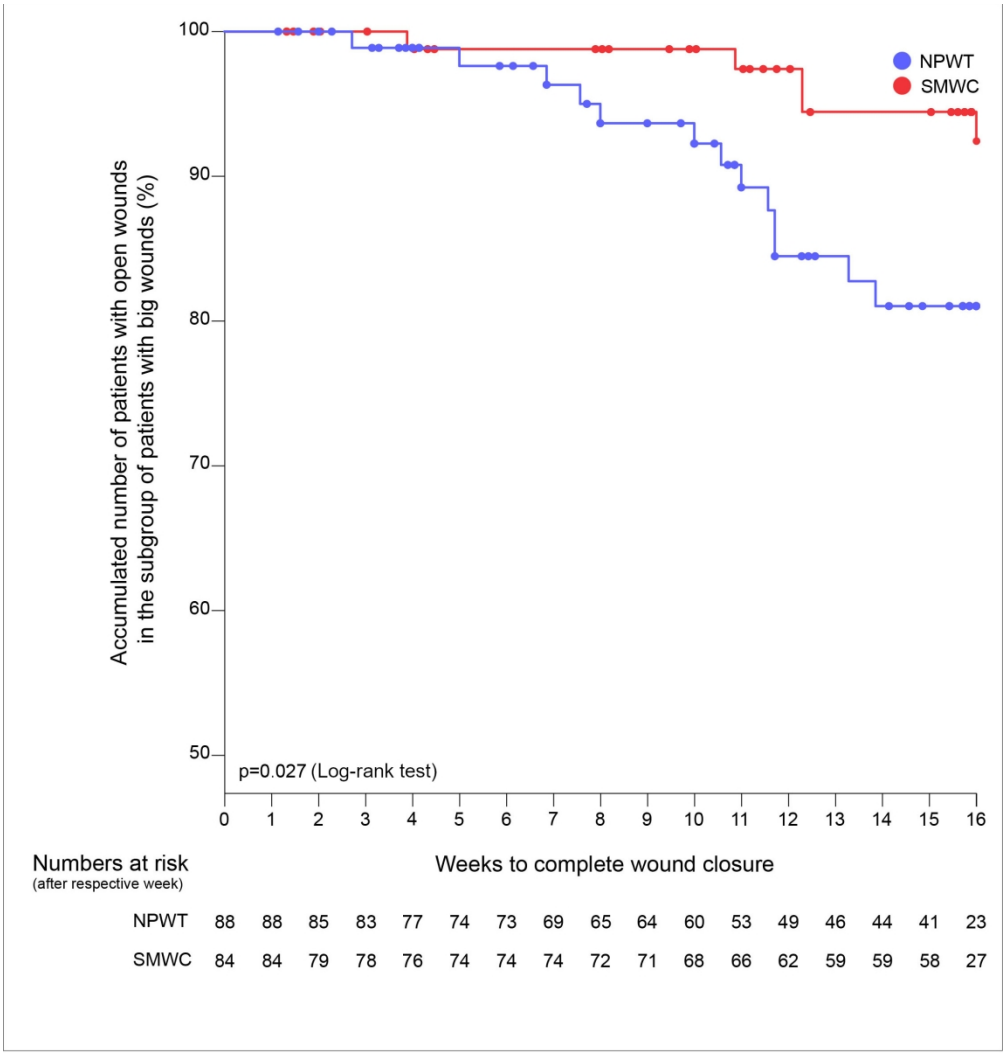


Figure 3: Time until complete, sustained and verified wound closure for the subgroup of big wounds

189x198mm (300 x 300 DPI)

