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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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026345
Article Type:	Original research
Date Submitted by the Author:	28-Aug-2018
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Keywords:	negative pressure wound therapy, standard moist wound care, wound healing, benefit assessment, wound treatment, health care research

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

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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

71 **Strengths and limitations of this study**

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

84 **Background**

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

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

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3 102 implementation of adequate post marketing surveillance. However, in order to be able to answer the question
4 103 about (added) patient benefit and reimbursability of the treatment method by the social health insurance,
5 104 qualitatively adequate clinical studies are necessary. Social health insurance systems ensure health care for a
6 105 large part of the population in many European countries. The patient relevant benefit of examination and
7 106 treatment methods is always in focus. The German authorities are known to have the toughest evaluation
8 107 methods in Europe, which are based exclusively on the rules of evidence-based medicine. German decisions
9 108 often set an example in Europe.

10 109 In Germany the Federal Joint Committee (German: Gemeinsamer Bundesausschuss (G-BA)) is the legislative
11 110 institution of the German healthcare self-administration system [13]. It issues directives for the benefit catalogue
12 111 of the statutory health insurance funds and specifies measures for quality assurance in inpatient and outpatient
13 112 areas of the health care system. In the inpatient sector, the Federal Joint Committee has the right to prohibit
14 113 medical services for reimbursement, if the treatment method has no (added) benefit and no potential to be a
15 114 valuable treatment alternative or is harmful for the patients. In the outpatient sector, a method can only be carried
16 115 out at the expense of the statutory health insurance funds if the G-BA permits this. All decisions are based on the
17 116 benefit assessment which is usually carried out by the independent scientific Institute for Quality and Efficiency
18 117 in Health Care (German: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)) [14]. The
19 118 benefit basically refers to the treatment method used, not to the medical device. Benefit assessment therefore
20 119 considers all studies that include an adequate comparison of the treatment method with the currently accepted
21 120 standard, a placebo or no therapy. Thus, it is also possible to carry out a study with more than one medical
22 121 device.

23 122 In 2004, the G-BA commissioned a benefit assessment on NPWT for the IQWiG in order to support decision-
24 123 making on reimbursement of NPWT by German statutory health insurance funds in outpatient care. The body of
25 124 evidence available has been deemed insufficient to clearly prove an additional clinical benefit of NPWT. The
26 125 large number of prematurely terminated and unpublished trials has also been a reason for concern [15-17]. Since
27 126 the evidence situation was unchanged in a subsequent evaluation, the G-BA decided in August 2010 that NPWT
28 127 would not be reimbursable in German outpatient care. In the following years several researchers performed
29 128 updates or similar systematic literature reviews on the use of NPWT for chronic wounds. The reviews of Ubbink
30 129 et al in 2008 [18, 19], Gregor et al in 2008 [17], Peinemann and Sauerland in 2011 [20], Dumville et al in 2013
31 130 [21], an assessment in the home setting [22] and a health technology assessment particularly issued for the
32 131 evaluation of NPWT for managing diabetic foot ulcers [23] in 2014, as well as the most recent work of Liu et al
33 132 in 2017 [24] all concluded that although NPWT may have a positive effect, the trials that have been performed

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3 133 have methodological flaws and sufficient, unbiased evidence of whether wounds heal better or worse with
4 134 NPWT than with conventional treatment is still missing. Two trials performed by Armstrong 2005 [25] and
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6 135 Blume 2008 [26] provided a solid basis for planning a RCT that meets national and international quality
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8 136 requirements [15, 20].

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10 137 In 2007, the G-BA decided to suspend the method evaluation of NPWT for an initial period of 3 years in order to
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12 138 evaluate the treatment method within a so-called model project. This included the conduct of clinical studies.

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14 139 The G-BA defined basic requirements for the overall project. Further quality requirements were based on
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16 140 IQWiG's general methods [27]. This essentially concerned the formulation of a study hypothesis that supports G-
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18 141 BA's overall question if NPWT can be reimbursed in German outpatient care without any limitation; the
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20 142 selection of a comparator that represents the current treatment standard in Germany; and implementation of all
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22 143 measures to ensure a sufficient certainty of results.

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24 144 Following the announcement of the G-BA, the German statutory health insurance funds initiated a project
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26 145 through a European tender in which a randomized controlled clinical trial was one part and the diabetic foot
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28 146 ulcer has been chosen to be representative for chronic wounds.

147 Methods**148 Aim of the study**

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

153 Study Design

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

160 Patient and Public Involvement

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

163 Participants

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

169 Adult patients (age >18 years) with at least 4-week-old chronic diabetic foot ulcers corresponding to Wagner 2 to
170 4 were screened for study participation by the local investigators. The initially planned minimum ulcer age of 6
171 weeks was reduced to 4 weeks during the course of the study. The entry criteria of a minimum of 4 weeks ulcer
172 history has been chosen in order to optimally represent the typical initial contact of patients with the physician.
173 Written informed consent was obtained from every participant after being informed about all aspects of the trial
174 and before randomization and any trial-related procedure. Patients estimated to be at risk of non-compliance with
175 study requirements were excluded. Diabetic foot wounds after adequate wound pretreatment as well as
176 amputation wounds below the upper ankle joint were eligible for inclusion. Patients with necrotic tissue that
177 could not be removed by debridement or amputation were excluded. If a sufficient covering of exposed blood

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3 178 vessels within or directly surrounding the wound was not possible or the vessels carried an increased risk of
4 179 bleeding with hemodynamic consequences, the patient was excluded from participating in the study. Outpatients
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6 180 were excluded if receiving anticoagulation therapy or suffering from a high grade impaired clotting function with
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8 181 a heightened risk of bleeding with hemodynamic consequences. The use of NPWT devices on the study wound
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10 182 within six weeks prior to study start represented an exclusion criterion in order to demonstrate a clear therapeutic
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12 183 effect of each treatment arm. As the participating health insurance funds provided integrated care contracts for
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14 184 outpatient NPWT, it was only possible to include patients in the study who were members of a participating
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16 185 health insurance fund.

17 186 Basic data were collected for all patients considered for study participation during screening and have been
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19 187 updated during the randomization visit. No recording of the actual ulcer age was made, as experience has shown
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21 188 that this usually cannot be adequately stated by the patients. Within this healthcare research study, clinical
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23 189 diagnoses rather than surrogate parameters were recorded to describe the patient population. Respective
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25 190 available evidence-based guidelines were referred to in the study protocol. Study sites have been selected based
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27 191 on their qualifications and experience using a pre-study qualification checklist and annual quality reports of the
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29 192 respective institution (if available).

30 193 **Randomization and masking**

31 194 Patients were randomly allocated to the treatment arms in a 1:1 ratio using a computer generated list located on a
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33 195 centralized web-based tool. The randomization list consisted of permuted blocks of variable length (4, 6) which
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35 196 were randomly arranged. Patients were stratified by study site and by Wagner-Armstrong stage within each site
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37 197 (<Wagner-Armstrong stage 2C and \geq Wagner-Armstrong stage 2C). Each registered investigator received
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39 198 individual access to the website, randomization tool and case report forms (CRF). The investigators were
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41 199 responsible for adequately implementing the assigned therapy. Due to the physical differences between the
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43 200 treatment regimens it was not possible to blind either participant or physician to the treatment assignment.
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45 201 Confirmation of wound closure was performed by independent, blinded assessment of wound photographs.

46 202 **Procedures**

47 203 All patients underwent an amputation, debridement or at least thorough wound cleansing no longer than six
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49 204 hours before randomization and start of study treatment. Wound bed preparation before study start has been
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51 205 performed according to patient's needs and study wound treatment has been applied according to randomization
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53 206 once the wound bed was ready for the definite treatment in order to achieve complete wound closure. Patients
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55 207 received an extensive examination of overall health status and specific diabetes associated disorders during
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57 208 screening with an update at the randomization visit including diagnostics for peripheral artery disease (PAD)

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3 209 using Rutherford's chronic limb ischemia classification [29]. In the study protocol, factors influencing the
4 210 patient-relevant therapeutic objective of complete wound healing were defined, which were examined with
5 211 regard to their actual influence within the study. Therapeutic factors such as pressure relief were deliberately not
6 212 selected, as optimal patient care is assumed, errors in treatment are not the focus of this evaluation, and this type
7
8 213 of influencing factors should be evenly distributed to both arms of therapy by randomization. Study therapy
9 214 could be started either in-hospital or as outpatient and was intended to be continued in outpatient care whenever
10 215 possible.

11 216 In the intervention group commercially available CE-marked NPWT devices of the manufacturers Kinetic
12 217 Concepts Incorporated (KCI) and Smith & Nephew were used in the discretion of the clinical investigator
13 218 according to clinical routine and manufacturer's instructions [28]. Recommendations for use can be found on the
14 219 manufacturers' websites. Before study start, the participating study sites were allocated to the manufacturers. A
15 220 direct comparison of the used products was explicitly not planned, since the therapy method and not the medical
16 221 products are to be evaluated. NPWT as interim therapy needed to be discontinued once the condition of a wound
17 222 was suitable for closing, either spontaneously by epithelialization or surgically. It was determined in the study
18 223 protocol that the optimal preparation of the wound for subsequent therapy aiming to achieve complete wound
19 224 closure requires a granulation area of at least 95 %. Control therapy was defined as any SMWC according to
20 225 local clinical standards and guidelines [7, 30]. Healthcare providers were obligated to provide patients with best
21 226 practice. In the control arm it was permitted to apply any local wound treatment standard used in the respective
22 227 study site that did not have an experimental status or was NPWT. To ensure the best quality of local wound
23 228 treatment, the study sites were trained for both the intervention arm by the manufacturers and the control arm by
24 229 the German Society for Wound Healing and Wound Treatment which provided parts of its curriculum and
25 230 experienced instructors.

26 231 The maximum study treatment time was 16 weeks after randomization. Study visits needed to be performed at
27 232 week one, three, five, 12 and 16 and included a complete wound examination. Study participants were followed
28 233 up until 6 months after randomization. The initially planned follow-up period of 12 months was reduced to 6
29 234 months in the course of the study. The amendment to the study protocol was endorsed by the Ethics Committee
30 235 and immediately communicated to all participating trial sites.

31 236 **Outcomes**

32 237 Our primary outcome comprised the two primary effectiveness endpoints wound closure rate and the time until
33 238 complete wound closure within a maximum study treatment period of 16 weeks. Complete wound closure was
34 239 defined as 100% epithelialization of the wound, no drainage, no suture material and no need for wound dressing

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

243 During study planning, possible factors influencing the primary endpoints were identified. Presence and stage of
244 a diabetic neuropathic osteoarthropathy, severity of the foot wound according to Wagner Armstrong (<stadium
245 2c and \geq stadium 2c), diagnosis of a peripheral arterial occlusive disease (paVK) and the stadiums according to
246 Fontaine and Rutherford classification, presence and stages of chronic venous insufficiency (CVI), presence of
247 extreme foot deformities and malpositions, untreated or therapy-refractory inflammation in the wound area,
248 chronic anemia, proven by a hemoglobin value <10 g/dl during screening and after 16 weeks, presence of a heel
249 necrosis, presence of a lymphedema, infection, infection with resistant strains, glycated hemoglobin (HbA1c)
250 level, dialysis, treatment with hyperbaric oxygen therapy (HBO) or normothermal therapy, application of
251 recombinant or autologous growth factors to the study wound, and application of skin or dermal substitutes and
252 with living cells that produce growth factors. These covariates were analyzed for their effect on the two primary
253 endpoints. Covariates were excluded from the analysis if the number of missing values was too high or they did
254 not occur at all.

255 Secondary outcomes were wound closure rate after six months; time until optimal preparation of the wound bed
256 (a minimum of 95% granulation) within 16 weeks; recurrence within 6 months and amputation within 16 weeks.

257 The initial planned secondary endpoint of time until wound closure within 6 months was abandoned during the
258 course of the study. It was found that a time-to-event survey was not possible outside the active study treatment
259 period. This was mostly due to the fact that after this 16-week period weekly study visits were no longer an
260 obligation and further patient care was no longer bound to the study site. Only one follow-up visit was planned
261 and carried out after 6 months, in which wound or healing status and recurrences were documented.

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

270 **Statistical analysis**

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3 271 Sample size calculation was performed using the expected difference between wound closure rates in both
4 272 treatment arms based on information extracted from previously published studies. Armstrong and Lavery
5 273 described a rate of complete wound closure in 56% of patients with NPWT and in 39% of patients in the
6 274 corresponding control group [25]. Blume showed a rate of complete wound closure in 43% of patients treated
7 275 with NPWT and 29% of patients in the control group [26]. We assumed a complete wound closure rate of 45%
8 276 for NPWT and 30% in the SMWC group, resulting in a minimum difference of 15% after a treatment time of 16
9 277 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
10 278 total sample size of 162 patients per group was calculated. The computer program of Dupont and Plummer was
11 279 used for sample size calculation [31].

12 280 We performed all analyses based on the intention-to-treat (ITT) population that includes all randomized
13 281 participants who have a valid baseline and at least one valid post baseline wound assessment. As a secondary
14 282 approach a per-protocol (PP) analysis has been performed excluding patients with any serious protocol
15 283 deviations, temporary changes from SMWC to NPWT, permanent wound treatment changes or without valid
16 284 documentation until wound closure confirmation or end of maximum treatment time (EOMT). Safety data are
17 285 presented on an 'as treated' basis. Subgroup analysis is presented for small vs big wound subpopulations. There
18 286 was no interim analysis.

19 287 The superiority hypothesis was tested in parallel for wound closure rate and time to wound closure
20 288 within 16 weeks. Incidence of complete wound closure was analyzed using a chi-squared test (Fisher's exact test)
21 289 comparing the two treatment arms. Time to complete wound closure was compared between the two treatment
22 290 arms using a log-rank test. The method of Bonferroni-Holm was used for adjustment of the α -error for parallel
23 291 confirmatory testing of both primary endpoints. Missing values have been incorporated as censored values.
24 292 Safety and secondary endpoints were analyzed using conventional univariate testing.

25 293 Within a priori planned subgroup analysis the ITT population was divided into a group of small wounds and a
26 294 group of big wounds based on the wound surface area documented during the randomization visit. Wounds
27 295 smaller than or equal to the total median wound surface (483 mm²) were assigned to the subgroup "small
28 296 wounds". Patients with wound surface areas larger than the median value were assigned to the subgroup "large
29 297 wounds". Since no citable scientific definition of a large wound was available at the time of study planning and
30 298 the clinical experts involved could not make a decision, the median of all wounds was chosen as the criterion for
31 299 the division into the two subgroups.

32 300 IBM SPSS Statistics (version 23) was used for all analyses.

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3 301 This study is registered with ClinicalTrials.gov number NCT01480362 and in the German Clinical Trial
4 302 Registry, number DRKS00003347.

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6 303 A data monitoring committee was formed to oversee overall study performance and safety.

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8 304 **Role of the funding source**

9
10 305 Through a European tender the study was initiated by a consortium of 19 statutory German health insurance
11 306 funds, which provided integrated care contracts for all study participants and for up to 7000 patients with acute
12 307 and chronic wounds in Germany; defined basic rules for study design based on the requirements of the German
13 308 authorities; and provided a critical review of the study protocol and the final report. The study was funded by the
14 309 manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the
15 310 NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary
16 311 support and information about the used material. The manufacturers had no role in study design, data collection,
17 312 data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including
18 313 statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

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315 **Results**

316 Between Dec 23, 2011 and August 12, 2014 386 patients were enrolled and randomly assigned to receive NPWT
 317 (181) or SMWC (187) in the DiaFu-study (**Error! Reference source not found.**) in overall 40 study sites (that
 318 recruited minimum 1 patient and maximum 76 patients. A full list of investigator can be found in the appendix.
 319 13 investigators randomized more than 10 patients. 23 study sites enrolled only between 1 and 4 patients. Most
 320 of these study sites refused further study participation due lack of time and staff for adequately performing the
 321 documentation. In the further course of the trial research nurses have been hired by the independent scientific
 322 institute overseeing the trial in order to support the documentation in the study sites whenever needed.
 323 Baseline characteristics of the patients in the NPWT-and the SMWC-arm are similar both in the ITT and the PP
 324 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%)	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)	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	N=171	N=174
	244 (70·7%)	121 (70·8%)	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%)

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

328
 329 Wound closure rate in the ITT population was higher in the NPWT arm but this was not significant (p 0.53) as
 330 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

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

334
 335 Wounds treated with NPWT had a slightly lower risk of remaining open than those of patients receiving SMWC
 336 (RR 0.97 [95% CI: 0.89-1.06]).

337 Beginning in week five the number of study patients with open wounds in the NPWT-arm was lower than in the
 338 SMWC-arm (Figure 2). There is no significant difference in the wound healing time between the two treatment
 339 arms (p = 0.244, Log Rank Test). Since the cumulative number of patients with open wounds was more than
 340 70% after 16 weeks, we were not able to calculate medians for time to wound closure.

341 Of the a priori defined factors potentially influencing wound closure nine factors needed to be excluded because
 342 the number of missing values was too high or they were never documented by the investigators. The covariate
 343 peripheral arterial occlusive disease had significant influence on the time until wound closure (p 0.026) and
 344 infection had a significant influence on the wound healing rate (p 0.012). However, both influencing factors
 345 were almost evenly distributed over both study arms by randomization. Thus the group comparison has not been
 346 influenced by these confounders.

347 After 6 months the wound closure rate was higher in the SMWC- than in the NPWT-arm (36 of 174 [20·7 %] vs
348 24 of 171 [14· 0 %]), but the difference was not significant (p 0·12).