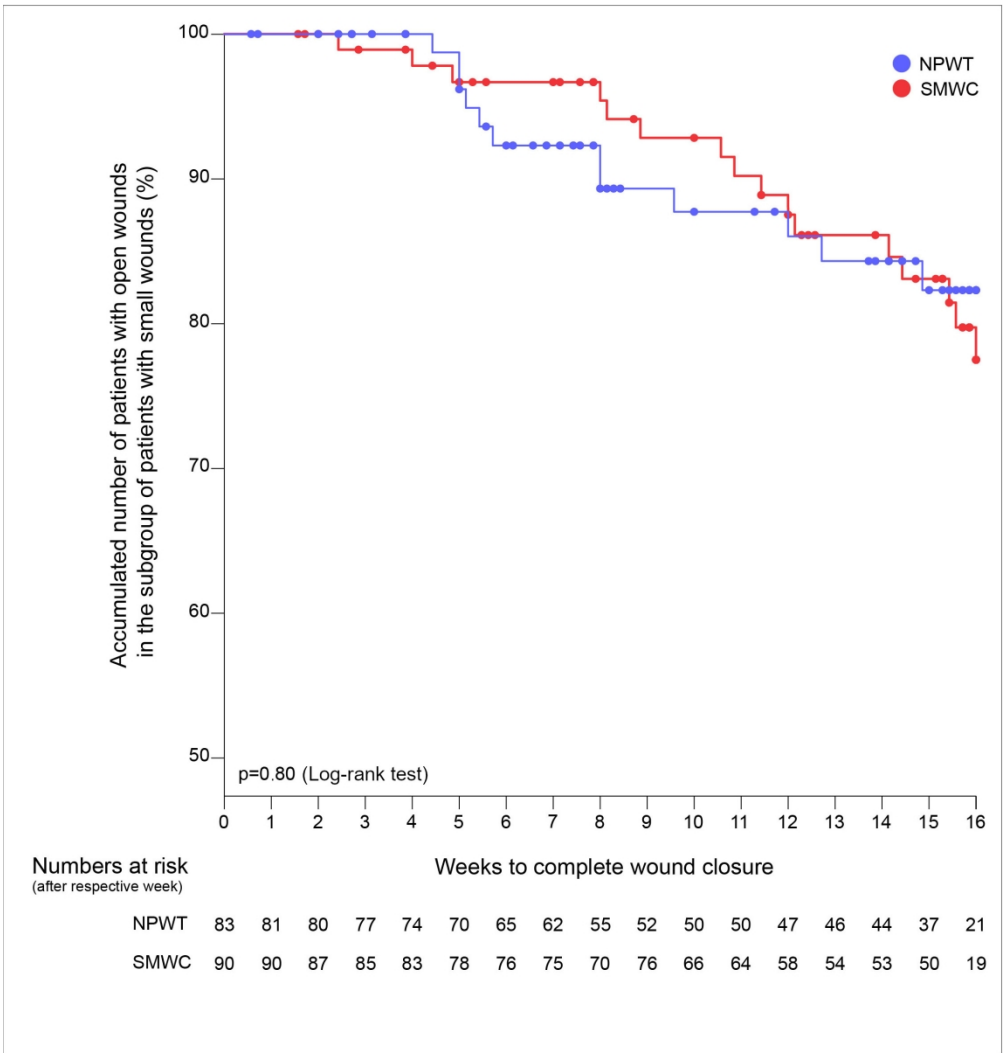


Figure 4: Time until complete, sustained and verified wound closure for the subgroup of small wounds

189x198mm (300 x 300 DPI)

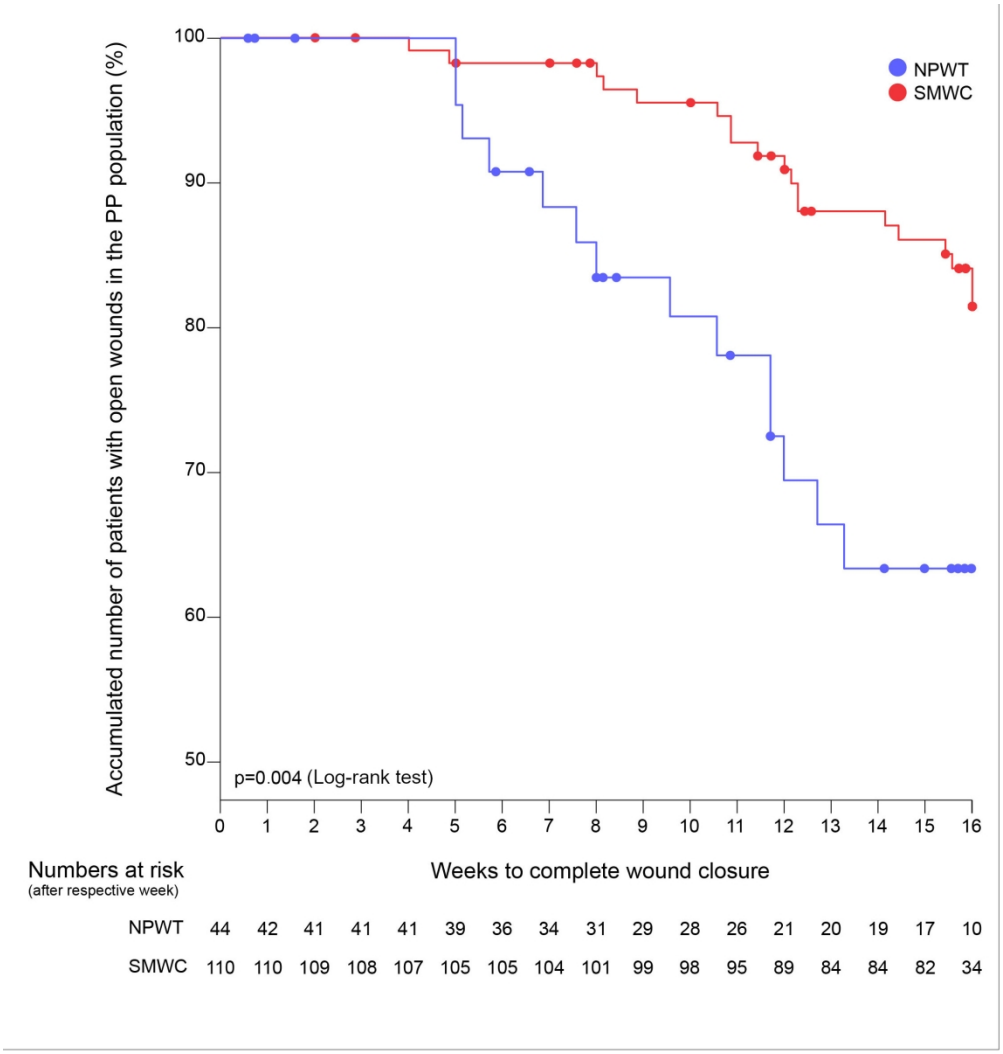


Figure 5: Time until complete, sustained and verified wound closure in the PP-population

189x198mm (300 x 300 DPI)

Supplement

Baseline parameters of the ITT population		Total N=345 (100 %)	NPWT N=171 (49.6%)	SMWC N=174 (50.4%)
Alcohol	**Occasionally**	157 of 341 (46%)	83 of 169 (48.5%)	74 of 172 (42.3%)
	Chronic	10 of 341 (2.9%)	3 of 169 (1.8%)	7 of 172 (4.0%)
	No	174 of 341(51%)	83 of 171 (48.5%)	91 of 174 (52%)
Smoking		293 of 342 (85.7%)	144 of 169 (84.3%)	149 of 173 (85.1%)
	Number of years Mean (SD)	34.8 (13.5)	36.5 (14.9)	33.1 (12.1)
	Packs / day Mean	1.1	1.1	1.2
Drugs	**Occasionally**	1 of 341 (0.3%)	1 of 169 (0.6%)	0 of 172 (0%)
	Chronic	2 of 341 (0.6%)	0 of 169 (0%)	2 of 172 (1.1%)
	No	338 of 341 (97.7%)	168 of 169 (98.2%)	170 of 172 (97.1%)
Allergies		37 of 343 (10.7%)	16 of 170 (9.4%)	21 of 173 (12.0%)
Subjective assessment of nutritional condition				
	Well-nourished	325 of 342 (94.2%)	162 of 169 (94.7%)	163 of 173 (93.7%)
	Moderately malnourished or suspected malnutrition	11 of 342 (3.2%)	4 of 169 (2.3%)	7 of 173 (4%)
	Malnourished	0 of 342 (0%)	0 of 169 (0%)	0 of 173 (0%)

Supplement Table 1: Supplementary baseline characteristics of the Intention To Treat (ITT) population

The table shows baseline parameters of the ITT population. Data are Number (N) and Percentage (%), Mean or Mean and Standard Deviation (SD).

Wound surface area (mm^2) in the ITT population	**Calculated from width and length (according to eCRF entry) NPWT N=171**	**Results of the photo analysis with the W.H.A.T. NPWT N=171**	**Calculated from width and length (according to eCRF entry) SMWC N=174**	**Results of the photo analysis with the W.H.A.T. SMWC N=174**
Randomization	1060 (1536) 550 (1236) N=171 (2)	687 (879) 321 (760) N=118 (10)	1141 (3247) 471 (1007) N=174 (0)	664 (1050) 316 (658) N=129 (13)
Week 1	847 (1489) 397 (801) N=171 (15)	643 (820) 329 (750) N=118 (32)	1085 (3234) 395 (867) N=174 (25)	713 (1065) 307 (749) N=129 (36)

Week 3	810 (1472) 314 (860) N=171 (24)	590 (742) 273 (633) N=118 (28)	1025 (3242) 390 (913) N=174 (22)	701 (1212) 266 (768) N=129 (35)
Week 5	717 (1379) 275 (769) N=171 (37)	607 (828) 231 (843) N=118 (42)	759 (1466) 267 (824) N=174 (41)	610 (1119) 219 (635) N=129 (38)
Week 8	636 (1322) 220 (712) N=171 (52)	495 (770) 182 (561) N=118 (48)	674 (1410) 186 (783) N=174 (42)	501 (937) 165 (481) N=129 (42)
Week 12	549 (858) 165 (964) N=171 (110)	457 (742) 134 (494) N=118 (88)	570 (940) 169 (632) N=174 (124)	493 (950) 133 (498) N=129 (104)
Week 16	440 (810) 79 (471) N=171 (80)	334 (649) 114 (363) N=118 (66)	493 (1095) 69 (415) N=174 (63)	351 (750) 77 (320) N=129 (56)

Supplement Table 2: Wound surface area at each observation time point during the study treatment time of maximum 16 weeks in the ITT population

The table shows the wound surface area at each study visit until the end of maximum study treatment time after 16 weeks calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis with the Wound Healing Analyzing Tool (W.H.A.T.) in the ITT population. An elliptical wound surface area has been calculated from the documented width and length (eCRF) [(pi / 4) x length x width = area]. Data show Mean and Standard Deviation (SD) and Median and Inter Quartile Range (IQR) as well the Number (N) of values available for analysis and the numberof values substituted by the last observation carried forward (LOCF) method (in brackets).

Wound volume (mm^3) in the ITT population	**NPWT** **N=171**	**SMWC** **N=174**
Randomization	22498 (58930) 4710 (15048) N=171 (2)	21740 (74181) 4759 (12888) N=174 (0)
Week 1	13203 (28709) 2487 (6908) N=171 (15)	19979 (73143) 3533 (11407) N=174 (26)
Week 3	10708 (28521) 1884 (6857) N=171 (24)	16217 (67494) 2293 (8831) N=174 (23)
Week 5	7700 (19719) 1166 (5338)	11286 (32566) 1365 (7539)

	N=171 (37)	N=174 (42)
Week 8	5592 (11535) 785 (4604) N=171 (78)	8772 (27674) 812 (5258) N=174 (67)
Week 12	5333 (12422) 565 (3913) N=171 (119)	6639 (16454) 625 (4083) N=174 (133)
Week 16	3880 (10534) 141 (1890) N=171 (83)	5465 (14874) 200 (1587) N=174 (64)

Supplement Table 3: Wound volume at each observation time point during the study treatment time of maximum 16 weeks in the ITT population

The table shows the wound volume at each study visit until the end of the maximum study treatment time of 16 weeks in the ITT population. Wound volume was calculated from width, length and depth as documented in the eCRF. Data show Mean and Standard Deviation (SD) and Median and Inter Quartile Range (IQR) as well the number (N) of values available for analysis and the number of values substituted by the last observation carried forward (LOCF) method (in brackets).