349 The time until optimal preparation of the wound for further treatment to achieve a complete epithelization (min
350 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

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

356 In the ITT-population wound surface area and wound volume decreased continuously during the study treatment
357 time of 16 weeks in both treatment arms. The results of the blinded photo analysis using the Wound Healing
358 Analyzing Tool (W.H.A.T.) were smaller than the values documented by the clinical investigators. In the
359 NPWT-arm values for the wound surface area decreased faster during the beginning of the treatment time, but
360 aligned with the values of the SMWC-arm after week five. Starting from a similar wound volume, values in the
361 NPWT-arm decreased faster and remained consistently smaller until the end of the treatment period than those in
362 the SMWC-arm. In the NPWT-arm granulation tissue increased faster at the beginning of the treatment period
363 until week 8 and aligned with the measures in the SMWC-arm at the end of the treatment time. Values for fibrin
364 were low and decreased slightly faster in the NPWT-arm than in the SMWC arm. The value for necrotic tissue
365 was very low and did not differ relevantly between the treatment arms. The results of the W.H.A.T. evaluation
366 deviate markedly from the values documented by the investigators and show the opposite course for granulation
367 tissue and fibrin. In the PP-population wound surface area started at smaller baseline levels and decreased faster
368 than in the ITT-population whereas the measures were smaller in the NPWT arm than in the SMWC arm.
369 Wound volume started higher in the NPWT arm and ended at similar levels for the treatment arms after
370 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

402 minimum of one SAE (45 patients with one SAE; 13 patients with two or more SAEs). The difference between
 403 the treatment arms was not significant (p 0.50). None of the SAEs in the NPWT group were documented as
 404 definitely or possibly related to the medical device by investigators. In one case in the SMWC group the
 405 investigator documented a definite relationship between the SAE and SMWC. In one case the investigator
 406 documented a possible relationship to SMWC in the NPWT group. Table 3 gives a detailed overview on the AEs
 407 documented within the study treatment time of 112 days.

Adverse Events (AE) N=269	NPWT N=167	SMWC N=102
Day of occurrence (N)	167	102
Mean (SD)	37.5 (28.6)	42.7 (29.2)
Median (IQR)	30.0 (40.0)	38.0 (50.0)
Duration in days (N)	157	97
Mean (SD)	19.7 (29.0)	25.3 (38.6)
Median (IQR)	10.0 (20.0)	13.0 (22.0)
Severity (N)	161	102
Mild	64 (39.8%)	24 (23.5%)
Moderate	54 (33.5%)	38 (37.3%)
Severe	43 (26.7%)	40 (39.2%)
AE expected / unexpected (N)	159	100
Expected	52 (32.7%)	27 (27.0%)
Unexpected	107 (67.3%)	73 (73.0%)
Relationship to the medical device (N)	157	100
Yes	16 (10.2%)	0 (0%)
Possible	11 (7.0%)	2 (2.0%)*
No	117 (74.5%)	94 (94.0%)
Not assessable	13 (8.3%)	4 (4.0%)
* No treatment change to NPWT has been documented.		
Relationship to SMWC (N)	110	75
Yes	0 (0%)	2 (2.7%)
Possible	5 (4.5%)	0 (0%)
No	96 (87.3%)	67 (89.3%)
Not assessable	9 (8.2%)	6 (8.0%)
Relationship to treatment procedure (N)	148	96
Yes	6 (4.1%)	4 (4.2%)
Possible	15 (10.1%)	2 (2.1%)
No	111 (75.0%)	80 (83.3%)
Not assessable	16 (10.8%)	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%)

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

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

414 An overview of the measures for small and big wounds and detailed results for this subgroup analysis can be
 415 found in the appendix. In the subgroup of big wounds, wound closure rate was significantly higher in the NPWT
 416 arm within 16 weeks (p 0.08). Patients with big wounds have a lower risk of not achieving wound closure within
 417 16 weeks when treated with NPWT (RR 0.91 [95%CI: 0.82-1.0]). In the subgroup of big wounds a significantly
 418 faster wound closure was achieved in the NPWT arm (p 0.027) (Figure 3). Time until complete, sustained and
 419 verified wound closure was not significantly different between the treatment arms in the subgroup of small
 420 wounds (Figure 4).

421 In the subgroup of small wounds the time to reach 95 % granulation tissue was significantly shorter for the
 422 patients treated with NPWT (p 0.005). Time until optimal wound bed preparation was shorter in the NPWT arm
 423 in the subgroup of big wounds, but did not significantly differ to the result of the SMWC arm (p 0.27). There are
 424 no relevant or significant differences in the overall number of patients with amputation or resection between the
 425 treatment arms in both subgroups. Both major amputations were performed in patients with big wounds treated
 426 with NPWT. Due to the low overall number of recurrences (N=16) we were not able to perform a subgroup
 427 analysis for this outcome parameter.

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3 428 In the PP-population patients treated with NPWT showed a 14.5 % higher wound closure rate within 16 weeks
4 429 than patients treated with SMWC (Appendix), but the difference was not significant ($p=0.053$). Wounds treated
5 430 with NPWT had a lower risk of remaining open after 16 weeks (RR 0.82 [95%CI: 0.66-1.03]) than wounds
6 431 treated with SMWC. Time to wound closure in the NPWT arm was significantly shorter ($p=0.004$) (Figure 5).
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8 432 After 6 months, wound closure rate in the SMWC-arm was higher than in the NPWT-arm, but the difference was
9 433 not significant ($p=0.84$). As in the ITT population, optimal wound bed preparation was achieved significantly
10 434 faster in patients receiving NPWT ($p<0.001$). Patients receiving NPWT had a higher risk of recurrence than
11 435 those in the control group (RR 1.50 [95%CI: 0.37-6.01]), however there was no significant difference between
12 436 the treatment arms regarding the total number of recurrences ($p=0.38$) or the number of patients with recurrences
13 437 ($p=0.69$). 9 patients in the NPWT group and 21 (21.4%) patients in the SMWC group had an amputation or
14 438 resection (NPWT RR 1.07 [95%CI: 0.53-2.15]). Neither the number of patients with amputations or resections
15 439 (NPWT 9 (20.5%) SMWC 21 (21.4%) $p=0.83$) nor the number of amputations or resections performed (NPWT
16 440 11 SMWC 28 $p=0.86$) differ significantly between the treatment arms. No major amputations were performed in
17 441 the PP population. Like in the ITT population, pain levels were very low, showing no relevant difference
18 442 between the treatment arms, and further decreased during the study treatment period. In the PP-population EQ5D
19 443 values are higher than in the ITT population during screening, but still show that all patients have significant
20 444 problems. In the NPWT arm QoL measures are similar to those of the SMWC arm for patients reaching end of
21 445 maximum treatment time before end of therapy. EQ5D shows higher values for patients reaching the end of
22 446 therapy during the study treatment time of 16 weeks. Detailed results for the PP population can be found in the
23 447 appendix.
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25 448 29 (17.0%) patients in the NPWT group had a temporary therapy change to SMWC (mean duration 20.5 ± 21.6
26 449 days). In the SMWC group, 17 (9.8%) patients had a temporary therapy change to NPWT (mean duration $28.9 \pm$
27 450 21.6 days). For only 2 of the 29 NPWT patients (6.9%) with a temporary therapy change to SMWC the wound
28 451 closure was achieved within 16 weeks, whereas 16.2% (23 von 142) of the wounds of the NPWT patients
29 452 without therapy change were completely closed.
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31 453 A total of 57.3% (98 of 171) of the patients randomized to NPWT completed treatment before achieving a
32 454 granulation surface of the wound of at least 95%. Significantly fewer patients with this premature end of NPWT
33 455 (4.7%, $N=8$) achieved a complete wound closure than patients with no premature end of therapy (9.9, $N=17$) (p
34 456 $=0.008$). Mean NPWT-duration until premature end of therapy was 28.5 days (SD 24.1), while a mean
35 457 granulation area of 59.6% (SD 30.5) was achieved.

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3 458 For 131 patients (76· 6 %) in the NPWT arm less than the required three dressing changes per week were
4 459 documented. 19 patients (14· 5 %) with this protocol violation achieved a complete wound closure. Six (15·4%)
5 460 of the 39 NPWT patients who received at least 3 therapy changes per week achieved a complete wound closure.
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8 461 In the electronic Case Report Forms (eCRF) a wound closure was documented for 96 patients (NPWT 56 of 171;
9 462 SMWC 40 of 174), but only for 46 patients (NPWT 25; SMWC 21) all criteria for a complete, verified and
10 463 sustained wound closure have been met. For the wound closure visit seven wound photographs (NPWT 7;
11 464 SMWC 0) and for the wound closure confirmation visit four photographs (NPWT 3; SMWC 1) were missing. In
12 465 addition, two of the existing wound photographs for the wound closure (NPWT 0; SMWC 2) and two
13 466 photographs for the wound closure confirmation (NPWT 1, SMWC 3) were not assessable by the blinded
14 467 observers due to serious quality issues. Furthermore 23 (NPWT 15; SMWC 8) existing and assessable wound
15 468 photographs were not able to confirm the wound closure and 3 (NPWT 1; SMWC 2) photographs were not able
16 469 to confirm the wound closure after 14 days.
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470 Discussion

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

488 The DiaFu-study was designed to evaluate effectiveness and safety of NPWT for chronic diabetic foot wounds in
489 real-life clinical practice while avoiding any bias that have been described by several systematic reviews [15-18,
490 20, 21, 24, 32]. Methods against bias have been implemented successfully, but within this study shortcomings in
491 documentation quality negatively impact the results.

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

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

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3 501 and cross checks using quality reports. This ensured that all prerequisites were met for guideline-compliant
4 502 patient care. Nevertheless, even in the application of NPWT there were deviations from the standards. Anyway,
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6 503 questioning the quality of investigators' treatment was not the main focus of this health services research trial.
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8 504 Evaluating the individual treatment quality within a single RCT is neither feasible nor effective.

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10 505 Other than previous studies the DiaFu-study evaluated the effectiveness of NPWT most closely to real-life using
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12 506 a patient population as diverse as in clinical practice. The DiaFu-study therefore included patients with chronic
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14 507 diabetic foot ulcers, regardless of whether a simple wound cleansing, tissue debridement or even amputation was
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16 508 necessary prior to application of wound therapy targeted to achieve complete wound closure. Thus, results can
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18 509 easier be generalized and applied in routine practice settings, but the problems of the clinical routine also affect
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20 510 data quality.

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22 511 Some of the previous studies did choose granulation tissue formation for primary outcome. Wound bed
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24 512 preparation and granulation tissue formation are important prerequisites for wound healing, but the selection of a
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26 513 patient-relevant primary endpoint and the implementation of adequate measures against bias as required by the
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28 514 German authorities have been a priority during planning. Preparing the wound bed significantly faster with
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30 515 NPWT is an important result for the therapeutic approach, but is not a proof of effectiveness and cannot serve as
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32 516 a basis for the benefit assessment of NPWT. Thus, complete wound healing needed to be chosen to be the
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34 517 primary outcome rather than the evaluation of the functionality within in the purpose of the evaluated medical
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36 518 device, which is still part of a complex treatment process.

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38 519 In order to support the decision making process of the German G-BA on general reimbursement of NPWT in
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40 520 German outpatient care the DiaFu-study was conducted with a population according to the clinical routine
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42 521 without excluding certain patient groups; with therapy application in the discretion of the attending physician;
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44 522 and with evaluation of patient relevant outcome. Within this setting we were not able to show a significant
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46 523 superiority of NPWT for achieving wound closure, but despite all limitations NPWT showed a significant
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48 524 superiority in wound bed preparation. This indicates that NPWT works according to its intended use and has at
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50 525 least a potential to be a valuable treatment alternative. Anyway, in the complex treatment process of the diabetic
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52 526 wound a satisfactory rate of wound healing was reached with neither NPWT or with SMWC.

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55 528 **Conclusions**

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57 529 NPWT is not superior to SMWC when evaluated in German real-life clinical practice. Missing compliance with
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59 530 therapy guidelines and poor documentation quality lead to restrictions in achieving the patient-relevant endpoint
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531 complete wound closure and prevent a clear proof of effectiveness. The question if NPWT is superior to SMWC

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3 532 for treating diabetic foot wounds remains unanswered due to the limitations of the DiaFu-study. An overall low
4 533 number of wound closures indicate problems with the overall treatment quality. The results of the PP-population
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6 534 suggest that without the negative impact of premature treatment cessation, temporary changes of the randomized
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8 535 therapy and partly incomplete documentation, NPWT may be more effective for treating diabetic foot wounds
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10 536 than SMWC. NPWT should be evaluated again after implementation of a sufficient, well-considered and widely-
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12 537 accepted concept for quality control. The simple provision of information on existing standards and guidelines
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14 538 seems to be not sufficient. Control mechanisms must be implemented. An adequate quality assurance system
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16 539 must be established in Germany. In a future health care research study the treatment outcome before and after the
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18 540 implementation of these quality measures should be evaluated, for which the results of this trial may serve as a
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20 541 basis. Practitioners worldwide should review their processes with regard to the problems described here.
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3 543 **Ethics approval and consent to participate**

4 544 Ethical approval of the main ethical committee (EC): Ethical Committee of the University of Witten-Herdecke,
5
6 545 has been fully granted without any conditions. Due to performing the trial according to § 23b MPG (German
7
8 546 Medical Device Act), participating study sites in Germany only received a consultation for the main clinical
9
10 547 investigator according to professional law by the respective EC. All investigators have been fully approved by
11
12 548 the respective ECs. An evaluation of the study's content by ECs of participating study sites in Germany was not
13
14 549 applicable. All study participants gave written informed consent prior to randomization and any trial related
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16 550 procedure.

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19 552 **Data sharing**

20 553 The datasets used and/or analyzed during the current study are available from the corresponding author on
21
22 554 reasonable request. Datasets are available in German language.

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24 555

25
26 556 **Competing interests**

27
28 557 All authors have completed the ICMJE uniform disclosure form at www.icmje.org/doi_disclosure.pdf and
29
30 558 declare:

31 559 The German statutory health insurance companies commissioned the Witten/Herdecke University (UW/H) to
32
33 560 plan, conduct, analyze and publish the study. Dörthe Seidel is an employee of the UW/H. The study has been
34
35 561 financed by the manufacturers KCI (Acclity) and Smith&Nephew. Dörthe Seidel received a consulting fee for
36
37 562 the presentation of the study during an event organized by the manufacturer Hartmann. During study planning
38
39 563 and conduct Edmund Neugebauer was an employee of the UW/H. He was the director of the IFOM.

40 564 The clinical investigators Martin Storck, Holger Lawall, Gernold Wozniak, Peter Maukner, Dirk Hochlenert,
41
42 565 Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink
43
44 566 received a case fee of 1000 € for each patient included in the DiaFu-study in order to compensate for the
45
46 567 additional organizational and especially the documentation effort during trial conduct. Furthermore all
47
48 568 investigators received compensation for travelling to the investigator meetings. The institutions of the
49
50 569 investigators used integrated care contracts for NPWT during study conduct in order to provide best practice for
51
52 570 the study participants during outpatient care.

53 571 Gernold Wozniak and Walter Wetzel-Roth are members of the scientific advisory board of the manufacturer
54
55 572 Kinetic Concepts Incorporated (KCI) (now Acclity).

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1
2
3 574 **Funding**

4 575 Through a European tender the study was initiated by a consortium of 19 statutory German health insurance
5
6 576 funds, which provided integrated care contracts for all study participants and for up to 7000 patients with acute
7
8 577 and chronic wounds in Germany; defined basic rules for study design based on the requirements of the German
9
10 578 authorities; and provided a critical review of the study protocol and the final report. The study was funded by the
11
12 579 manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the
13
14 580 NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary
15
16 581 support and information about the used material. The manufacturers had no role in study design, data collection,
17
18 582 data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including
19
20 583 statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

21 584

22 585 **Authors' contributions**

23
24 586 Dörthe Seidel was the principal coordinating investigator. She conceived the study, reviewed the scientific
25
26 587 literature, and was responsible for study design, data analysis, data interpretation, writing and reviewing of the
27
28 588 report. She is the lead author and takes overall responsibility for this report. She affirms that the manuscript is an
29
30 589 honest, accurate, and transparent account of the study being reported; that no important aspects of the study have
31
32 590 been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have
33
34 591 been explained.

35 592 Martin Storck and Holger Lawall were study investigators and contributed to study design, data collection and
36
37 593 interpretation, and reviewed the report.

38 594 Gernold Wozniak, Peter Maukner, Walter Wetzel-Roth and Dirk Hochlenert were study investigators and
39
40 595 contributed to data collection and data interpretation and reviewed the report.

41
42 596 Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink were study
43
44 597 investigators and contributed to data collection and reviewed the report.

45
46 598 Edmund Neugebauer contributed to study design and data interpretation and reviewed the report.

47 599 All authors approved the final version of the report.

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51 601 **Acknowledgements**

52 602 The authors thank all investigators, nurses, patients and partners for supporting the study.

53 603 At least one patient was included in the following facilities: HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für
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15 642 GmbH & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim; Institut für Diabetesforschung
16
17 643 Münster GmbH Hohenzollernring 70 48145 Münster.
18
19 644 The study was initiated by a consortium of 19 statutory German health insurance funds represented by the AOK
20
21 645 federal association (AOK-Bundesverband – AOK-BV), the association of alternative health insurance funds
22
23 646 (Verband der Ersatzkrankenkassen – vdek) and the minors (Knappschaft). In order to guarantee outpatient care
24
25 647 for all study participants without any restrictions, the contracting health insurance companies provided integrated
26
27 648 care contracts for outpatient negative pressure wound therapy.
28
29 649 A project advisory board was implemented to coordinate all processes and project partners. The board comprised
30
31 650 two representatives each from the statutory health insurance funds, the management company and the sponsor as
32
33 651 well as one representative each from the participating medical device manufacturers (KCI and smith & nephew).
34
35 652 Representing the contracting authority (statutory German health insurance funds) Dr. Gerhard Schillinger (AOK-
36
37 653 BV) and Ute Leonhard (vdek) acted as contact persons for all aspects of the project.
38
39 654 The management company “Gesundheitsforen Leipzig” has been entirely responsible for the logistics of the
40
41 655 study. Central tasks of the management company included the recruitment of study sites and patients, the
42
43 656 development of the IT infrastructure including the documentation, communication and invoicing software as
44
45 657 well as the processing of all payments.
46
47 658 The manufacturers Kinetic Concepts Incorporated (KCI) (Acelity) and smith & nephew provided the NPWT
48
49 659 devices as well as support and training for the investigators and financed the study.
50
51 660 The Private University of Witten/Herdecke gGmbH acted as the Sponsor of the trial and the Institute for
52
53 661 Research in Operative Medicine with its former director Prof. E.A.M. Neugebauer, the current interim head Prof.
54
55 662 Rolf Lefering and the head of the division for clinical research Dörthe Seidel was responsible for the scientific
56
57 663 conception, the evaluation as well as the reporting and publication of the study. Prof. Dr. Rolf Lefering was
58
59 664 responsible for the statistical planning and analysis. PD Dr. Peter Krüger was responsible for the data
60
665 management of the study. Special thanks are going to Stefan Bauer, who supported the data management as well
666 as the statistical analysis and reporting.