Wound tissue composition in the ITT population	NPWT Granulation N=171		NPWT Fibrin N=171		NPWT Necrosis N=171		SMWC Granulation N=174		SMWC Fibrin N=174		SMWC Necrosis N=174	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.
Randomization	34 (36) 20 (70) 171 (2)	22 (25) 12 (37) 118 (8)	21 (28) 10 (30) 170 (4)	71 (27) 79 (46) 118 (8)	3 (10) 0 (0) 169 (5)	7 (15) 0 (5) 118 (8)	34 (37) 20 (71) 174 (3)	24 (26) 14 (39) 129 (12)	22 (29) 10 (40) 174 (1)	69 (28) 79 (44) 129 (12)	2 (9) 0 (0) 172 (2)	7 (14) 0 (8) 129 (12)
Week 1	58 (35) 70 (70) 171 (16)	21 (25) 10 (36) 118 (32)	19 (22) 10 (30) 71 (19)	73 (27) 81 (47) 118 (32)	5 (13) 0 (2) 169 (23)	6 (12) 0 (5) 118 (32)	49 (35) 50 (70) 174 (28)	21 (25) 10 (36) 129 (36)	24 (27) 15 (31) 174 (27)	74 (26) 85 (40) 129 (36)	6 (15) 0 (5) 172 (30)	5 (9) 0 (5) 129 (36)
Week 3	67 (31) 80 (55) 171 (26)	16 (23) 5 (25) 118 (27)	18 (22) 10 (30) 171 (30)	80 (25) 91 (30) 118 (27)	5 (13) 0 (0) 169 (28)	4 (11) 0 (1) 118 (27)	57 (32) 60 (60) 174 (24)	21 (25) 10 (36) 129 (35)	25 (26) 20 (35) 174 (25)	77 (25) 85 (36) 129 (35)	5 (13) 0 (3) 172 (30)	3 (7) 0 (1) 129 (35)
Week 5	70 (30) 80 (45) 171 (36)	15 (22) 6 (21) 118 (43)	18 (24) 10 (25) 171 (38)	83 (22) 91 (26) 118 (43)	4 (13) 0 (0) 169 (42)	2 (8) 0 (1) 118 (43)	62 (31) 63 (50) 174 (44)	18 (26) 4 (32) 129 (36)	23 (25) 10 (39) 174 (47)	80 (26) 93 834) 129 (36)	4 (12) 0 (0) 172 (46)	3 (10) 0 (0) 129 (36)
Week 8	74 (30) 90 (40) 171 (53)	16 (23) 4 (27) 118 (48)	17 (24) 10 (20) 171 (56)	82 (24) 93 (33) 118 (48)	4 (13) 0 (0) 171 (59)	2 (6) 0 (0) 118 (48)	70 (29) 80 (40) 174 (44)	17 (24) 3 (33) 129 (43)	17 (21) 10 (20) 174 (49)	80 (25) 92 (36) 129 (43)	5 (13) 0 (0) 174 (52)	3 (11) 0 (0) 129 (43)
Week 12	75 (30) 90 (40) 171(115)	15 (23) 4 (22) 118 (89)	17 (25) 5 (20) 171(118)	83 (24) 96 (23) 118 (89)	4 (13) 0 (0) 171(119)	1 (5) 0 (0) 118 (89)	73 (29) 80 (38) 174(124)	16 (23) 3 (29) 129(102)	16 (20) 10 (20) 174(125)	82 (23) 93 (32) 129(102)	5 (13) 0 (0) 172(126)	2 (6) 0 (0) 129(102)
Week 16	77 (30) 90 (40) 171 (78)	13 (22) 1 (17) 118 (66)	14 (22) 2 (20) 171 (79)	86 (24) 98 (19) 118 (66)	3 (10) 0 (0) 171 (82)	1 (6) 0 (0) 118 (66)	76 (30) 90 (40) 174 (62)	17 (24) 4 (31) 129 (576	15 (24) 5 (20) 174 (65)	81 (24) 93 (35) 129 (56)	3 (13) 0 (0) 174 (66)	2 (6) 0 (0) 129 (56)

Supplement Table 4: Wound tissue composition at each observation time point during the study treatment time of maximum 16 weeks in the ITT population.

Wound tissue composition (granulation, fibrin, and necrosis) is presented for the data documented in the eCRF and for the data derived from the photo analysis using the Wound Healing Analyzing Tool (W.H.A.T.). Data show Mean and Standard Deviation (SD) and Median and Inter Quartile Range (IQR) as well the number (N) of values analyzed for the ITT population and the number (N) of values substituted by the last observation carried forward (LOCF) method (in brackets).

Pain **in the ITT population**	**Total** **N=345**	**NPWT** **N=171**	**SMWC** **N=174**
Screening	2.1 (2.4) 1 (4) N=344 (0)	2.1 (2.3) 1 (4) N=171 (0)	2.1 (2.4) 1 (4) N=173 (0)
Week 1	1.7 (2.2) 1 (3) N=344 (6)	1.6 (2.2) 0 (2) N=171 (1)	1.8 (2.2) 1 (3) N=173 (5)
Week 3	1.5 (2.0) 1 (2) N=344 (27)	1.3 (1.9) 0 (2) N=171 (11)	1.7 (2.1) 1 (3) N=173 (16)
Week 5	1.3 (1.9) 0 (2) N=344 (45)	1.2 (1.9) 0 (2) N=171 (21)	1.4 (2.0) 0 (2) N=173 (24)
Week 8	1.3 (1.9) 0 (2) N=344 (70)	1.2 (1.9) 0 (2) N=171 (38)	1.3 (1.9) 0 (2) N=173 (32)
Week 12	1.1 (1.8) 0 (2) N=344 (115)	1.2 (1.9) 0 (2) N=171 (64)	1.1 (1.8) 0 (2) N=173 (51)
Week 16	1.0 (1.7) 0 (1) N=344 (129)	1.0 (1.7) 0 (2) N=171 (76)	0.9 (1.7) 0 (1) N=173 (53)

Supplement Table 5: Pain in the course of the study treatment time of maximum 16 weeks in the ITT population

The table shows the results of the pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT population. Data show Mean and Standard Deviation (SD) and Median and Inter Quartile Range (IQR) as well the Number (N) of values analyzed for the ITT population and the number (N) of values substituted by the last observation carried forward (LOCF) method (in brackets).