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

For peer review only

1
2
3 669 **List of figures:**

4 670 Figure 1: Trial profile (CONSORT)

5
6 671 Figure 2: Time until complete, sustained and verified wound closure in the ITT-population

7
8 672 Figure 3: Time until complete, sustained and verified wound closure for the subgroup of big wounds

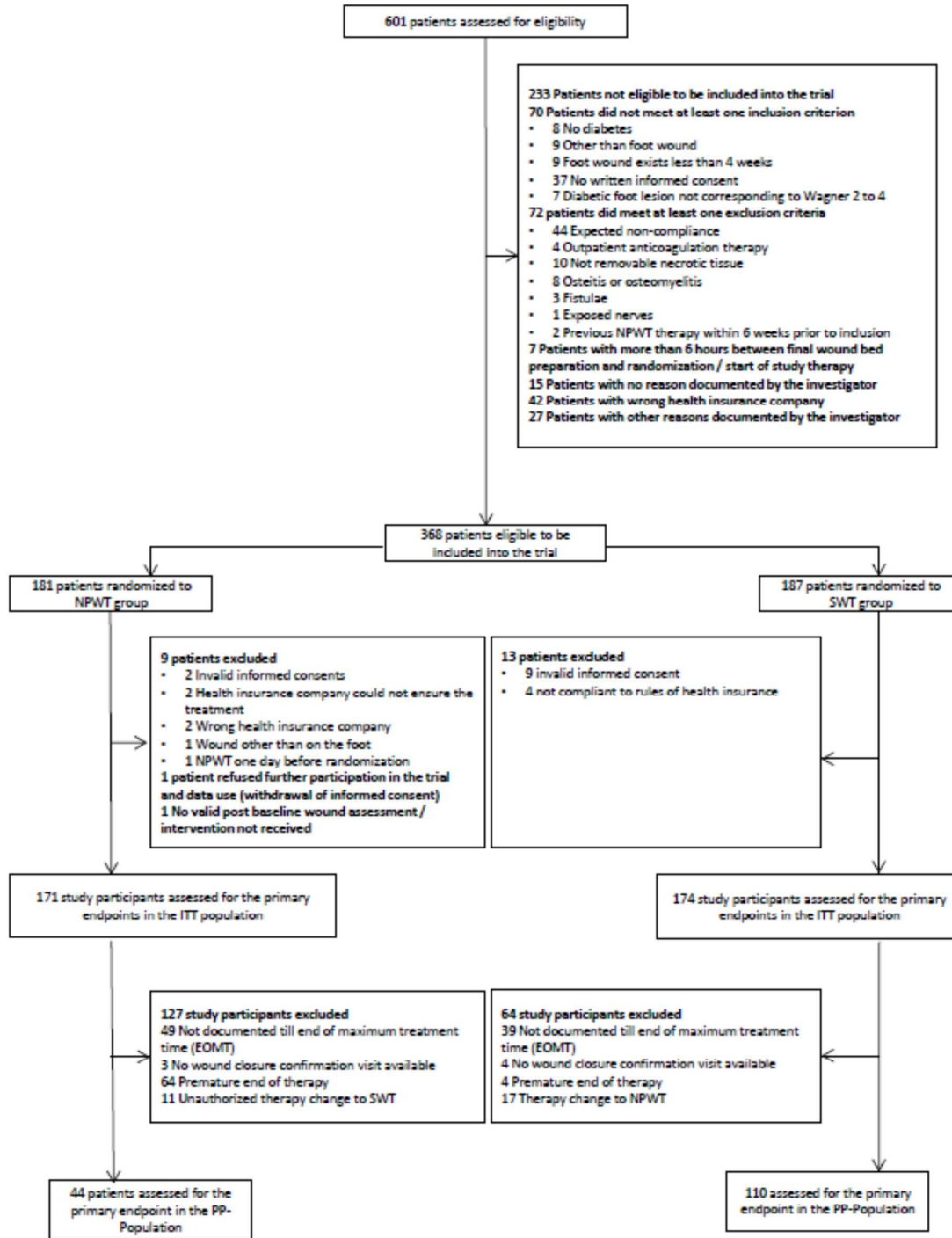
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10 673 Figure 4: Time until complete, sustained and verified wound closure for the subgroup of small wounds

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12 674 Figure 5: Time until complete, sustained and verified wound closure in the PP-population

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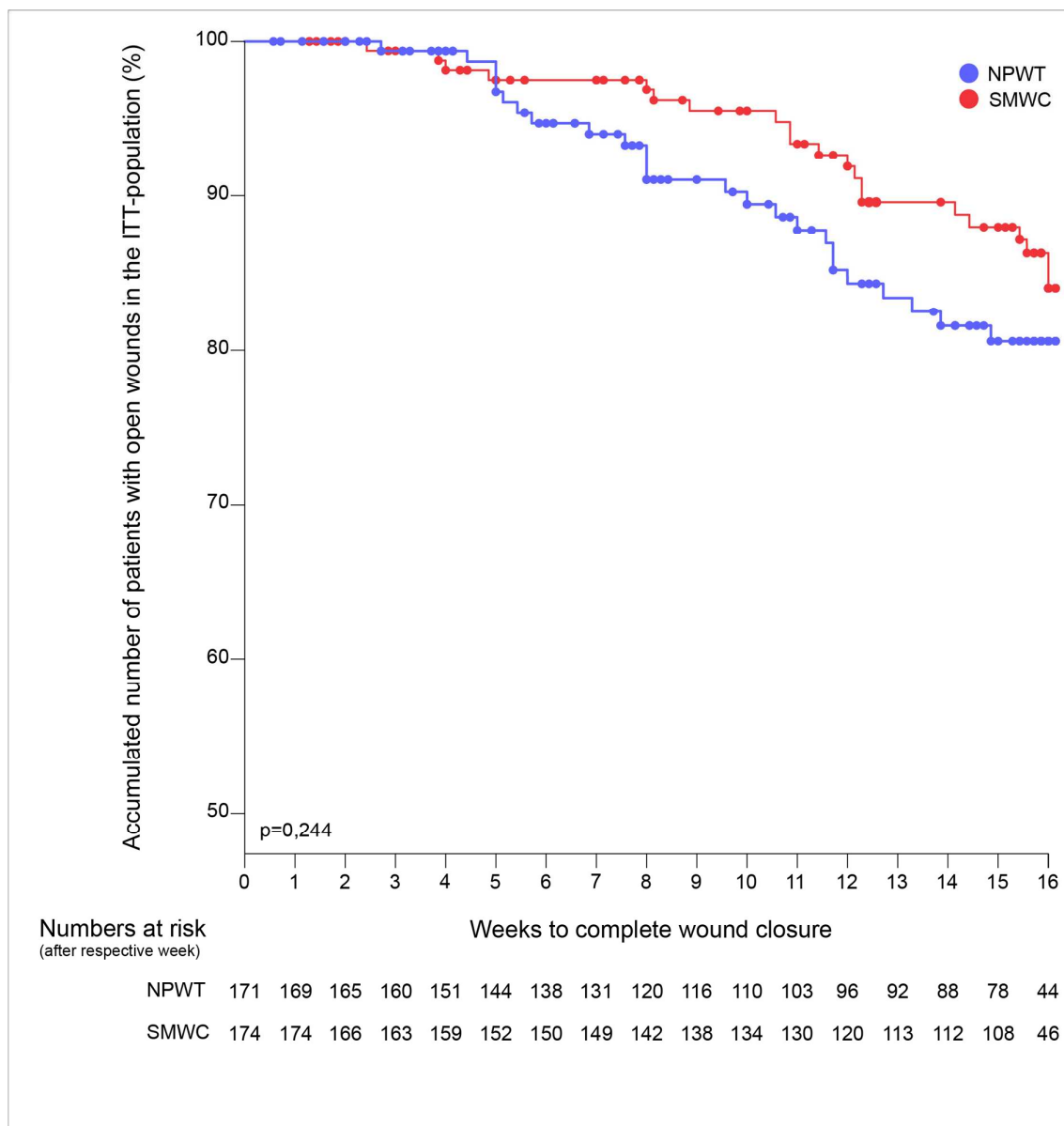
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676 **Figures:**
 677
 678 Figure 1:



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680 Figure 2:



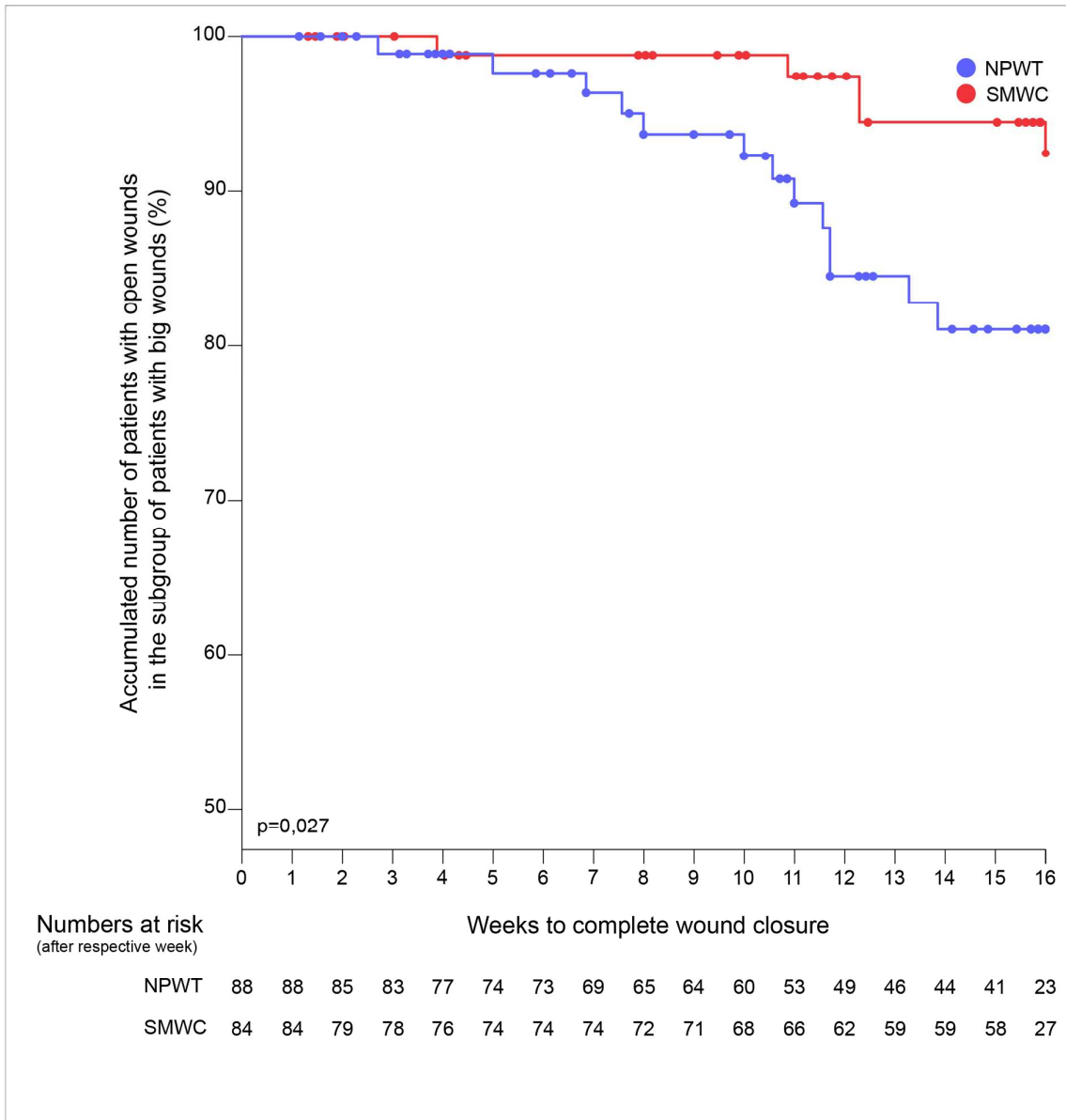
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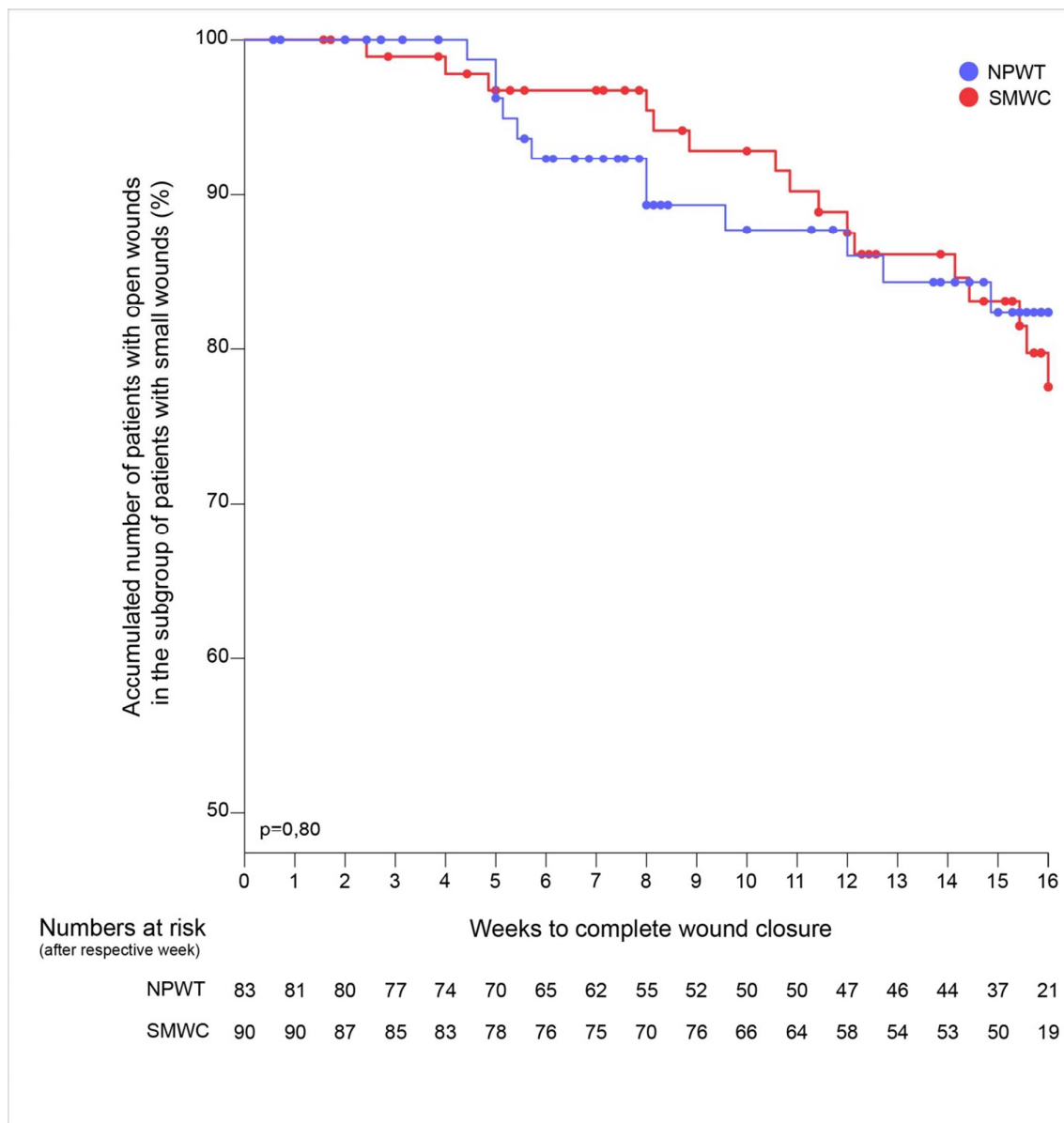
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687 Figure 4:



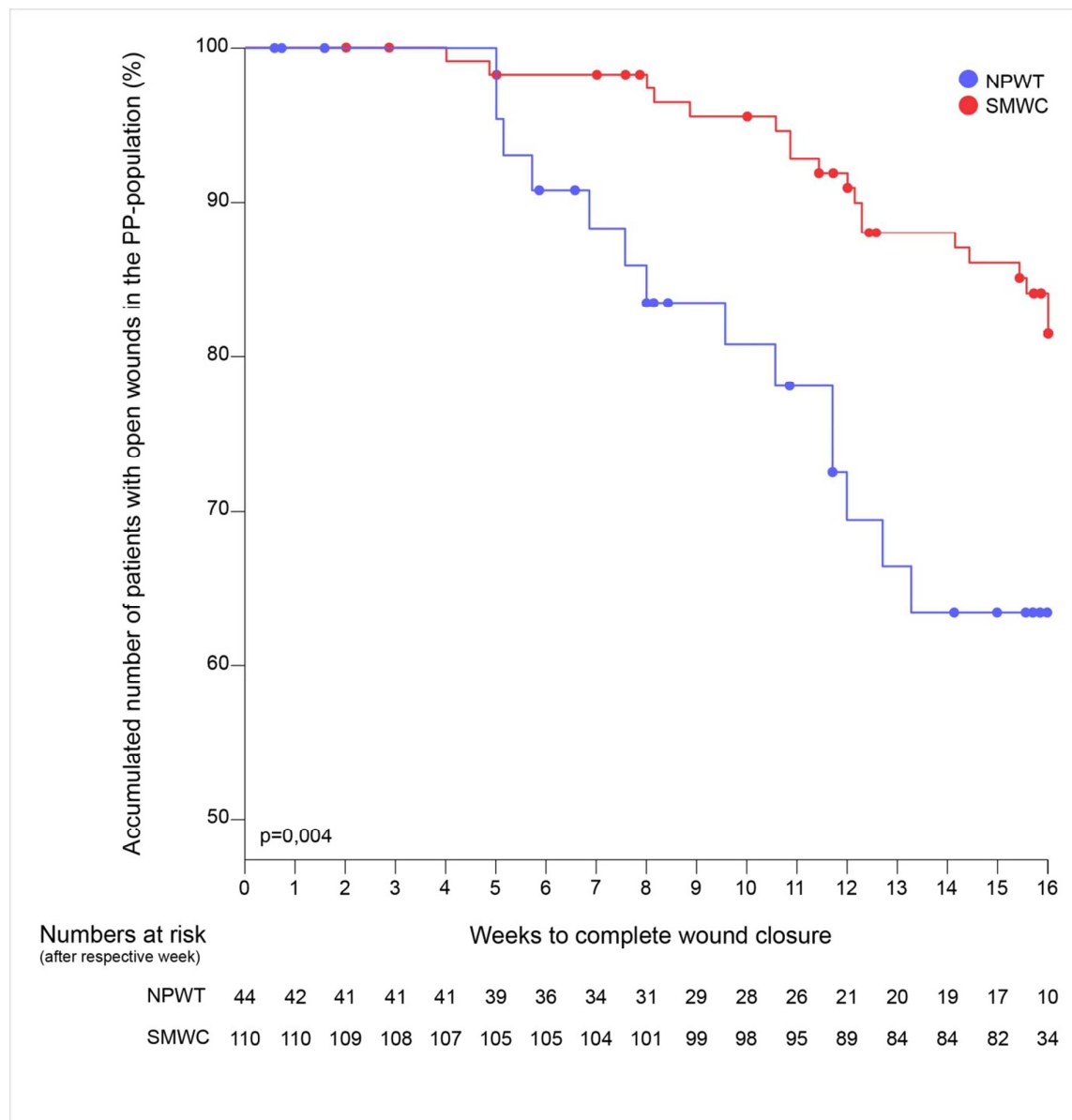
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690 Figure5:

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Supplementary Appendix

Table of contents:

- List of investigators
- Supplementary discussion
- Supplementary tables

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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	N=154	N=44	N=110
Mean (SD)	67·4 (10·6)	66·5 (11·0)	67·8 (10·4)
Height in cm	N=153	N=43	N=110
Mean (SD)	173·8 (12·9)	173·5 (17·4)	174·0 (10·7)
Weight in kg	N=150	N=42	N=108
Mean (SD)	95·4 (23·3)	96·2 (21·6)	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.