Quality of Life (EQ5D) **in the ITT population**	**Total** **N=345**	**NPWT** **N=171**	**SMWC** **N=174**
Screening	0.53 (0.25) 0.53 (0.18) N=317 (5)	0.53 (0.27) 0.53 (0.2) N=156 (2)	0.53 (0.24) 0.53 (0.18) N=159 (3)

End of therapy	0.68 (0.23) 0.76 (0.34) N=75 (2)	0.67 (0.24) 0.77 (0.29) N=62 (2)	0.72 (0.17) 0.66 (0.35) N=13 (0)
End of maximum study treatment time	0.63 (0.24) 0.63 (0.28) N=158 (4)	0.66 (0.22) 0.66 (0.28) N=63 (2)	0.61 (0.25) 0.63 (0.24) N=95 (2)
Follow up after 6 months	0.68 (0.24) 0.71 (0.39) N=190 (5)	0.69 (0.26) 0.77 (0.35) N=93 (3)	0.67 (0.23) 0.63 (0.39) N=97 (2)

Supplement Table 6: Quality of life (EQ5D) in the course of the study treatment time of 16 week in the ITT-population
Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the ITT population. Data show Mean and Standard Deviation (SD) and Median and Inter Quartile Range (IQR) as well the Number (N) of values analyzed for the ITT population and the Number (N) of values substituted by the last observation carried forward (LOCF) method (in brackets).

Results for the subgroup of small wounds	**Total** **N=173 of 345**	**NPWT N=83** **of 171**	**SMWC** **N=90 of 174**	**Difference** **[95%CI]** **p**
Wound closure rate within 16 weeks **N** **%** **[95%CI]**	28 of 173 16.2% [10.7 – 21.7]%	12 of 83 14.5% [6.9 – 22.0]	16 of 90 17.8% [9.9 – 25.7]	4 3.3% [-7.6 - 14.2] 0.6 (U)
Time until optimal preparation of the wound bed (min 95 % granulation tissue) within 16 weeks $N_{available\ values}$ **Mean (SD)** **Median (IQR)** **Min-Max**	100 38.6 (37.4) 26.5 (50.0) 0-114	52 28.5 (30.0) 20.0 (28.0) 0-113	48 49.5 (41.6) 48.0 (79.0) 0-114	21.0 (11.0) [6.9 – 35.1] 0.005*
No. of study participants with amputations or resections within 16 weeks N **%** **[95%CI]**	35 of 173 20.2% [14.2 - 26.2]	19 of 83 22.9% [13.9 - 31.9]	16 of 90 17.8% [9.9 - 25.7]	3 5.1% [-6.9 – 17.1] 0.45 (F)

No. of performed amputations and resections N	50	22	28	6
No. of patients with minor amputations within 16 weeks N (%)	35 (20.2%)	19 (22.9%)	16 (17.8%)	3 (5.1%) 0.45 (F)
No. of patients with major amputations within 16 weeks N (%)]	0 (0%)	0 (0%)	0 (0%)	0 (0%) -
Wound closure rate at follow up after 6 months N **%** **[95%CI]**	37 von 173 21,4% [15.3 – 27.5]	13 of 83 15.7% [7.8 – 23.5] .	24 of 90 26.7% [17.5 – 35.8] .	11 11% [-1.0 - 23.0] 0.10 (U)

Supplement Table 7: Results for the subgroup of small wounds

The table shows the wound closure rate, time until optimal preparation of the wound bed (min. 95% granulation), and amputations and resections within the maximum study treatment time of 16 weeks and wound closure rate within the study observation time of 6 months for the subgroup of small wounds. Data show the Number (N) of study participants and the Percentage (%), Mean and Standard Deviation (SD); Median and Inter Quartile Range (IQR); and Minimum (Min) and Maximum (Max). F=Fisher Exact Test; U=Man Whitney U-Test; *Student's t-test

Results for the subgroup of large wounds	**Total** **172 of 345**	**NPWT** **N=88 of 171**	**SMWC** **N=84 of 174**	**Difference** **[95%CI]** **p**
Wound closure rate within 16 weeks N **%** **[95%CI]**	18 of 172 10,5% [5.9 – 15.0]	13 of 88 14.8% [7.4 – 22,2] .	5 of 84 6.0% [0.9 – 11.0] .	8 8.8% [-0.2 - 17.8] 0.08 (U)
Time until optimal preparation of the wound bed (min 95 % granulation tissue) within 16 weeks (days) $N_{available\ values}$ **Mean (SD)** **Median (IQR)** **Min-Max**	80 47.8 (40.8) 36.5 (70.0) 0 - 127	47 43.4 (37.9) 35.0 (61.0) 0 - 127	33 54.0 (44.6) 56.0 (105.0) 0 -115	 10.6 (6.7) [-7.6 – 28.8] 0.27*

No. of patients with amputations or resections within 16 weeks **N** **%** **[95%CI]**	36 of 172 20.9 [14.9 – 27.0] %	16 of 88 18.2% [10.1 – 26.2]	20 of 84 23.8% [14.7 – 32.9]	4 5.6% [-6.6 – 17.8] 0.45 (F)
No. of performed amputations and resections N	52	23	29	6 0.41 (U)
No. of patients with minor amputations N (%)	34 (19.8%)	14 (15.9%)	20 (23.8%)	0.25 (F)
No. of patients with major amputations N (%)	2 (1.2%)	2 (2.3%)	0 (0%)	0.50 (F)
Wound closure rate at follow up after 6 months N	23 of 172	11 of 88	12 of 84	1
% **[95%CI]**	13.4% [8.3 – 18.5]	12.5% [5.6 – 19.4] .	14.3% [6.8 – 21.8] .	-1.8% [-12.0 – 8.4] 0.82 (U)

Supplement Table 8: Results for the subgroup of large wounds

The table shows the wound closure rate, time until optimal preparation of the wound bed (min. 95% granulation), and amputations and resections within the maximum study treatment time of 16 weeks and the wound closure rate within the study observation time of 6 months for large wounds. Data show the Number (N) of study participants the Percentage (%), Mean and Standard Deviation (SD); Median and Inter Quartile Range (IQR); and Minimum (Min) and Maximum (Max). F=Fisher Exact Test; U=Man Whitney U-Test; *Student's t-test