Observation time point	Wound surface NPWT		Wound surface SMWC	
	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)	687 (879)	1141 (3247)	664 (1050)
	550 (1236)	321 (760)	471 (1007)	316 (658)
	N=171 (2)	N=118 (10)	N=174 (0)	N=129 (13)
Week 1	847 (1489)	643 (820)	1085 (3234)	713 (1065)
	397 (801)	329 (750)	395 (867)	307 (749)
	N=171 (15)	N=118 (32)	N=174 (25)	N=129 (36)
Week 3	810 (1472)	590 (742)	1025 (3242)	701 (1212)
	314 (860)	273 (633)	390 (913)	266 (768)
	N=171 (24)	N=118 (28)	N=174 (22)	N=129 (35)
Week 5	717 (1379)	607 (828)	759 (1466)	610 (1119)
	275 (769)	231 (843)	267 (824)	219 (635)
	N=171 (37)	N=118 (42)	N=174 (41)	N=129 (38)
Week 8	636 (1322)	495 (770)	674 (1410)	501 (937)
	220 (712)	182 (561)	186 (783)	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) [$(\pi / 4) \times \text{length} \times \text{width} = \text{area}$]. 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)

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3 Table S3: Change of wound volume in the course of the study treatment time of maximum 16 weeks in the ITT-population.
4 Change of wound volume (length x width x depth) in the course of the study treatment time of maximum 16 weeks calculated
5 from width, length and depth as documented in the eCRF. Data show mean (SD) and median (IQR) as well the number (N) of
6 values analyzed for the ITT population (number (N) of values substituted by the last observation carried forward (LOCF)
7 method).
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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)	22 (25)	21 (28)	71 (27)	3 (10)	7 (15)	34 (37)	24 (26)	22 (29)	69 (28)	2 (9)	7 (14)
	20 (70)	12 (37)	10 (30)	79 (46)	0 (0)	0 (5)	20 (71)	14 (39)	10 (40)	79 (44)	0 (0)	0 (8)
	171 (2)	118 (8)	170 (4)	118 (8)	169 (5)	118 (8)	174 (3)	129 (12)	174 (1)	129 (12)	172 (2)	129 (12)
Week 1	58 (35)	21 (25)	19 (22)	73 (27)	5 (13)	6 (12)	49 (35)	21 (25)	24 (27)	74 (26)	6 (15)	5 (9)
	70 (70)	10 (36)	10 (30)	81 (47)	0 (2)	0 (5)	50 (70)	10 (36)	15 (31)	85 (40)	0 (5)	0 (5)
	171 (16)	118 (32)	71 (19)	118 (32)	169 (23)	118 (32)	174 (28)	129 (36)	174 (27)	129 (36)	172 (30)	129 (36)
Week 3	67 (31)	16 (23)	18 (22)	80 (25)	5 (13)	4 (11)	57 (32)	21 (25)	25 (26)	77 (25)	5 (13)	3 (7)
	80 (55)	5 (25)	10 (30)	91 (30)	0 (0)	0 (1)	60 (60)	10 (36)	20 (35)	85 (36)	0 (3)	0 (1)
	171 (26)	118 (27)	171 (30)	118 (27)	169 (28)	118 (27)	174 (24)	129 (35)	174 (25)	129 (35)	172 (30)	129 (35)
Week 5	70 (30)	15 (22)	18 (24)	83 (22)	4 (13)	2 (8)	62 (31)	18 (26)	23 (25)	80 (26)	4 (12)	3 (10)
	80 (45)	6 (21)	10 (25)	91 (26)	0 (0)	0 (1)	63 (50)	4 (32)	10 (39)	93 834	0 (0)	0 (0)
	171 (36)	118 (43)	171 (38)	118 (43)	169 (42)	118 (43)	174 (44)	129 (36)	174 (47)	129 (36)	172 (46)	129 (36)
Week 8	74 (30)	16 (23)	17 (24)	82 (24)	4 (13)	2 (6)	70 (29)	17 (24)	17 (21)	80 (25)	5 (13)	3 (11)
	90 (40)	4 (27)	10 (20)	93 (33)	0 (0)	0 (0)	80 (40)	3 (33)	10 (20)	92 (36)	0 (0)	0 (0)
	171 (53)	118 (48)	171 (56)	118 (48)	171 (59)	118 (48)	174 (44)	129 (43)	174 (49)	129 (43)	174 (52)	129 (43)
Week 12	75 (30)	15 (23)	17 (25)	83 (24)	4 (13)	1 (5)	73 (29)	16 (23)	16 (20)	82 (23)	5 (13)	2 (6)
	90 (40)	4 (22)	5 (20)	96 (23)	0 (0)	0 (0)	80 (38)	3 (29)	10 (20)	93 (32)	0 (0)	0 (0)
	171(115)	118 (89)	171(118)	118 (89)	171(119)	118 (89)	174(124)	129(102)	174(125)	129(102)	172(126)	129(102)
Week 16	77 (30)	13 (22)	14 (22)	86 (24)	3 (10)	1 (6)	76 (30)	17 (24)	15 (24)	81 (24)	3 (13)	2 (6)
	90 (40)	1 (17)	2 (20)	98 (19)	0 (0)	0 (0)	90 (40)	4 (31)	5 (20)	93 (35)	0 (0)	0 (0)
	171 (78)	118 (66)	171 (79)	118 (66)	171 (82)	118 (66)	174 (62)	129 (576)	174 (65)	129 (56)	174 (66)	129 (56)

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4 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
5 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
6 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
7 carried forward (LOCF) method).
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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)	0,61 (0,25)
	0,66 (0,28)	0,63 (0,24)
	N=63 (2)	N=95 (2)
Follow up after 6 months	0,69 (0,26)	0,67 (0,23)
	0,77 (0,35)	0,63 (0,39)
	N=93 (3)	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 mm ²	Small wounds				Big wounds			
	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	NPWT (N=171)	SMWC (N=174)	p
Small wounds	N=83	N=90	
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	NPWT (N=171)	SMWC (N=174)	P
Big wounds	N=88	N=84	
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	Total	NPWT	SMWC	p
Small wounds	N=173	N=83	N=90	
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	Total	NPWT	SMWC	p
Big wounds	N=172	N=88	N=84	

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.

Observation time point	Wound surface NPWT		Wound surface SMWC	
	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)

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4 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
5 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
6 values substituted by the last observation carried forward (LOCF) method).
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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).

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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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026345.R1
Article Type:	Original research
Date Submitted by the Author:	14-Jun-2019
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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

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3 1 **Negative Pressure Wound Therapy compared with standard moist wound care on**
4 **diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT**

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1
2
3 **37 Abstract**

4
5 **38 Objectives**

6
7 39 The aim of the DiaFu-study was to evaluate effectiveness and safety of negative pressure wound therapy
8 40 (NPWT) in patients with diabetic foot wounds in clinical practice.

9
10 **41 Design**

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12 42 In this controlled clinical superiority trial with blinded outcome assessment patients were randomized in a 1:1
13 43 ratio stratified by study site and ulcer severity grade using a web-based-tool.

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15 **44 Setting**

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17 45 This German-national study was conducted in 40 surgical and internal medicine in- and outpatient facilities
18 46 specialized in diabetes foot care.

19
20 **47 Participants**

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22 48 368 patients were randomized and 345 participants were included in the modified ITT-population. Consentable,
23 49 compliant adult patients suffering from a diabetic foot ulcer at least for 4 weeks and without contraindication for
24 50 NPWT were allowed to be included.

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26 **51 Interventions**

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28 52 NPWT was compared with SMWC according to local standards and guidelines.

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30 **53 Primary and secondary outcome measures**

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32 54 Primary endpoints were wound closure rate and time to closure within 16 weeks. Secondary endpoints were
33 55 wound and treatment related adverse events, amputations, time until optimal wound bed preparation, wound size
34 56 and wound tissue composition, pain, and quality of life within 16 weeks, and recurrences and wound closure rate
35 57 within 6 months.

36
37 **58 Results**

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39 59 In the ITT-population 25 patients in the NPWT-arm (14.6%) and 21 patients in the SMWC-arm (12.1%)
40 60 achieved wound closure ($p=0.53$). Wound closure time was not significantly different between the treatment
41 61 arms ($p=0.244$). 96 patients in the NPWT-arm and 72 patients in the SMWC-arm had at least one adverse event
42 62 ($p=0.007$), but only 11 events have been possibly related to NPWT. Documentation deficiencies, premature
43 63 cessation of NPWT and temporary changes of the randomized treatment had a negative impact on the outcome
44 64 wound closure.

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46 **65 Conclusions**

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48 66 NPWT was not superior to SMWC in diabetic foot wounds in clinical practice. Overall wound closure rate was
49 67 low. Deviations from guidelines limit the treatment success.

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51 **68 Trial registration**

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53 69 Clinical Trials.gov: NCT01480362

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71 **Strengths and limitations of this study**

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

90 **Background**

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

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3 101 use of vacuum sealing was described in 1993 by Fleischmann et al. [8] and the commercially available product
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5 102 was developed later in the 1990s [9, 10]. Positive effects of NPWT on wound healing have been suggested in
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7 103 various basic studies [10, 11]. At the time of planning the DiaFu-study, the clinical evidence largely consisted of
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9 104 clinician perception, case reports and series, small cohort studies, and weakly-powered or low-quality
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11 105 randomized trials that documented broad use of NPWT in various clinical settings and constituted a substantial
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13 106 number of publications but an overall small amount of evidence [12-15]. Two trials performed by Armstrong
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15 107 2005 [16] and Blume 2008 [17] provided a solid basis for planning a study that meets national and international
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17 108 quality requirements. Several systematic and technical reviews on the use of NPWT for post-surgical and
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19 109 chronic wounds have been performed in recent years.

20 110 A specific review for the use of NPWT in diabetic foot wounds performed by Dumville et al in 2013 [18], an
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22 111 assessment in the home setting by Rhee et al. in 2014 [19] and a health technology assessment particularly issued
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24 112 for the evaluation of NPWT for managing diabetic foot ulcers [20] in 2014, as well as the most recent work of
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26 113 Liu et al in 2017 [21, 22] all concluded that although NPWT may have a positive effect, the trials that have been
27
28 114 performed have methodological flaws and sufficient, unbiased evidence of whether wounds heal better or worse
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30 115 with NPWT than with conventional treatment is still missing.

31 116 In Germany, the issue of evidence for efficacy and safety of NPWT in acute and chronic wounds was first
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33 117 addressed in 2002 when it was to be decided whether NPWT could be reimbursed without restrictions in
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35 118 outpatient care. The German Federal Joint Committee (German: Gemeinsamer Bundesausschuss [G-BA])
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37 119 commissioned systematic reviews and meta-analyses to the national institute for quality and efficiency in health
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39 120 care (German: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG]). Reports were
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41 121 published in 2006 and 2007 by the IQWiG and the G-BA concluded that the body of evidence available was
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43 122 insufficient to clearly proof an additional benefit of NPWT.

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45 123 Finally in 2007, the G-BA decided to evaluate the treatment method NPWT within a so-called model project.
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47 124 This included the conduct of clinical studies. The G-BA defined basic requirements for the overall project.
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49 125 Further quality requirements were based on IQWiG's general methods [23]. This essentially concerned the
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51 126 formulation of a study hypothesis that supports G-BA's overall question if NPWT can be reimbursed in German
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53 127 outpatient care without any limitation; the selection of a comparator that represents the current treatment
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55 128 standard in Germany; and implementation of all measures to ensure a sufficient certainty of results.

56 129 Following the announcement of the G-BA, the German statutory health insurance funds initiated an overall
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58 130 project through a European tender in which the treatment benefit of NPWT should be evaluated in acute and
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60 131 chronic wounds. The diabetic foot ulcer has been chosen to be evaluated as representative for chronic wounds in

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3 132 a randomized controlled clinical superiority study comparing the effectiveness of NPWT and SMWC in clinical
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5 133 practice.
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For peer review only

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3 **134 Methods**

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7 **136 Aim of the study**

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9 137 The aim of our DiaFu-study was to evaluate whether the effectiveness and safety of NPWT is superior to
10 138 standard moist wound care (SMWC) in real-life clinical practice. Unlike previous studies, in this health care
11 139 research study with a pragmatic approach the question should be answered as to whether the treatment method is
12 140 effective and safe when used under routine conditions.

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18 **142 Study Design**

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20 143 The DiaFu-study was a German-national, multicenter, randomized controlled clinical superiority trial with
21 144 blinded assessment of wound closure, wound size and wound tissue qualities using photographs. This German
22 145 national study was conducted both in hospital departments and outpatient facilities with a special qualification
23 146 for diabetic foot care. Study treatment was allowed to be started both in in- and outpatient care and should be
24 147 continued outpatient whenever possible. Ethical approval of the Lead Ethical Committee of the University of
25 148 Witten/Herdecke has been fully granted without any conditions. More detailed information on the study design
26 149 can be found in the study protocol publication that is available open access [24].

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35 **151 Patient and Public Involvement**

36 152 Patients were not involved in the design, recruitment or conduct of the study. The results of this study will not be
37 153 disseminated directly to study participants.

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43 **155 Participants**

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45 156 In order to conduct a pragmatic trial comparing NPWT and SMWC in patients with diabetes and foot wounds, a
46 157 patient population was included that largely corresponded to clinical routine. In- and exclusion criteria have been
47 158 selected based on manufacturers' contraindications and FDA warnings, the necessity to excluded patients in need
48 159 of protection and who are unable to give their consent, and the intention to avoid general study-related influences
49 160 on the results.

50
51 161 Adult patients (age >18 years) with at least 4-week-old chronic diabetic foot ulcers corresponding to Wagner 2 to
52 162 4 were screened for study participation by the local investigators. Before inclusion, the study protocol required
53 163 either a debridement or, if necessary, an amputation of foot parts, or at least a thorough wound cleansing,
54 164 depending on the individual needs of the patients, in order to achieve the optimal outcome of wound treatment.

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3 165 Thus, chronic diabetic foot wounds after adequate wound pretreatment as well as post-surgical amputation
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5 166 wounds below the upper ankle joint were eligible for inclusion. The initially planned minimum ulcer age of 6
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7 167 weeks was reduced to 4 weeks during the course of the study. Patients estimated to be at risk of non-compliance
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9 168 with study requirements, with wounds with necrotic tissue present that could not be removed by debridement or
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11 169 amputation, with exposed blood vessels within or directly surrounding the wound not possible to be sufficiently
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13 170 covered or with an increased risk of bleeding with hemodynamic consequences, and outpatients receiving
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15 171 anticoagulation therapy or suffering from a high grade impaired clotting function with a heightened risk of
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17 172 bleeding with hemodynamic consequences were excluded from the DiaFu-study. The use of NPWT devices on
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19 173 the study wound within six weeks prior to study start represented an exclusion criterion in order to demonstrate a
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21 174 clear therapeutic effect of each treatment arm.

22 175 Written informed consent was obtained from every participant after being informed about all aspects of the trial
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24 176 and before randomization and any trial-related procedure. As the statutory health insurance funds provided
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26 177 integrated care contracts for outpatient NPWT, it was only possible to include patients in the study who were
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28 178 members of a participating health insurance fund.

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30 179 Basic data were collected for all patients considered for study participation during screening and have been
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32 180 updated during the randomization visit. Study sites have been selected based on their qualifications and
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34 181 experiences using a pre-study qualification checklist and annual quality reports of the respective institution (if
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36 182 available).