Demographic and baseline parameters of the PP Population	**Total** **N=154** **(100%)**	**NPWT** **N=44** **(28.6%)**	**SMWC** **N=110** **(71.4%)**
Male	113 of 154 (73.4%)	29 of 44 (65.9%)	84 of 110 (76.4%)
Female	41 of 154 (26.6%)	15 of 44 (34.1%)	26 of 110 (23.6%)
Age in years **Mean (SD)**	N=154 67.4 (10.6)	N=44 66.5 (11.0)	N=110 67.8 (10.4)
Height in cm **Mean (SD)**	N=153 173.8 (12.9)	N=43 173.5 (17.4)	N=110 174.0 (10.7)
Weight in kg **Mean (SD)**	N=150 95.4 (23.3)	N=42 96.2 (21.6)	N=108 95.1 (24.0)

Alcohol	N=153	N=44	N=109
Occasionally	71 (46.4%)	22 (50.0%)	49 (45.0%)
Chronic	3 (2.0%)	1 (2.3%)	2 (1.8%)
No	79 (51.6%)	21 (47.7%)	58 (53.2%)
Smoking	138 of 154 (89.6%)	42 of 44 (95.5%)	96 of 110 (87.3%)
Number of years (Mean (SD))	37.0 (9.2)	42.0 (2.8)	36.3 (9.7)
Packs / day (Mean)	1.0	1.0	1.0
Drugs	N=153	N=44	N=109
Occasionally	0 (0%)	0 (0%)	0 (0%)
Chronic	1 (0.7%)	0 (0%)	1 (0.9%)
No	152 (99.3%)	44 (100%)	108 (99.1%)
Requiring dialysis	11 of 154 (7.1 %)	2 of 44 (4.5%)	9 of 110 (8.2%)
Allergies	16 of 154 (10.4%)	6 of 44 (13.6%)	10 of 110 (9.1%)
Subjective assessment of nutritional condition	N=150	N=43	N=107
Well-nourished	147 (98.0%)	42 (97.7%)	105 (98.1%)
Moderately malnourished or suspected malnutrition	3 (2.0%)	1 (2.3%)	2 (1.9%)
Malnourished	0 (0%)	0 (0%)	0 (0%)
Peripheral arterial occlusive disease (PAOD)	N=109 (70.8%)	N=29 (65.9%)	N=80 (72.7%)
without critical limb ischemia	103 (94.5%)	28 (96.6%)	75 (93.8%)
with critical limb ischemia	6 (5.5%)	1 (3.4%)	5 (6.3%)
Revascularisation before study start	N=9 (5.8%)	N=1 (2.3%)	N=8 (7.3%)
Percutaneous transluminal angioplasty (PTA)	5 (55.6%)	0 (0.0%)	5 (62.5%)
PTA + Stent	0 (0%)	0 (0%)	0 (0%)
Veins-Bypass	1 (11.1%)	1 (100.0%)	0 (11.1%)
Polytetrafluoroethylene (PTFE) Bypass	1 (11.1%)	0 (0%)	1 (12.5%)
Thromboendarterectomy and patch plastic	2 (22.2%)	0 (0%)	2 (25.0%)
Revascularization with influence on the wound	9 of 9 (100%)	1 of 1 (100%)	0 of 8 (100%)
Sufficient revascularization result	9 of 9 (100%)	1 of 1 (100%)	8 of 8 (100%)
Insufficient revascularization result	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)
Revascularization result not assessable	0 of 9 (0%)	0 of 1 (0%)	0 of 8 (0%)

Supplement Table 9: Patient demographics and baseline characteristics of the Per Protocol (PP) population

Data are Number (N) and Percentage (%) and Mean and Standard Deviation (SD). "N=" is stating the number of patients with actual available information. Findings, diagnoses and procedures documented by the clinical investigators are presented.

Time until optimal wound bed preparation (min 95 % granulation tissue)	**Total N=100**	**NPWT N=38**	**SMWC N=62**	**Mean difference [95%CI] p***
Mean (SD)	43.8 (42.3)	23.8 (31.7)	56.0 (43.5)	32.2
Median (IQR)	30.0 (76)	8.5 (28.0)	56.0 (96.0)	[16.3 – 48.1]
Min - Max	0 - 127	0 - 127	0 - 115	
				<0.001

Supplement Table 10: Time until optimal preparation of the wound for further treatment (minimum 95 % granulation tissue) in the PP population

Data show the number (N) of study participants with available values for the analysis in total and for both treatment arms; Mean and Standard Deviation (SD); Median and Inter Quartile Range (IQR); and Minimum (Min) and Maximum (Max).
*Student's t-test

Amputations & Resections in the PP population	**Total N=154**	**NPWT N=44)**	**SMWC N=110**	**Difference p**
No. of patients with amputation or resection N (%) [95%CI]	30 of 154 19.5 % [13,2 – 25,7]	9 of 44 20.5 % [8,5 - 32,4]	21 of 110 19.1 % [11,7 – 26,4]	12 1.4% [-12.6 – 15.4] 0.83 (F)
No. of amputations or resections N	39	11	28	17 0.86 (U)
No. of study participants with Minor-Amputations N (%)	30 (18.9%)	9 (12.8%)	21 (21.4%)	12 0.83 (F)
No. of study participants with Major-Amputations N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%) -

Supplement Table 11: Amputations and resections in the PP population

Data show the Number (N) of study participants available for the analysis in total and for both treatment arms and the Number (N) and the percentage (%) of study participants with amputations or resections, the number of amputations and

resections performed and the number and the percentage of participants with minor and major amputations. F = Fisher's Exact Test; U = Mann-Whitney U-Test.

Wound surface area (mm^2) in the PP population	Calculated from width and length (according to eCRF entry) NPWT N=44	Results of the photo analysis with W.H.A.T. NPWT N=44	Calculated from width and length (according to eCRF entry) SMWC N=44	Results of the photo analysis with W.H.A.T. SMWC N=110
Randomization	964 (1392) 345 (1426) N= 44 (1)	633 (795) 299 (705) N=41 (3)	878 (1266) 373 (889) N= 110 (0)	669 (1143) 294 (692) N=102 (9)
Week 1	525 (696) 224 (408) N= 44 (5)	524 (614) 318 (561) N=41 (8)	827 (1238) 306 (863) N= 110 (16)	706 (1138) 289 (775) N=102 (27)
Week 3	428 (635) 176 (378) N= 44 (6)	477 (737) 165 (424) N=41 (9)	803 (1306) 238 (867) N= 110 (7)	714 (1316) 259 (656) N=102 (26)
Week 5	355 (590) 100 (291) N= 44 (8)	418 (602) 165 (435) N=41 (15)	650 (1157) 161 (670) N= 110 (18)	607 (1212) 167 (545) N=102 (29)
Week 8	284 (528) 53 (217) N= 44 (8)	320 (530) 83 (264) N=41 (16)	569 (1072) 106 (443) N= 110 (17)	479 (990) 123 (397) N=102 (29)
Week 12	283 (580) 14 (130) N= 44 (24)	289 (537) 62 (175) N=41 (32)	528 (1024) 79 (419) N= 110 (71)	474 (1006) 111 (407) N=102 (80)
Week 16	190 (416) 0 (95) N= 44 (14)	179 (333) 30 (204) N=41 (25)	386 (1124) 31 (159) N= 110 (19)	319 (724) 65 (256) N=102 (42)

Supplement Table 12: Wound surface area at each observation time point during the study treatment time of maximum 16 weeks in the PP population

The table shows the wound surface area at each study visit until the end of maximum study treatment time after 16 weeks calculated data from width and length as documented in the eCRF and for the data derived from the photo analysis with the Wound Healing Analyzing Tool (W.H.A.T.) in the PP population. An elliptical wound surface area has been calculated from the documented width and length (eCRF) [(pi / 4) x length x width = area]. Data show Mean and Standard Deviation (SD) and Median and Inter Quartile Range (IQR) as well the Number (N) of values available for analysis and the numberof values substituted by the last observation carried forward (LOCF) method (in brackets).

Wound volume (mm^3) in the PP population	NPWT N=44	SMWC N=110
Randomization	33359 (95749) 5746 (17330) N=44 (1)	14742 (36523) 3905 (11189) N=110 (0)
Week 1	11606 (26991) 1824 (6113) N=44 (5)	13525 (34844) 2470 (9479) N=110 (16)
Week 3	8636 (24698) 777 (3199) N=44 (6)	11907 (32047) 1864 (8039) N=110 (7)
Week 5	5480 (13967) 271 (1790) N=44 (7)	8981 (25570) 1027 (4745) N=110 (18)
Week 8	3955 (9056) 192 (809) N=44 (16)	6899 (18607) 506 (3915) N=110 (29)
Week 12	6052 (16114) 71 (681) N=44 (25)	5964 (15930) 361 (1890) N=110 (77)
Week 16	3246 (11245) 0 (319) N=44 (15)	3396 (10783) 57 (609) N=110 (19)

Supplement Table 13: Wound volume at each observation time point during the study treatment time of maximum 16 weeks in the PP population

The table shows the wound volume at each study visit until the end of the maximum study treatment time of 16 weeks in the PP population. Wound volume was calculated from width, length and depth as documented in the eCRF. Data show Mean and Standard Deviation (SD) and Median and Inter Quartile Range (IQR) as well the number (N) of values available for analysis and the number of values substituted by the last observation carried forward (LOCF) method (in brackets).

Wound tissue composition in the PP population	NPWT Granulation N=44		NPWT Fibrin N=44		NPWT Necrosis N=44		SMWC Granulation N=110		SMWC Fibrin N=110		SMWC Necrosis N=110	
	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.	eCRF	W.H.A.T.
Randomization	32 (37) 10 (68) 44 (1)	23 (26) 13 (37) 41 (2)	18 (27) 3 (28) 44 (1)	68 (27) 69 (45) 41 (2)	2 (7) 0 (0) 44 (1)	9 (15) 0 (15) 41 (2)	38 (38) 25 (80) 110 (0)	26 (27) 16 (42) 102 (9)	21 (29) 10 (33) 110 (0)	67 (29) 77 (56) 102 (9)	1 (7) 0 (0) 108 (2)	7 (15) 0 (8) 102 (9)
Week 1	72 (37) 90 (50) 44 (5)	22 (26) 9 (41) 41 (8)	7 (13) 0 (10) 44 (6)	70 (28) 75 (50) 41 (8)	2 (7) 0 (0) 44 (7)	9 (15) 0 (11) 41 (8)	54 (35) 63 (70) 110 (16)	24 (27) 13 (42) 102 (27)	22 (24) 13 (28) 110 (16)	72 (27) 78 (42) 102 (27)	5 (14) 0 (1) 108 (19)	5 (9) 0 (6) 102 (27)
Week 3	77 (32) 93 (34) 44 (6)	16 (24) 2 (29) 41 (9)	11 (19) 0 (20) 44 (7)	79 (26) 91 (37) 41 (9)	1 (4) 0 (0) 44 (7)	6 (14) 0 (1) 41 (9)	61 (31) 70 (50) 110 (9)	24 (27) 15 (42) 102 (26)	25 (25) 20 (35) 110 (10)	75 (26) 83 (41) 102 (26)	4 (11) 0 (0) 108 (13)	3 (7) 0 (1) 102 (26)
Week 5	82 (29) 95 (20) 44 (7)	10 (16) 4 (11) 41 (16)	9 (19) 2 (10) 44 (8)	87 (17) 93 (21) 41 (16)	1 (4) 0 (0) 44 (9)	3 (9) 0 (1) 41 (16)	65 (29) 73 (46) 110 (19)	19 (27) 4 (34) 102 (27)	24 (24) 13 (37) 110 (22)	78 (27) 93 (35) 102 (27)	3 (9) 0 (0) 108 (22)	3 (11) 0 (0) 102 (27)
Week 8	85 (27) 100 (20) 44 (9)	15 (25) 1 (16) 41 (16)	6 (13) 0 (5) 44 (10)	82 (26) 96 (35) 41 (16)	2 (6) 0 (0) 44 (9)	3 (8) 0 (0) 41 (16)	74 (27) 80 (31) 110 (18)	20 (26) 3 (38) 102 (30)	18(21) 10 (18) 110 (21)	77 (27) 91 (43) 102 (30)	3 (10) 0 (0) 108 (25)	3 (12) 0 (0) 102 (30)
Week 12	86 (26) 100 (18) 44 (26)	13 (24) 1 (13) 41 (34)	6 (14) 0 (4) 44 (26)	85 (26) 99 (20) 41 (32)	2 (9) 0 (0) 44 (28)	2 (6) 0 (0) 41 (32)	77 (27) 85 (29) 110 (72)	18 (25) 3 (36) 101 (78)	16 (20) 10 (20) 110 (73)	80 (25) 92 (36) 102 (79)	3 (11) 0 (0) 108 (73)	2 (6) 0 (0) 102 (80)
Week 16	87 (25) 100 (15) 44 (14)	12 (22) 0 (14) 41 (25)	6 (14) 0 (1) 44 (16)	86 (24) 100 (20) 41 (25)	0.1 (1) 0 (0) 44 (15)	1 (6) 0 (0) 41 (25)	80 (30) 95 (20) 110 (18)	19 (25) 5 (36) 102 (42)	14 (24) 0 (20) 110 (21)	80 (26) 92 (36) 102 (42)	2 (11) 0 (0) 108 (24)	1 (5) 0 (0) 102 (42)