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39 184 **Randomization and masking**

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41 185 Patients were randomly allocated to the treatment arms in a 1:1 ratio using a computer generated list located on a
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43 186 centralized web-based tool. The randomization list consisted of permuted blocks of variable length (4, 6) which
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45 187 were randomly arranged. Patients were stratified by study site and by Wagner-Armstrong stage within each site
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47 188 (<Wagner-Armstrong stage 2C and \geq Wagner-Armstrong stage 2C). The randomization lists were generated with
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49 189 the help of a self-created Java program and integrated into the study database. Each registered investigator
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51 190 received individual access to the randomization tool via the study website, but without knowledge of future
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53 191 treatment assignment, which provided adequate allocation concealment. The investigators were responsible for
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55 192 adequately implementing the assigned therapy. Due to the physical differences between the treatment regimens it
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57 193 was not possible to blind either participant or physician to the treatment assignment. Verification of complete
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59 194 wound closure was performed by independent, blinded assessment of wound photographs. Determination of
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3 195 wound size and percentage wound tissue quality was also performed by central, blinded outcome assessors based
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5 196 on the wound photographs using the Wound Healing Analyzing Tool (W.H.A.T.).
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9 198 **Procedures**

10 199 Before randomization and start of study treatment all patients underwent one or more of the following no longer
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12 200 than six hours before randomization: amputation, debridement or thorough wound cleansing. Patients received
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14 201 an extensive examination of overall health status, specific diabetes associated disorders, and relevant influence
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16 202 factors on wound healing during screening with an update at the randomization visit. Study therapy was allowed
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18 203 to be started either in-hospital or as outpatient and was intended to be continued in outpatient care whenever
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20 204 possible.
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23 205 In the intervention group commercially available CE-marked NPWT devices of the manufacturers Kinetic
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25 206 Concepts Incorporated (KCI) and Smith & Nephew were used in the discretion of the clinical investigator
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27 207 according to clinical routine and manufacturer's instructions [24]. Recommendations for use can be found on the
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29 208 manufacturers' websites. As part of the European tender for the overall project, the German statutory health
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31 209 insurance funds awarded lots for the provision of the medical products by the respective manufacturers.
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33 210 Germany was divided into 4 supply areas. During the award procedure, Smith & Nephew received 1 lot and KCI
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35 211 3 lots. Thus, devices and consumables of Smith & Nephew were used for the north and northern east region of
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37 212 Germany and for the rest of Germany the therapy systems of KCI were used. Within the study, NPWT was
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39 213 required to be used for wound bed preparation in order to achieve at least 95% granulation of the wound area.
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41 214 After optimal preparation of the wound, complete closure could be achieved either by secondary intention with
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43 215 dressings or by surgical closure with subsequent removal of the suture. Control therapy was defined as any
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45 216 SMWC according to local clinical standards and guidelines [25, 26]. Healthcare providers were obligated to
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47 217 provide patients with best practice. In the control arm it was permitted to apply any local wound treatment
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49 218 standard used in the respective study site that did not have an experimental status or was NPWT. To ensure the
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51 219 best quality of local wound treatment, the study sites were trained for both the intervention arm by the
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53 220 manufacturers and the control arm by the German Society for Wound Healing and Wound Treatment which
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55 221 provided parts of its curriculum and experienced instructors.

56 222 The maximum study treatment time was 16 weeks after randomization. Study visits needed to be performed at
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58 223 week one, three, five, 12 and 16 and included a complete wound examination. Wound closure was possible to be
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60 224 achieved at any time within the study treatment period of 42 days and had to be documented in a wound closure
225 visit as well as in a wound closure confirmation visit after 14 days. Study participants were followed up until 6

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3 226 months after randomization. The initially planned follow-up period of 12 months was reduced to 6 months in the
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5 227 course of the study. The amendment to the study protocol was endorsed by the Ethics Committee and
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7 228 immediately communicated to all participating study sites.
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10 230 **Outcomes**

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12 231 Our primary outcome comprised the two primary effectiveness endpoints wound closure rate and the time until
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14 232 complete wound closure within a maximum study treatment period of 16 weeks. Complete wound closure was
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16 233 defined as 100% epithelialization of the wound, no drainage, no suture material and no need for wound dressing
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18 234 or adjuvants. Wound closure needed to sustain a minimum of 14 days after the first diagnosis and to be
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20 235 confirmed by independent blinded observers using wound photographs. If wound closure was achieved by
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22 236 surgical methods, the endpoint was not reached until the above criteria were met (e.g. only after removal of the
23
24 237 suture). The determination of sufficient wound bed conditioning and the indication for surgical closure was
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26 238 carried out by the treating physician, as in clinical practice. The treating physician was not blinded to treatment
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28 239 allocation. During study planning, the following concomitant diseases and therapeutic measures with a possible
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30 240 influence on the primary study outcome wound closure (confounders) were identified:

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32 241 diabetic neuropathic osteoarthropathy (DNOAP), severity of the foot wound according to Wagner Armstrong
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34 242 peripheral arterial occlusive disease , chronic venous insufficiency (CVI), extreme foot deformities and
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36 243 malpositions, untreated or therapy-refractory inflammation in the wound area, chronic anemia, heel necrosis,
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38 244 lymphedema, infection, heightened glycated hemoglobin (HbA1c) level, dialysis, hyperbaric oxygen (HBO) or
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40 245 normothermal therapy, application of recombinant or autologous growth factors to the study wound, and
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42 246 application of skin or dermal substitutes and with living cells that produce growth factors.

43 247 Secondary outcomes were wound closure rate after six months; time until optimal preparation of the wound bed
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45 248 (a minimum of 95% granulation), amputations and resections, wound size and wound tissue composition, pain
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47 249 and quality of life within 16 weeks; and recurrence within six months. The initial planned secondary endpoint of
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49 250 time until wound closure within 6 months was abandoned during the course of the study. It was found that a
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51 251 time-to-event survey was not possible outside the active study treatment period. This was mostly due to the fact
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53 252 that after this 16-week period weekly study visits were no longer an obligation and further patient care was no
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55 253 longer bound to the study site. Only one follow-up visit was planned and carried out after 6 months, in which
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57 254 wound or healing status and recurrences were documented.

58 255 Minor and major amputations were considered separately, whereas the disarticulation at the midtarsal joint
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60 256 (Chopart's amputation) was considered still to be minor. Wound size and wound tissue composition (percentage

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3 257 of granulation tissue, fibrin and necrosis) were monitored at each study visit. Quality of life (QoL) was measured
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5 258 using the questionnaire Euro Quol 5D (EQ5D) at inclusion, end of the maximum treatment time or end of the
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7 259 therapy and at the six-month follow-up visit. At each study visit participants were asked to provide their
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9 260 assessment of wound-associated pain on a numerical rating scale (0 to 10). The incidence of serious adverse
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11 261 events (SAEs) within six months and the incidence of device-related and wound-related adverse events occurring
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13 262 within 16 weeks or until wound closure confirmation were safety endpoints of this trial.
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16 264 **Statistical analysis**

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18 265 Sample size calculation was performed using the expected difference between wound closure rates in both
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20 266 treatment arms based on information extracted from previously published studies. Armstrong and Lavery
21
22 267 described a rate of complete wound closure in 56% of patients with NPWT and in 39% of patients in the
23
24 268 corresponding control group [16]. Blume showed a rate of complete wound closure in 43% of patients treated
25
26 269 with NPWT and 29% of patients in the control group [17]. We assumed a complete wound closure rate of 45%
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28 270 for NPWT and 30% in the SMWC group, resulting in a minimum difference of 15% after a treatment time of 16
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30 271 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
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32 272 total sample size of 162 patients per group was calculated. The computer program of Dupont and Plummer was
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34 273 used for sample size calculation [27].

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36 274 We performed all analyses based on a modified intention-to-treat (ITT) population that includes all randomized
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38 275 participants who have a valid baseline and at least one valid post baseline wound assessment. As a secondary
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40 276 approach a per-protocol (PP) analysis has been performed excluding patients with any serious protocol
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42 277 deviations, temporary changes from SMWC to NPWT, permanent wound treatment changes or without valid
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44 278 documentation until wound closure confirmation or end of maximum treatment time (EOMT). Safety data are
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46 279 presented on an 'as treated' basis. Subgroup analysis is presented for small vs big wound subpopulations. There
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48 280 was no interim analysis.

49 281 The superiority hypothesis was tested in parallel for wound closure rate and time to wound closure
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51 282 within 16 weeks. Incidence of complete wound closure was analyzed using a chi-squared test (Fisher's exact test)
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53 283 comparing the two treatment arms. Time to complete wound closure was compared between the two treatment
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55 284 arms using a log-rank test. The method of Bonferroni-Holm was used for adjustment of the α -error for parallel
56
57 285 confirmatory testing of both primary endpoints. Missing values have been incorporated as censored values.
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59 286 Covariates thought to influence wound closure were analyzed for their effect on the two primary endpoints.
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287 Covariates were excluded from the analysis if the number of missing values was too high. First, the relevant

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3 288 covariates were tested by means of a univariate analysis with regard to their effect on wound closure rate and
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5 289 time without consideration of the treatment arms. If there was a significant influence, the frequency of
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7 290 occurrence in the treatment arms was analyzed. Secondary, multivariate analyses were performed for both
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9 291 primary endpoints, taking into account treatment assignment and including all relevant covariates. The
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11 292 multivariate analysis of the primary endpoint wound closure rate was performed with binary logistic regression
12
13 293 to describe the influence of the independent covariates (regressors) on the dependent dichotomous variable
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15 294 wound closure. The multivariate analysis of the primary endpoint time to wound closure was performed using a
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17 295 COX regression model.

18 296 Safety and secondary endpoints were analyzed using conventional univariate testing.

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20 297 Within a priori planned subgroup analysis the ITT population was divided into a group of small wounds and a
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22 298 group of big wounds based on the wound surface area documented during the randomization visit. Wounds
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24 299 smaller than or equal to the total median wound surface (483 mm²) were assigned to the subgroup "small
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26 300 wounds". Patients with wound surface areas larger than the median value were assigned to the subgroup "large
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28 301 wounds". Since no citable scientific definition of a large wound was available at the time of study planning and
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30 302 the clinical experts involved could not make a decision, the median of all wounds was chosen as the criterion for
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32 303 the division into the two subgroups. Confirmatory analysis of primary and secondary endpoints was repeated for
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34 304 the subgroups.

35 305 Missing values for the following outcome parameters were replaced using the Last Observation Carried Forward
36
37 306 (LOCF) method: wound closure rate, wound size and wound tissue quality, recurrence and amputation. The
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39 307 outcome parameters time to wound closure and time until optimal preparation of the wound bed did not require
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41 308 data replacement, since missing values are included in the analysis as right-censored values. If the wound closure
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43 309 is not confirmed to be closed after a minimum of 14 days, the wound is considered as an unsustained wound
44
45 310 closure. All missing quality of life values (EQ-5D) were replaced with the overall quality of life assessment
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47 311 (visual analogue scale), if available. If there was no quality of life assessment, there was no replacement. For
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49 312 missing values of the demographic and baseline characteristics, which are necessary for the estimation of the
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51 313 regression coefficients, no replacement was performed. IBM SPSS Statistics (version 23) was used for all
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53 314 analyses.

54 315 This study is registered with ClinicalTrials.gov number NCT01480362 and in the German Clinical Trial
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56 316 Registry, number DRKS00003347.

57 317 A data monitoring committee was formed to oversee overall study performance and safety.

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3 **319 Role of the funding source**

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5 320 Through a European tender the study was initiated by a consortium of 19 statutory German health insurance
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7 321 funds, which provided integrated care contracts for all study participants and for up to 7000 patients with acute
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9 322 and chronic wounds in Germany; defined basic rules for study design based on the requirements of the German
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11 323 authorities; and provided a critical review of the study protocol and the final report. The study was funded by the
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13 324 manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the
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15 325 NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary
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17 326 support and information about the used material. The manufacturers had no role in study design, data collection,
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19 327 data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including
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21 328 statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

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3 **330 Results**

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5 331 Between Dec 23, 2011 and August 12, 2014 386 patients were enrolled and randomly assigned to receive NPWT
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7 332 (181) or SMWC (187) in the DiaFu-study (**Error! Reference source not found.**) in overall 40 study sites, which
8
9 333 recruited minimum 1 patient and maximum 76 patients. A full list of investigator can be found in the appendix.
10
11 334 13 clinical investigators randomized more than 10 patients. 23 study sites enrolled only between 1 and 4 patients.
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13 335 Most of these study sites refused further study participation due lack of time and staff for adequately performing
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15 336 the documentation. In the further course of the trial research nurses have been hired by the independent scientific
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17 337 institute overseeing the trial in order to support the documentation in the study sites whenever needed.
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19 338 Baseline characteristics of the patients in the NPWT-and the SMWC-arm are similar in the ITT population
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21 339 (**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%)	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)	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]

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

343

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

345

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%)

346 Table 2: The table shows the baseline of the identified factors possibly influencing wound closure in the ITT- population.
 347 Findings, diagnoses and procedures documented by the investigators are presented. Data are N (%), Mean (SD), and
 348 Minimum – Maximum [Min – Max].
 349

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 (%).

350

351 Results for the primary outcomes in the ITT population

352 In the ITT population, the overall number of patients with wounds closed within 16 weeks was 46 of 345
 353 (13·3%). Wound closure rate was higher in the NPWT arm (14·6%) than in the SMWC arm (12·1%) but this
 354 was not significant (p 0·53) as the difference in healing rate between the two groups was only four patients
 355 (2·5%) (Table 4). Wounds treated with NPWT were approximately at the same risk of remaining open like
 356 patients receiving SMWC (RR 0·97 [95% CI: 0·89-1·06]).

357

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.

358

359 Beginning in week five the number of study patients with open wounds in the NPWT-arm was lower than in the
 360 SMWC-arm (Figure 2). There is no significant difference in the wound healing time between the two treatment
 361 arms (p = 0·244, Log Rank Test). Since the cumulative number of patients with open wounds was more than
 362 70% after 16 weeks, we were not able to calculate medians for time to wound closure.

363

364 Results for the secondary outcomes in the ITT population

365 After 6 months the wound closure rate was higher in the SMWC- than in the NPWT-arm (36 of 174 [20·7 %] vs
 366 24 of 171 [14· 0 %]), but the difference was not significant (p 0·12).

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372 The time until optimal preparation of the wound for further treatment to achieve a complete epithelization (min
373 95 % granulation tissue) was significantly shorter for patients treated with NPWT (p 0·021) (Table 5).

374

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	

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

379

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

390

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

397

398 No recurrences occurred during the study treatment time of 16 weeks. Between the end of the maximum study
 399 treatment time and the follow up at 6 months, 11 recurrences (6.4 %) occurred in the 171 patients in the NPWT
 400 arm. One patient had two recurrences. In the SMWC arm, five of 174 patients (2.9 %) had a recurrence. The
 401 difference is not significant (RR 2.24 [95%CI: 0.80-6.31]; (p 0.131)). , but the overall number of 17 recurrences
 402 in 16 patients was very low.

403
 404 A total of 102 amputations or resections were performed in 71 patients (table 6). There were 45 amputations in
 405 35 (20.5%) patients in the NPWT arm and 57 amputations in 36 (20.7 %) patients in the control arm. There is no
 406 significant difference in the number of patients with amputation or resection (p 1.00) or the overall number of
 407 performed interventions (p 0.89) between NPWT and SMWC arm. Patients treated with NPWT were
 408 approximately at the same risk of undergoing an amputation or resection like patients treated with SMWC (RR:
 409 0.99 [95%CI: 0.65-1.50]). A total of 69 patients (20 %) underwent a minor amputation (NPWT 33 [19.3 %]
 410 SMWC 36 [20.7 %], p 0.79). Two patients in the NPWT arm and no patient of the SMWC arm underwent a
 411 major amputation (p 0.25).

412

	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)

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2
3 413 Table 6: The table shows the number of study participants with amputations / resections and the number of amputations /
4 414 resections performed for the ITT-population. Data show the number (N) of participants, the percentage with the 95%
5 415 Confidence Interval (95%CI), or the number of events accompanied with the respective percentage values in total and for
6 416 both treatment arms. F = Fisher's Exact Test; U = Mann-Whitney U-Test.
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12 418 Overall, pain levels were very low and decreased further during the study treatment time. The values hardly
13 419 differ between the treatment arms at any observation time point. A table with pain levels can be found in the
14 420 appendix.
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19 422 At baseline Quality of life (EQ5D) had significant limitations in both treatment arms. Patients reaching the end
20 423 of treatment within 16 weeks showed improved EQ5D levels in the NPWT arm and in the SMWC arm. Similar
21 424 results have been found for patients who reached the end of the maximum treatment time without successful end
22 425 of therapy. At the follow-up time after 6-months all patients still show increased EQ5D levels in both treatment
23 426 arms. A table with detailed results for the EQ5D is provided in the appendix.
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31 428 Safety results

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33 429 269 adverse events (AE) (NPWT 167; SMWC 102) occurred during the active study treatment period of 112
34 430 days. For 96 (56· 1%) patients in the NPWT group and 72 patients (41· 4%) in the SMWC group at least one
35 431 adverse event has been documented (p 0·007) but only 16 (10· 2%) of the AEs in the NPWT group were decided
36 432 by the investigators to have a definite relation to the medical device. A total of 163 AEs occurring within the
37 433 study observation period of 6 months were classified as serious adverse events (SAE) in the opinion of the
38 434 investigators (NPWT 87, SMWC 76). In the NPWT arm, 63 patients (36·8 %) had at least one documented SAE.
39 435 45 patients had one and 18 patients had two or more SAEs. In the SMWC arm, 58 patients (33·3%) had a
40 436 minimum of one SAE (45 patients with one SAE; 13 patients with two or more SAEs). The difference between
41 437 the treatment arms was not significant (p 0·50). None of the SAEs in the NWPT group were documented as
42 438 definitely or possibly related to the medical device by investigators. In one case in the SMWC group the
43 439 investigator documented a definite relationship between the SAE and SMWC. In one case the investigator
44 440 documented a possible relationship to SMWC in the NPWT group. Table 7 gives a detailed overview on the AEs
45 441 documented within the study treatment time of 112 days.
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Adverse Events (AE)	NPWT	SMWC
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N=269	N=167	N=102
Day of occurrence (N)	167	102
Mean (SD)	37.5 (28.6)	42.7 (29.2)
Median (IQR)	30.0 (40.0)	38.0 (50.0)
Duration in days (N)	157	97
Mean (SD)	19.7 (29.0)	25.3 (38.6)
Median (IQR)	10.0 (20.0)	13.0 (22.0)
Severity (N)	161	102
Mild	64 (39.8%)	24 (23.5%)
Moderate	54 (33.5%)	38 (37.3%)
Severe	43 (26.7%)	40 (39.2%)
AE expected / unexpected (N)	159	100
Expected	52 (32.7%)	27 (27.0%)
Unexpected	107 (67.3%)	73 (73.0%)
Relationship to the medical device (N)	157	100
Yes	16 (10.2%)	0 (0%)
Possible	11 (7.0%)	2 (2.0%)*
No	117 (74.5%)	94 (94.0%)
Not assessable	13 (8.3%)	4 (4.0%)
* No treatment change to NPWT has been documented.		
Relationship to SMWC (N)	110	75
Yes	0 (0%)	2 (2.7%)
Possible	5 (4.5%)	0 (0%)
No	96 (87.3%)	67 (89.3%)
Not assessable	9 (8.2%)	6 (8.0%)
Relationship to treatment procedure (N)	148	96
Yes	6 (4.1%)	4 (4.2%)
Possible	15 (10.1%)	2 (2.1%)
No	111 (75.0%)	80 (83.3%)
Not assessable	16 (10.8%)	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%)

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

445

446 Secondary analyses and subgroups

447 The univariate analysis of predefined covariates potentially influencing wound closure in the ITT population
448 showed that only the presence of an infection at the time of randomization was significantly associated with both
449 the wound closure rate and time. The influencing factor "infection" was almost equally represented in both
450 treatment arms (NPWT 35.1 [27.9 – 42.2] % N=60; SCWT 32.8 [25.8 – 39.7] % N= 57), so the treatment
451 comparison was not influenced by this confounder. Of the a priori defined factors potentially influencing wound
452 closure nine factors needed to be excluded because the number of missing values was too high or they were
453 never documented by the investigators. The covariate peripheral arterial occlusive disease had significant
454 influence on the time until wound closure (p 0.026) and infection had a significant influence on the wound
455 healing rate (p 0.012). However, both influencing factors were almost evenly distributed over both study arms
456 by randomization. Thus the group comparison has not been influenced by these confounders.

457 In the ITT population in 173 study participants the median wound surface area was smaller than 484 mm² and in
458 172 study participants wounds were bigger than 484 mm². In the NPWT arm 48.5% (N=83) of patients had
459 small wounds and 51.5% (N=88) of patients had large wounds. The SMWC arm had 51.7% (N=90) small
460 wounds and 48.3% (N=84) big wounds. The differences between the treatment arms were not significant.

461 An overview of the measures for small and big wounds and detailed results for this subgroup analysis can be
462 found in the appendix. In the subgroup of big wounds, wound closure rate was significantly higher in the NPWT
463 arm within 16 weeks (p 0.08). Patients with big wounds have a lower risk of not achieving wound closure within
464 16 weeks when treated with NPWT (RR 0.91 [95%CI: 0.82-1.0]). In the subgroup of big wounds a significantly
465 faster wound closure was achieved in the NPWT arm (p 0.027) (Figure 3). Time until complete, sustained and
466 verified wound closure was not significantly different between the treatment arms in the subgroup of small
467 wounds (Figure 4).

468 In the subgroup of small wounds the time to reach 95 % granulation tissue was significantly shorter for the
469 patients treated with NPWT (p 0.005). Time until optimal wound bed preparation was shorter in the NPWT arm
470 in the subgroup of big wounds, but did not significantly differ to the result of the SMWC arm (p 0.27). There are
471 no relevant or significant differences in the overall number of patients with amputation or resection between the

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3 472 treatment arms in both subgroups. Both major amputations were performed in patients with big wounds treated
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5 473 with NPWT. Due to the low overall number of recurrences (N=16) we were not able to perform a subgroup
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7 474 analysis for this outcome parameter.
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11 476 Results for the primary and secondary outcomes in the PP population

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13 477 In the PP-population patients treated with NPWT showed a 14.5 % higher wound closure rate within 16 weeks
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15 478 than patients treated with SMWC (Appendix), but the difference was not significant (p 0.053). Wounds treated
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17 479 with NPWT had a lower risk of remaining open after 16 weeks (RR 0.82 [95%CI: 0.66-1.03]) than wounds
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19 480 treated with SMWC. Time to wound closure in the NPWT arm was significantly shorter (p=0.004) (Figure 5).
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21 481 After 6 months, wound closure rate in the SMWC-arm was higher than in the NPWT-arm, but the difference was
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23 482 not significant (p 0.84). As in the ITT population, optimal wound bed preparation was achieved significantly
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25 483 faster in patients receiving NPWT (p<0.001). Patients receiving NPWT had a higher risk of recurrence than
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27 484 those in the control group (RR 1.50 [95%CI: 0.37-6.01]), however there was no significant difference between
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29 485 the treatment arms regarding the total number of recurrences (p 0.38) or the number of patients with recurrences
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31 486 (p 0.69). 9 patients in the NPWT group and 21 (21.4%) patients in the SMWC group had an amputation or
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33 487 resection (NPWT RR 1.07 [95%CI: 0.53-2.15]). Neither the number of patients with amputations or resections
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35 488 (NPWT 9 (20.5%) SMWC 21 (21.4%) p 0.83) nor the number of amputations or resections performed (NPWT
36
37 489 11 SMWC 28 p 0.86) differ significantly between the treatment arms. No major amputations were performed in
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39 490 the PP population. In the PP-population wound surface area started at smaller baseline levels and decreased
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41 491 faster than in the ITT-population whereas the measures were smaller in the NPWT arm than in the SMWC arm.
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43 492 Wound volume started higher in the NPWT arm and ended at similar levels for the treatment arms after
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45 493 decreasing continuously during the treatment period. This effect was stronger in the SMWC arm. Wound volume
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47 494 measures were lower in the PP-population than in the ITT-population. Wound tissues had a similar course over
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49 495 time like in the ITT population but showed higher values for granulation as well as lower values for fibrin and
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51 496 necrosis in the PP population. Like in the ITT population, pain levels were very low, showing no relevant
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53 497 difference between the treatment arms, and further decreased during the study treatment period. In the PP-
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55 498 population EQ5D values are higher than in the ITT population during screening, but still show that all patients
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57 499 have significant problems. In the NPWT arm QoL measures are similar to those of the SMWC arm for patients
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59 500 reaching end of maximum treatment time before end of therapy. EQ5D shows higher values for patients reaching
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501 the end of therapy during the study treatment time of 16 weeks. Detailed results for the PP population can be
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found in the appendix.

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504 Additional results on treatment compliance and documentation quality

505 29 (17·0%) patients in the NPWT group had a temporary therapy change to SMWC (mean duration 20·5 ± 21·6
506 days). In the SMWC group, 17 (9·8%) patients had a temporary therapy change to NPWT (mean duration 28·9 ±
507 21·6 days). For only 2 of the 29 NPWT patients (6·9%) with a temporary therapy change to SMWC the wound
508 closure was achieved within 16 weeks, whereas 16·2% (23 von 142) of the wounds of the NPWT patients
509 without therapy change were completely closed.

510 A total of 57·3% (98 of 171) of the patients randomized to NPWT completed treatment before achieving a
511 granulation surface of the wound of at least 95%. Fewer patients with this premature end of NPWT (4·7%, N=8)
512 achieved a complete wound closure than patients with no premature end of therapy (9·9, N=17). Mean NPWT-
513 duration until premature end of therapy was 28·5 days (SD 24·1), while a mean granulation area of 59·6% (SD
514 30·5) was achieved.

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

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

527 Discussion

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

546 The DiaFu-study was designed to evaluate effectiveness and safety of NPWT for chronic diabetic foot wounds in
547 real-life clinical practice while avoiding any bias that have been described by several systematic reviews [18-22].

548 Methods against bias have been implemented whenever possible, but within this study shortcomings in
549 documentation quality and missing compliance to therapy guidelines negatively impact the results.

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

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3 558 Not addressing and analyzing all factors influencing the overall treatment outcome like targeted pressure relief,
4
5 559 infection control and adequate treatment of the underlying disease during the study treatment and observation
6
7 560 period may be seen as a limitation of this health care research study. Study sites have been selected based on a
8
9 561 self-disclosure by means of a qualification checklist and cross checks using quality reports. This ensured that all
10
11 562 prerequisites were met for guideline-compliant patient care. Nevertheless, even in the application of NPWT there
12
13 563 were deviations from the standards. Anyway, questioning the quality of investigators' treatment was not the main
14
15 564 focus of this health services research trial. Evaluating the individual treatment quality within a single RCT is
16
17 565 neither feasible nor effective.

18 566 Other than previous studies the DiaFu-study evaluated the effectiveness of NPWT most closely to real-life using
19
20 567 a patient population as diverse as in clinical practice. The DiaFu-study therefore included patients with chronic
21
22 568 diabetic foot ulcers of neuropathic and angiopathic origin, regardless of whether a simple wound cleansing,
23
24 569 tissue debridement or even amputation was necessary prior to application of wound therapy targeted to achieve
25
26 570 complete wound closure. Thus, results can easier be generalized and applied in routine practice settings, but the
27
28 571 problems of the clinical routine also affect data quality and statements about specific patient groups are not
29
30 572 possible.

31 573 Some of the previous studies did choose granulation tissue formation for primary outcome. Wound bed
32
33 574 preparation and granulation tissue formation are important prerequisites for wound healing, but the selection of a
34
35 575 patient-relevant primary endpoint and the implementation of adequate measures against bias as required by the
36
37 576 German authorities have been a priority during planning. Preparing the wound bed significantly faster with
38
39 577 NPWT is an important result for the therapeutic approach, but is not a proof of effectiveness and cannot serve as
40
41 578 a basis for the benefit assessment of NPWT. Thus, complete wound closure needed to be chosen to be the
42
43 579 primary outcome rather than the evaluation of the functionality within in the purpose of the evaluated medical
44
45 580 device, which is still part of a complex treatment process.

46
47 581 In order to support the decision making process of the German G-BA on general reimbursement of NPWT in
48
49 582 German outpatient care the DiaFu-study was conducted with a population according to the clinical routine
50
51 583 without excluding specific patient groups; with therapy application in the discretion of the attending physician;
52
53 584 and with evaluation of patient relevant outcome. Within this setting we were not able to show a significant
54
55 585 superiority of NPWT for achieving wound closure, but despite all limitations NPWT showed a significant
56
57 586 superiority in optimal wound bed preparation. This indicates that NPWT works according to its intended use and
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59 587 has at least a potential to be a valuable treatment alternative. Anyway, in the complex treatment process of the
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588 diabetic wound a satisfactory rate of wound closure was reached with neither NPWT or with SMWC.

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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.

1
2
3 **604 Ethics approval and consent to participate**

4
5 605 Ethical approval of the main ethical committee (EC): Ethical Committee of the University of Witten-Herdecke,
6
7 606 has been fully granted without any conditions. Due to performing the trial according to § 23b MPG (German
8
9 607 Medical Device Act), participating study sites in Germany only received a consultation for the main clinical
10
11 608 investigator according to professional law by the respective EC. All investigators have been fully approved by
12
13 609 the respective ECs. An evaluation of the study's content by ECs of participating study sites in Germany was not
14
15 610 applicable. All study participants gave written informed consent prior to randomization and any trial related
16
17 611 procedure.

18 612
19
20 **613 Data sharing**

21
22 614 The datasets used and/or analyzed during the current study are available from the corresponding author on
23
24 615 reasonable request. Datasets are available in German language.

25 616
26
27
28 **617 Competing interests**

29
30 618 All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and
31
32 619 declare:

33
34 620 The German statutory health insurance companies commissioned the Witten/Herdecke University (UW/H) to
35
36 621 plan, conduct, analyze and publish the study. Dörthe Seidel is an employee of the UW/H. The study has been
37
38 622 financed by the manufacturers KCI (Acelity) and Smith&Nephew. Dörthe Seidel received a consulting fee for
39
40 623 the presentation of the study during an event organized by the manufacturer Hartmann. During study planning
41
42 624 and conduct Edmund Neugebauer was an employee of the UW/H. He was the director of the IFOM.

43 625 The clinical investigators Martin Storck, Holger Lawall, Gernold Wozniak, Peter Maukner, Dirk Hochlenert,
44
45 626 Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink
46
47 627 received a case fee of 1000 € for each patient included in the DiaFu-study in order to compensate for the
48
49 628 additional organizational and especially the documentation effort during trial conduct. Furthermore all
50
51 629 investigators received compensation for travelling to the investigator meetings. The institutions of the
52
53 630 investigators used integrated care contracts for NPWT during study conduct in order to provide best practice for
54
55 631 the study participants during outpatient care.

56
57 632 Gernold Wozniak and Walter Wetzel-Roth are members of the scientific advisory board of the manufacturer
58
59 633 Kinetic Concepts Incorporated (KCI) (now Acelity).

60 634

635 **Funding**

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

645

646 **Authors' contributions**

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

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

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

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

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

660 All authors approved the final version of the report.

661

662 **Acknowledgements**

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

664 At least one patient was included in the following facilities: HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für
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15 703 GmbH & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim; Institut für Diabetesforschung
16
17 704 Münster GmbH Hohenzollernring 70 48145 Münster.

18 705 The study was initiated by a consortium of 19 statutory German health insurance funds represented by the AOK
19
20 706 federal association (AOK-Bundesverband – AOK-BV), the association of alternative health insurance funds
21
22 707 (Verband der Ersatzkrankenkassen – vdek) and the minors (Knappschaft). In order to guarantee outpatient care
23
24 708 for all study participants without any restrictions, the contracting health insurance companies provided integrated
25
26 709 care contracts for outpatient negative pressure wound therapy.

27
28 710 A project advisory board was implemented to coordinate all processes and project partners. The board comprised
29
30 711 two representatives each from the statutory health insurance funds, the management company and the sponsor as
31
32 712 well as one representative each from the participating medical device manufacturers (KCI and smith & nephew).
33
34 713 Representing the contracting authority (statutory German health insurance funds) Dr. Gerhard Schillinger (AOK-
35
36 714 BV) and Ute Leonhard (vdek) acted as contact persons for all aspects of the project.

37 715 The management company “Gesundheitsforen Leipzig” has been entirely responsible for the logistics of the
38
39 716 study. Central tasks of the management company included the recruitment of study sites and patients, the
40
41 717 development of the IT infrastructure including the documentation, communication and invoicing software as
42
43 718 well as the processing of all payments.

44
45 719 The manufacturers Kinetic Concepts Incorporated (KCI) (Acelity) and smith & nephew provided the NPWT
46
47 720 devices as well as support and training for the investigators and financed the study.

48
49 721 The Private University of Witten/Herdecke gGmbH acted as the Sponsor of the trial and the Institute for
50
51 722 Research in Operative Medicine with its former director Prof. E.A.M. Neugebauer, the current interim head Prof.
52
53 723 Rolf Lefering and the head of the division for clinical research Dörthe Seidel was responsible for the scientific
54
55 724 conception, the evaluation as well as the reporting and publication of the study. Prof. Dr. Rolf Lefering was
56
57 725 responsible for the statistical planning and analysis. PD Dr. Peter Krüger was responsible for the data
58
59 726 management of the study. Special thanks are going to Stefan Bauer, who supported the data management as well
60
727 as the statistical analysis and reporting.

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

For peer review only

1
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3 730 **List of figures:**
4

5 731 Figure 1: Trial profile (CONSORT)
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7 732 Figure 2: Time until complete, sustained and verified wound closure in the ITT-population
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9 733 Figure 3: Time until complete, sustained and verified wound closure for the subgroup of big wounds
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11 734 Figure 4: Time until complete, sustained and verified wound closure for the subgroup of small wounds
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13 735 Figure 5: Time until complete, sustained and verified wound closure in the PP-population
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Figure 1: Trial profile (CONSORT)

190x275mm (96 x 96 DPI)

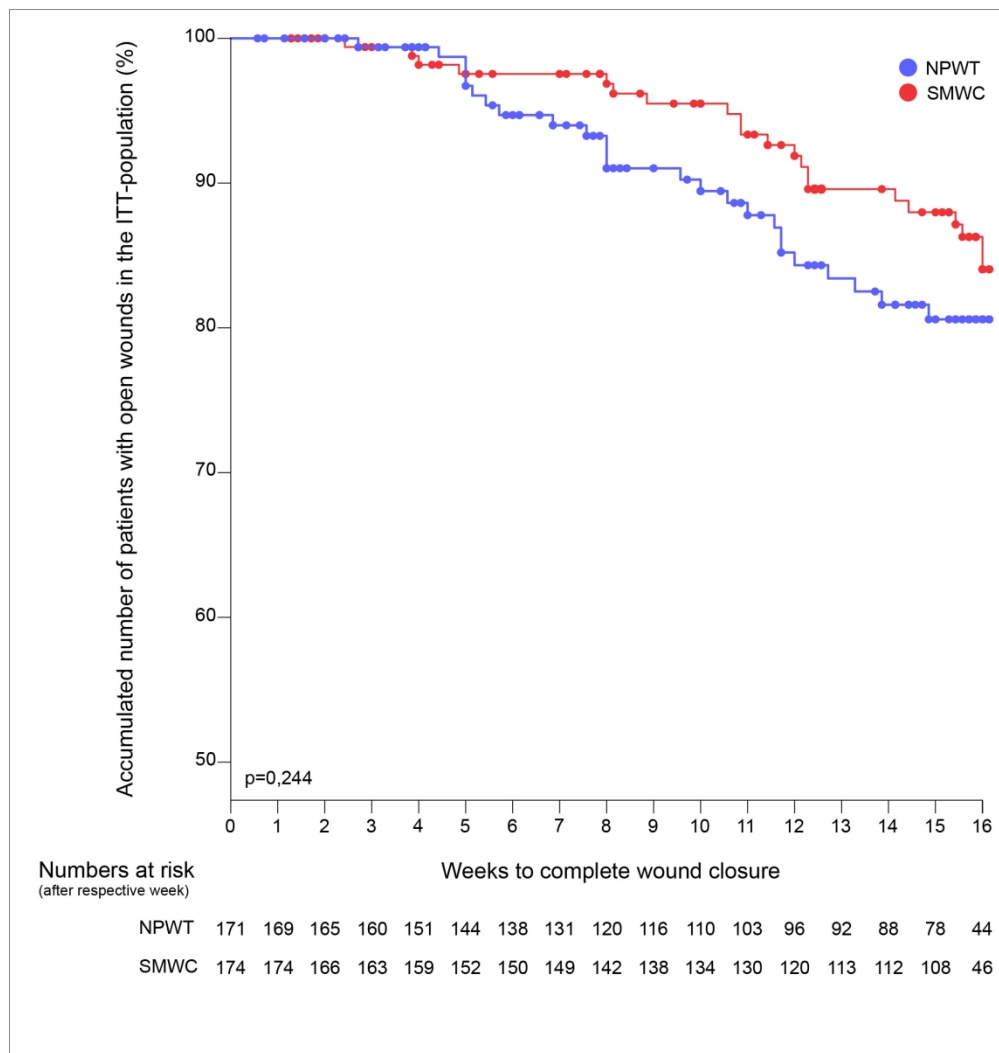


Figure 2: Time to wound closure in the ITT-population

189x198mm (300 x 300 DPI)