Supplement Table 14: Wound tissue composition at each observation time point during the study treatment time of maximum 16 weeks in the PP population

Wound tissue composition (granulation, fibrin, and necrosis) is presented for the data documented in the eCRF and for the data derived from the photo analysis using the Wound Healing Analyzing Tool (W.H.A.T.). Data show Mean and Standard Deviation (SD) and Median and Inter Quartile Range (IQR) as well the number (N) of values analyzed for the PP population and the number (N) of values substituted by the last observation carried forward (LOCF) method (in brackets).

Pain in the PP population	Total N=154	NPWT N=44	SMWC N=110
Screening	1.3 (2.1) 0 (2) N=44 (0)	1.8 (2.3) 1 (3) N=110 (0)	1,8 (2,3) 1 (3) N=110 (0)
Week 1	0.7 (1.5) 0 (1) N=44 (0)	1.4 (2.1) 0 (3) N=110 (5)	1,4 (2,1) 0 (3) N=110 (5)
Week 3	0.4 (0.7) 0 (1) N=44 (4)	1.3 (1.8) 0 (2) N=110 (3)	1,3 (1,8) 0 (2) N=110 (3)
Week 5	0.3 (0.8) 0 (0) N=44 (2)	1.0 (1.6) 0 (2) N=110 (5)	1,0 (1,6) 0 (2) N=110 (5)
Week 8	0.4 (1.1) 0 (0) N=44 (4)	0.9 (1.5) 0 (2) N=110 (9)	0,9 (1,5) 0 (2) N=110 (9)
Week 12	0.3 (1.0) 0 (0) N=44 (11)	0.7 (1.3) 0 (1) N=110 (18)	0,7 (1,3) 0 (1) N=110 (18)
Week 16	0.2 (0.7) 0 (0) N=44 (14)	0.5 (1.2) 0 (0) N=110 (13)	0,5 (1,2) 0 (0) N=110 (13)

Supplement Table 15: Pain evaluation at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population

Data show Mean and Standard Deviation (SD) and Median and Inter Quartile Range (IQR) as well the Number (N) of values analyzed for the PP population and the Number (N) of values substituted by the last observation carried forward (LOCF) method (in brackets).

Quality of Life (EQ5D) in the PP population	Total N=154	NPWT N=44	SMWC N=110
Screening	0.60 (0.21) 0.60 (0.24) N=142 (4)	0.61 (0.23) 0.63 (0.24) N=42 (1)	0.60 (0.20) 0.59 (0.25) N=100 (3)

End of therapy	0.76 (0.19) 0.76 (0.26) N=34 (2)	0.65 (0.20) 0.78 (0.20) N=26 (2)	0.81 (0.14) 0.87 (0.26) N=8 (0)
End of maximum study treatment time	0.66 (0.22) 0.63 (0.28) N=92 (2)	0.65 (0.25) 0.66 (0.43) N=19 (0)	0.66 (0.21) 0.63 (0.28) N=73 (2)
Follow up after 6 months	0.71 (0.23) 0.77 (0.34) N=99 (2)	0.75 (0.22) 0.78 (0.30) N=26 (0)	0.70 (0.23) 0.77 (0.34) N=73 (2)

Supplement Table 16: Quality of life evaluated with the EQ5D instrument at the pre-defined observation time points during the active study treatment time of 16 weeks in the PP population

Data show Mean and Standard Deviation (SD) and Median and Inter Quartile Range (IQR) as well the number (N) of values analyzed for the PP population and the Number (N) of values substituted by the last observation carried forward (LOCF) method (in brackets).

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6,8,9
Participants	4a	Eligibility criteria for participants	6,7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7,8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8,9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	9,10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12 Fig. 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig. 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12,13,14Tab. 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig. 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14-20
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	14-20
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	18-19
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	19-20
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3,21-22
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	21
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10-11

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.