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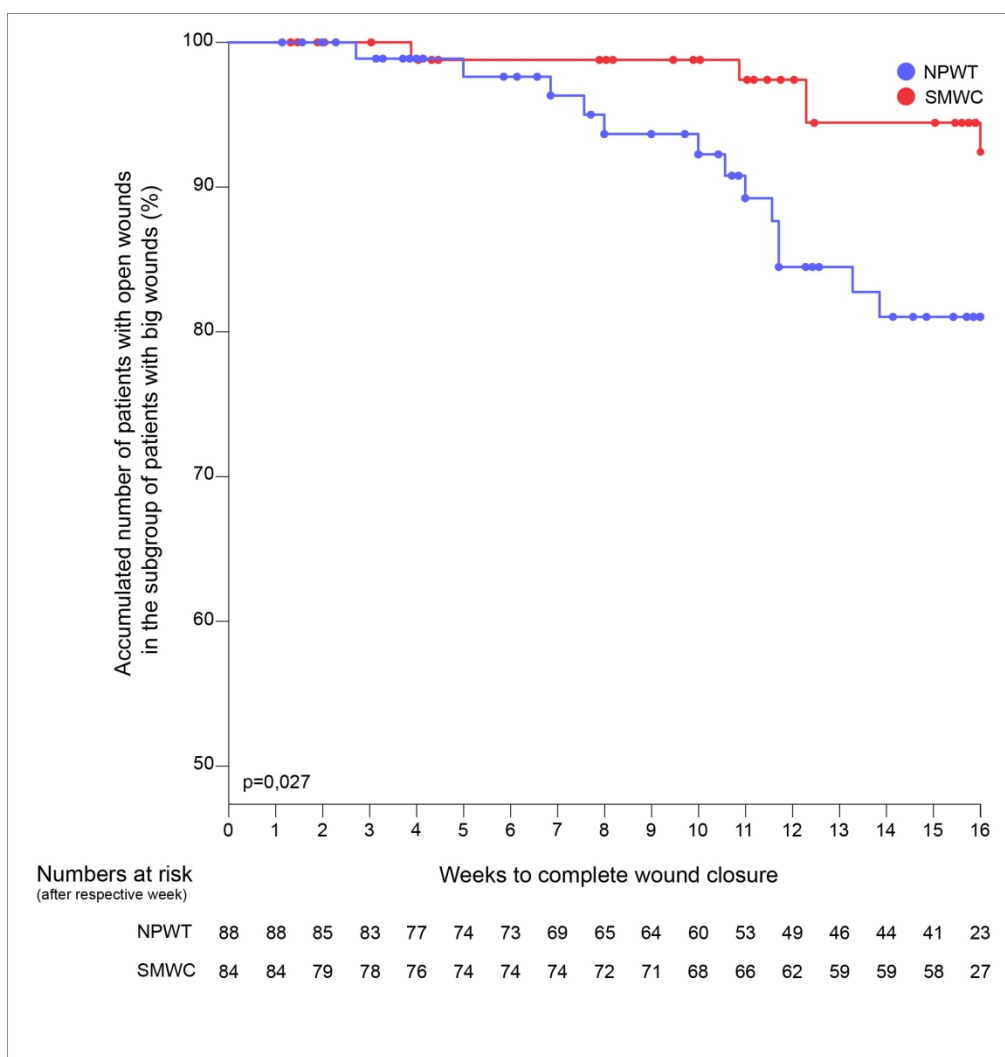


Figure 3: Time to wound closure in the subgroup of big wounds

189x198mm (300 x 300 DPI)

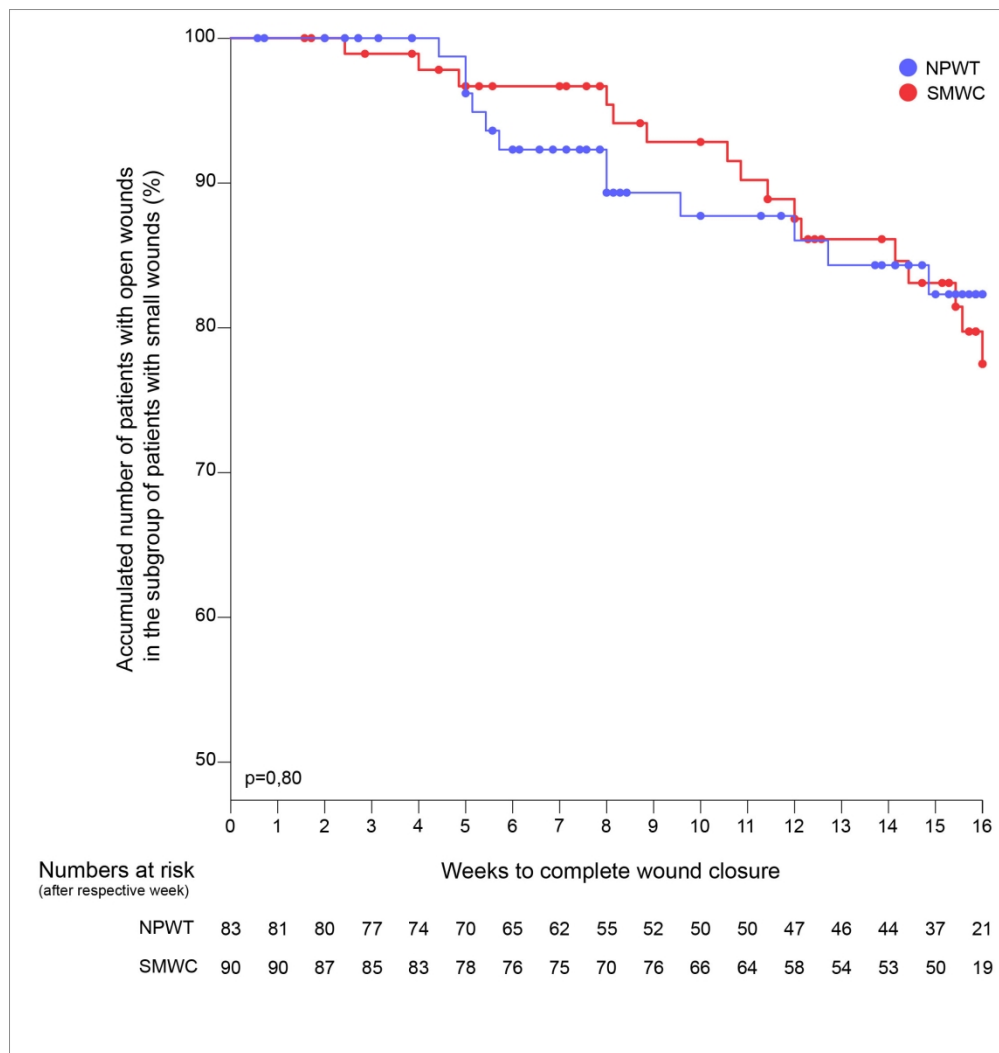


Figure 4: Time to wound closure in the subgroup of small wounds

189x198mm (300 x 300 DPI)

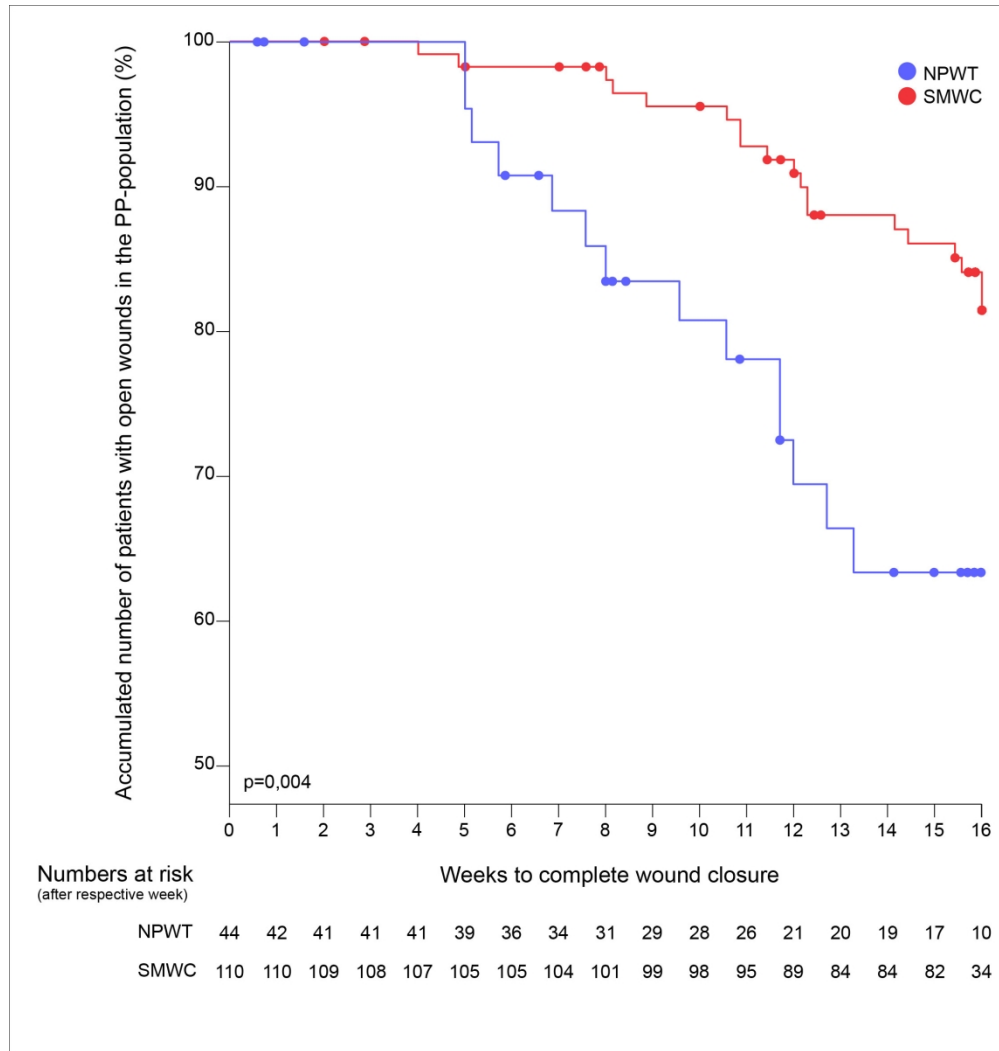


Figure 5: Time to wound closure in the PP-population

189x198mm (300 x 300 DPI)

Supplementary Appendix

Table of contents:

- List of investigators
- Supplementary discussion
- Supplementary tables

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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	N=154	N=44	N=110
Mean (SD)	67.4 (10.6)	66.5 (11.0)	67.8 (10.4)
Height in cm	N=153	N=43	N=110
Mean (SD)	173.8 (12.9)	173.5 (17.4)	174.0 (10.7)
Weight in kg	N=150	N=42	N=108
Mean (SD)	95.4 (23.3)	96.2 (21.6)	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.

Observation time point	Wound surface NPWT		Wound surface SMWC	
	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)	457 (742)	570 (940)	493 (950)
	165 (964)	134 (494)	169 (632)	133 (498)
	N=171 (110)	N=118 (88)	N=174 (124)	N=129 (104)
Week 16	440 (810)	334 (649)	493 (1095)	351 (750)
	79 (471)	114 (363)	69 (415)	77 (320)
	N=171 (80)	N=118 (66)	N=174 (63)	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) $[(\pi / 4) \times \text{length} \times \text{width} = \text{area}]$. 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)	21740 (74181)
	4710 (15048)	4759 (12888)
	N=171 (2)	N=174 (0)
Week 1	13203 (28709)	19979 (73143)
	2487 (6908)	3533 (11407)
	N=171 (15)	N=174 (26)
Week 3	10708 (28521)	16217 (67494)
	1884 (6857)	2293 (8831)
	N=171 (24)	N=174 (23)
Week 5	7700 (19719)	11286 (32566)
	1166 (5338)	1365 (7539)
	N=171 (37)	N=174 (42)
Week 8	5592 (11535)	8772 (27674)
	785 (4604)	812 (5258)
	N=171 (78)	N=174 (67)
Week 12	5333 (12422)	6639 (16454)
	565 (3913)	625 (4083)
	N=171 (119)	N=174 (133)
Week 16	3880 (10534)	5465 (14874)
	141 (1890)	200 (1587)
	N=171 (83)	N=174 (64)

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3 Table S3: Wound volume at each observation time point during the study treatment time of maximum 16 weeks in the ITT-
4 population. Wound volume (length x width x depth) was calculated from width, length and depth as documented in the
5 eCRF. Data show mean (SD) and median (IQR) as well the number (N) of values analyzed for the ITT population (number
6 (N) of values substituted by the last observation carried forward (LOCF) method).
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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)	22 (25)	21 (28)	71 (27)	3 (10)	7 (15)	34 (37)	24 (26)	22 (29)	69 (28)	2 (9)	7 (14)
	20 (70)	12 (37)	10 (30)	79 (46)	0 (0)	0 (5)	20 (71)	14 (39)	10 (40)	79 (44)	0 (0)	0 (8)
	171 (2)	118 (8)	170 (4)	118 (8)	169 (5)	118 (8)	174 (3)	129 (12)	174 (1)	129 (12)	172 (2)	129 (12)
Week 1	58 (35)	21 (25)	19 (22)	73 (27)	5 (13)	6 (12)	49 (35)	21 (25)	24 (27)	74 (26)	6 (15)	5 (9)
	70 (70)	10 (36)	10 (30)	81 (47)	0 (2)	0 (5)	50 (70)	10 (36)	15 (31)	85 (40)	0 (5)	0 (5)
	171 (16)	118 (32)	71 (19)	118 (32)	169 (23)	118 (32)	174 (28)	129 (36)	174 (27)	129 (36)	172 (30)	129 (36)
Week 3	67 (31)	16 (23)	18 (22)	80 (25)	5 (13)	4 (11)	57 (32)	21 (25)	25 (26)	77 (25)	5 (13)	3 (7)
	80 (55)	5 (25)	10 (30)	91 (30)	0 (0)	0 (1)	60 (60)	10 (36)	20 (35)	85 (36)	0 (3)	0 (1)
	171 (26)	118 (27)	171 (30)	118 (27)	169 (28)	118 (27)	174 (24)	129 (35)	174 (25)	129 (35)	172 (30)	129 (35)
Week 5	70 (30)	15 (22)	18 (24)	83 (22)	4 (13)	2 (8)	62 (31)	18 (26)	23 (25)	80 (26)	4 (12)	3 (10)
	80 (45)	6 (21)	10 (25)	91 (26)	0 (0)	0 (1)	63 (50)	4 (32)	10 (39)	93 834	0 (0)	0 (0)
	171 (36)	118 (43)	171 (38)	118 (43)	169 (42)	118 (43)	174 (44)	129 (36)	174 (47)	129 (36)	172 (46)	129 (36)
Week 8	74 (30)	16 (23)	17 (24)	82 (24)	4 (13)	2 (6)	70 (29)	17 (24)	17 (21)	80 (25)	5 (13)	3 (11)
	90 (40)	4 (27)	10 (20)	93 (33)	0 (0)	0 (0)	80 (40)	3 (33)	10 (20)	92 (36)	0 (0)	0 (0)
	171 (53)	118 (48)	171 (56)	118 (48)	171 (59)	118 (48)	174 (44)	129 (43)	174 (49)	129 (43)	174 (52)	129 (43)
Week 12	75 (30)	15 (23)	17 (25)	83 (24)	4 (13)	1 (5)	73 (29)	16 (23)	16 (20)	82 (23)	5 (13)	2 (6)
	90 (40)	4 (22)	5 (20)	96 (23)	0 (0)	0 (0)	80 (38)	3 (29)	10 (20)	93 (32)	0 (0)	0 (0)
	171(115)	118 (89)	171(118)	118 (89)	171(119)	118 (89)	174(124)	129(102)	174(125)	129(102)	172(126)	129(102)
Week 16	77 (30)	13 (22)	14 (22)	86 (24)	3 (10)	1 (6)	76 (30)	17 (24)	15 (24)	81 (24)	3 (13)	2 (6)
	90 (40)	1 (17)	2 (20)	98 (19)	0 (0)	0 (0)	90 (40)	4 (31)	5 (20)	93 (35)	0 (0)	0 (0)
	171 (78)	118 (66)	171 (79)	118 (66)	171 (82)	118 (66)	174 (62)	129 (576)	174 (65)	129 (56)	174 (66)	129 (56)

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2 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
3 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
4 (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).
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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)	0,61 (0,25)
	0,66 (0,28)	0,63 (0,24)
	N=63 (2)	N=95 (2)
Follow up after 6 months	0,69 (0,26)	0,67 (0,23)
	0,77 (0,35)	0,63 (0,39)
	N=93 (3)	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 mm ²	Small wounds				Big wounds			
	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	NPWT (N=171)	SMWC (N=174)	p
Small wounds	N=83	N=90	
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	NPWT (N=171)	SMWC (N=174)	P
Big wounds	N=88	N=84	
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 S8: 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	Total	NPWT	SMWC	p
Small wounds	N=173	N=83	N=90	
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	Total	NPWT	SMWC	p
Big wounds	N=172	N=88	N=84	

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.

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

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2 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
3 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
4 population (number (N) of values substituted by the last observation carried forward (LOCF) method).
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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).

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Supplementary Appendix

Table of contents:

- List of investigators
- Supplementary discussion
- Supplementary tables

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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	N=154	N=44	N=110
Mean (SD)	67.4 (10.6)	66.5 (11.0)	67.8 (10.4)
Height in cm	N=153	N=43	N=110
Mean (SD)	173.8 (12.9)	173.5 (17.4)	174.0 (10.7)
Weight in kg	N=150	N=42	N=108
Mean (SD)	95.4 (23.3)	96.2 (21.6)	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.

Observation time point	Wound surface NPWT		Wound surface SMWC	
	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)	457 (742)	570 (940)	493 (950)
	165 (964)	134 (494)	169 (632)	133 (498)
	N=171 (110)	N=118 (88)	N=174 (124)	N=129 (104)
Week 16	440 (810)	334 (649)	493 (1095)	351 (750)
	79 (471)	114 (363)	69 (415)	77 (320)
	N=171 (80)	N=118 (66)	N=174 (63)	N=129 (56)

Table S2: WChange of wound surface area in the course of the study treatment time of maximum 16 weeks at 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) [$(\pi / 4) \times \text{length} \times \text{width} = \text{area}$]. 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)	21740 (74181)
	4710 (15048)	4759 (12888)
	N=171 (2)	N=174 (0)
Week 1	13203 (28709)	19979 (73143)
	2487 (6908)	3533 (11407)
	N=171 (15)	N=174 (26)
Week 3	10708 (28521)	16217 (67494)
	1884 (6857)	2293 (8831)
	N=171 (24)	N=174 (23)
Week 5	7700 (19719)	11286 (32566)
	1166 (5338)	1365 (7539)
	N=171 (37)	N=174 (42)
Week 8	5592 (11535)	8772 (27674)
	785 (4604)	812 (5258)
	N=171 (78)	N=174 (67)
Week 12	5333 (12422)	6639 (16454)
	565 (3913)	625 (4083)
	N=171 (119)	N=174 (133)
Week 16	3880 (10534)	5465 (14874)
	141 (1890)	200 (1587)

	N=171 (83)	N=174 (64)
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Table S3: ~~W~~Change of wound volume in the course of at each observation time point during the study treatment time of maximum 16 weeks in the ITT-population. ~~Change of w~~Wound 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).

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

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Table S1: ~~W~~Change of wound tissue composition ~~in the course of at each observation time point during~~ the study treatment time of maximum 16 week in the ITT-population. ~~Change of W~~wound 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).

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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)	0,61 (0,25)
	0,66 (0,28)	0,63 (0,24)
	N=63 (2)	N=95 (2)
Follow up after 6 months	0,69 (0,26)	0,67 (0,23)
	0,77 (0,35)	0,63 (0,39)
	N=93 (3)	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 mm ²	Small wounds				Big wounds			
	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	NPWT (N=171)	SMWC (N=174)	p
Small wounds	N=83	N=90	
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	NPWT (N=171)	SMWC (N=174)	P
Big wounds	N=88	N=84	
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 S8: 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	Total	NPWT	SMWC	p
Small wounds	N=173	N=83	N=90	
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	Total	NPWT	SMWC	p
Big wounds	N=172	N=88	N=84	

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.

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

Table S18: Change of wWound 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 wound 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)

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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).

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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)	0.63 (0.28)
	N=19 (0)	N=73 (2)
Follow up after 6 months	0.75 (0.22)	0.70 (0.23)
	0.78 (0.30)	0.77 (0.34)
	N=26 (0)	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).

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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

1		assessing outcomes) and how	
2	11b	If relevant, description of the similarity of interventions	n.a.
3	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
4		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
5			
6	Results		
7	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and
8	diagram is strongly		were analysed for the primary outcome
9	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons
10	Recruitment	14a	Dates defining the periods of recruitment and follow-up
11		14b	Why the trial ended or was stopped
12	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
13			
14			
15			
16	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was
17			by original assigned groups
18	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its
19	estimation		precision (such as 95% confidence interval)
20		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
21	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing
22			pre-specified from exploratory
23			
24			
25	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
26			
27	Discussion		
28	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
29	Generalisability	21	Generalisability (external validity, applicability) of the trial findings
30	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
31			
32	Other information		
33	Registration	23	Registration number and name of trial registry
34	Protocol	24	Where the full trial protocol can be accessed, if available
35	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders
36			

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39 *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
40 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.
41 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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026345.R2
Article Type:	Original research
Date Submitted by the Author:	07-Nov-2019
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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

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3 1 **Negative Pressure Wound Therapy compared with standard moist wound care on**
4 **diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT**

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1
2
3 **37 Abstract**

4
5 **38 Objectives**

6
7 39 The aim of the DiaFu-study was to evaluate effectiveness and safety of negative pressure wound therapy (NPWT)
8 40 in patients with diabetic foot wounds in clinical practice.

9
10 **41 Design**

11
12 42 In this controlled clinical superiority trial with blinded outcome assessment patients were randomized in a 1:1 ratio
13 43 stratified by study site and ulcer severity grade using a web-based-tool.

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15 **44 Setting**

16
17 45 This German-national study was conducted in 40 surgical and internal medicine in- and outpatient facilities
18 46 specialized in diabetes foot care.

19
20 **47 Participants**

21
22 48 368 patients were randomized and 345 participants were included in the modified ITT population. Adult patients
23 49 suffering from a diabetic foot ulcer at least for 4 weeks and without contraindication for NPWT were allowed to
24 50 be included.

25
26 **51 Interventions**

27
28 52 NPWT was compared with standard moist wound care (SMWC) according to local standards and guidelines.

29
30 **53 Primary and secondary outcome measures**

31
32 54 Primary endpoints were wound closure rate and time to closure within 16 weeks. Secondary endpoints were
33 55 wound- and treatment-related adverse events (AEs), amputations, time until optimal wound bed preparation,
34 56 wound size and wound tissue composition, pain, and quality of life within 16 weeks, and recurrences and wound
35 57 closure rate within 6 months.

36
37 **58 Results**

38
39 59 In the ITT population 25 patients in the NPWT-arm (14·6%) and 21 patients in the SMWC-arm (12·1%) achieved
40 60 wound closure ($p=0\cdot53$). Wound closure time was not significantly different between the treatment arms ($p=0\cdot24$).
41 61 96 patients in the NPWT-arm and 72 patients in the SMWC-arm had at least one AE ($p=0\cdot007$), but only 11 AEs
42 62 have been possibly related to NPWT. Documentation deficiencies, premature cessation of NPWT and temporary
43 63 changes of the randomized treatment negatively impacted the outcome wound closure.

44
45 **64 Conclusions**

46
47 65 NPWT was not superior to SMWC in diabetic foot wounds in clinical practice. Overall wound closure rate was
48 66 low. Deviations from guidelines limit the treatment success.

49
50 **67 Trial registration**

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52 68 Clinical Trials.gov: NCT01480362

53
54 **70 Strengths and limitations of this study**

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3 71 • The DiaFu study included patients with diabetic foot ulcers both with peripheral neuropathy and
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5 72 peripheral arterial occlusive disease, which corresponds to the typical mixed patient population in real-
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7 73 life clinical practice and enables a general statement about effectiveness and safety of NPWT in the typical
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9 74 medical care situation.
- 10
11 75 • The study does not provide any information on the effectiveness of NPWT in specific patient groups,
12
13 76 which was not intended and may be seen as a limitation.
- 14
15 77 • In this health services research study hospitals and outpatient facilities were selected by means of a
16
17 78 qualification checklist and clinical investigators were obliged to provide patients with the best clinical
18
19 79 practice in compliance with all relevant guidelines, but there was no active monitoring of the
20
21 80 implementation of these guidelines.
- 22
23 81 • To ensure the best quality of local wound treatment and to achieve optimal baseline conditions, the study
24
25 82 sites were trained for both NPWT and SMWC, but treatment application was at the discretion of the
26
27 83 clinical investigators.
- 28
29 84 • Methods against bias were applied whenever possible, but due to the nature of the compared treatment
30
31 85 methods, a direct blinding of patients and clinical investigators was not possible and blinded outcome
32
33 86 assessment could only be implemented for the endpoints wound closure and wound size development
34
35 87 over time by means of wound photographs.
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37 88

89 **Background**

90 More than 400 million people worldwide suffer from diabetes [1, 2] and about 15% of all these patients will
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92 develop a diabetic foot ulcer (DFU) during their lifetime [3, 4]. Approximately 50-70% of all lower limb
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94 amputations are due to diabetes [4]. DFUs represent complex chronic wounds with a major impact on patients`
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96 morbidity, mortality and quality of life. Beside an optimal diabetes and infection control, pressure relieving
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98 strategies and restoring pulsatile blood flow, effective local wound care is part of the holistic approach necessary
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100 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

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3 101 commercially available product was developed later in the 1990s [9, 10]. Positive effects of NPWT on wound
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5 102 healing have been suggested in various basic studies [10, 11]. At the time of planning the DiaFu-study, the clinical
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7 103 evidence largely consisted of clinician perception, case reports and series, small cohort studies, and weakly-
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9 104 powered or low-quality randomized trials that documented broad use of NPWT in various clinical settings and
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11 105 constituted a substantial number of publications but an overall small amount of evidence [12-15]. Two randomized
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13 106 controlled trials (RCTs) performed by Armstrong 2005 [16] and Blume 2008 [17] provided a solid basis for
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15 107 planning a study.

16 108 In the recent years, a specific review for the use of NPWT in diabetic foot wounds performed by Dumville et al in
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18 109 2013 [18], an assessment in the home setting by Rhee et al. in 2014 [19] and a health technology assessment
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20 110 particularly issued for the evaluation of NPWT for managing diabetic foot ulcers [20] in 2014, as well as the most
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22 111 recent work of Liu et al in 2017 [21, 22] all concluded that although NPWT may have a positive effect, the trials
23
24 112 that have been performed have methodological flaws and sufficient, unbiased evidence of whether wounds heal
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26 113 better or worse with NPWT than with conventional treatment is still missing.

27
28 114 In Germany, the issue of evidence for efficacy and safety of NPWT in acute and chronic wounds was first
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30 115 addressed in 2002 when the German Federal Joint Committee (German: Gemeinsamer Bundesausschuss [G-BA])
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32 116 needed to decide whether NPWT could be reimbursed without restrictions in outpatient care.

33
34 117 Finally, in 2007 taking into account all available evidence the G-BA decided that the benefits of the treatment
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36 118 method NPWT should be evaluated in a so-called model project. This included the conduct of clinical studies for
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38 119 which the G-BA defined basic requirements. This essentially concerned the formulation of a study hypothesis that
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40 120 supports G-BA's overall question if NPWT can be reimbursed in German outpatient care without any limitation;
41
42 121 the selection of a comparator that represents the current treatment standard in Germany; and implementation of all
43
44 122 measures to ensure a sufficient certainty of the results.

45 123 Following the announcement of the G-BA, the German statutory health insurance funds initiated an overall project
46
47 124 through a European tender. The DFU has been chosen to be the representative for chronic wounds in a RCT
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49 125 comparing NPWT and standard moist wound care (SMWC) in clinical practice.

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3 **126 Methods**
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7 **128 Aim of the study**
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9 129 The aim of the DiaFu-study was to evaluate whether the effectiveness and safety of NPWT is superior to SMWC
10 130 in German real-life clinical practice.
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13 131

14 **132 Study Design**
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16 133 The DiaFu-study was a German-national, multicenter, randomized controlled clinical superiority trial with blinded
17 134 assessment of wound closure, wound size and wound tissue qualities using photographs. This German national
18 135 study was conducted both in hospital departments and outpatient facilities with a special qualification for diabetic
19 136 foot care. Study treatment was allowed to be started both in in- and outpatient care and should be continued
20 137 outpatient whenever possible. Ethical approval of the Lead Ethical Committee of the University of
21 138 Witten/Herdecke has been fully granted without any conditions. More detailed information on the study design
22 139 can be found in the study protocol publication that is available open access [23].
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31 **141 Patient and Public Involvement**
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33 142 Patients were not involved in the design, recruitment or conduct of the study. The results of this study will not be
34 143 disseminated directly to study participants.
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38 **145 Participants**
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40 146 Following a pragmatic approach with the aim to include a patient population best representing real-life clinical
41 147 practice, in- and exclusion criteria have been selected based on manufacturers' contraindications and FDA
42 148 warnings, the necessity to excluded patients in need of protection and who are unable to give their consent, and
43 149 the intention to avoid general study-related influences on the results.
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47 150 Adult patients (age >18 years) with at least 4-week-old chronic diabetic foot ulcers corresponding to Wagner 2 to
48 151 4 were screened for study participation by the local investigators. Before inclusion, the study protocol required
49 152 either a debridement or, if necessary, an amputation of foot parts, or at least a thorough wound cleansing, depending
50 153 on the individual needs of the patients, in order to achieve the optimal outcome of wound treatment. Thus, chronic
51 154 diabetic foot wounds after adequate wound pretreatment as well as post-surgical amputation wounds below the
52 155 upper ankle joint were eligible for inclusion. The initially planned minimum ulcer age of 6 weeks was reduced to
53 156 4 weeks during the course of the study. Patients estimated to be at risk of non-compliance with study requirements,
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3 157 with wounds with necrotic tissue present that could not be removed by debridement or amputation, with exposed
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5 158 blood vessels within or directly surrounding the wound not possible to be sufficiently covered or with an increased
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7 159 risk of bleeding with hemodynamic consequences (mainly relevant for posterior tibial artery
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9 160 dorsalis pedis artery), and outpatients receiving anticoagulation therapy or suffering from a high-grade impaired
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11 161 clotting function with a heightened risk of bleeding with hemodynamic consequences were excluded from the
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13 162 DiaFu-study. The use of NPWT devices on the study wound within six weeks prior to study start represented an
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15 163 exclusion criterion in order to demonstrate a clear therapeutic effect of each treatment arm.

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17 164 Written informed consent was obtained from every participant after being informed about all aspects of the trial
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19 165 and before randomization and any trial-related procedure. As the statutory health insurance funds provided
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21 166 integrated care contracts for outpatient NPWT, it was only possible to include patients in the study who were
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23 167 members of a participating health insurance fund.

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25 168 Basic data were collected for all patients considered for study participation during screening and have been updated
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27 169 during the randomization visit. Study sites have been selected based on their qualifications and experiences using
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29 170 a pre-study qualification checklist and annual quality reports of the respective institution (if available).

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31 172 **Randomization and masking**

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33 173 Patients were randomly allocated to the treatment arms in a 1:1 ratio using a computer-generated list located on a
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35 174 centralized web-based tool. The randomization list consisted of permuted blocks of variable length (4, 6) which
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37 175 were randomly arranged. Patients were stratified by study site and by Wagner-Armstrong stage within each site
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39 176 (<Wagner-Armstrong stage 2C and \geq Wagner-Armstrong stage 2C). The randomization lists were generated with
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41 177 the help of a self-created Java program and integrated into the study database. Each registered investigator received
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43 178 individual access to the randomization tool via the study website, but without knowledge of future treatment
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45 179 assignment, which provided adequate allocation concealment. The investigators were responsible for adequately
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47 180 implementing the assigned therapy. Due to the physical differences between the treatment regimens it was not
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49 181 possible to blind either participant or physician to the treatment assignment. Verification of complete wound
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51 182 closure was performed by independent, blinded assessment of wound photographs. Determination of wound size
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53 183 and percentage wound tissue quality was also performed by central, blinded outcome assessors based on the wound
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55 184 photographs using the Wound Healing Analyzing Tool (W.H.A.T.). The determination of sufficient wound bed
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57 185 conditioning and the indication for surgical closure was carried out by the treating physician, as in clinical practice.
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59 186 The treating physician was not blinded to treatment allocation.

60 187

188 **Procedures**

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

199 In the intervention arm commercially available CE-marked NPWT devices of the manufacturers Kinetic Concepts
200 Incorporated (KCI) and Smith & Nephew were used in the discretion of the clinical investigator according to
201 clinical routine and manufacturer's instructions [23]. Recommendations for use can be found on the manufacturers'
202 websites. As part of the European tender for the overall project, the German statutory health insurance funds
203 awarded lots for the provision of the medical products by the respective manufacturers. Germany was divided into
204 4 supply areas. During the award procedure, Smith & Nephew received 1 lot and KCI 3 lots. Thus, devices and
205 consumables of Smith & Nephew were used for the north and northern east region of Germany and for the rest of
206 Germany the therapy systems of KCI were used. Within the study, NPWT was required to be used for wound bed
207 preparation in order to achieve at least 95% granulation of the wound area. After optimal preparation of the wound,
208 complete closure could be achieved either by secondary intention with dressings or by surgical closure with
209 subsequent removal of the suture.

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

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

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3 219 visit as well as in a wound closure confirmation visit after 14 days. Study participants were followed up until 6
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5 220 months after randomization. The initially planned follow-up period of 12 months was reduced to 6 months in the
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7 221 course of the study. The amendment to the study protocol was endorsed by the Ethics Committee and immediately
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9 222 communicated to all participating study sites.

10 223

11 224 **Outcomes**

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14 225 The primary outcomes were wound closure rate and the time until complete wound closure within a maximum
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16 226 study treatment period of 16 weeks. Complete wound closure was defined as 100% epithelialization of the wound,
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18 227 no drainage, no suture material and no need for wound dressing or adjuvants. Wound closure needed to sustain a
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20 228 minimum of 14 days after the first diagnosis and to be confirmed by independent blinded observers using wound
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22 229 photographs. If wound closure was achieved by surgical methods, the endpoint was not reached until the above
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24 230 criteria were met (e.g. only after removal of the suture).

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26 231 Secondary outcomes were wound closure rate after six months; time until optimal preparation of the wound bed
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28 232 (a minimum of 95% granulation), amputations and resections, wound size and wound tissue composition, pain and
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30 233 quality of life within 16 weeks; and recurrence within six months. The initial planned secondary endpoint of time
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32 234 until wound closure within 6 months was abandoned during the course of the study. It was found that a time-to-
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34 235 event survey was not possible outside the active study treatment period. This was mostly due to the fact that after
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36 236 this 16-week period weekly study visits were no longer an obligation and further patient care was no longer bound
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38 237 to the study site.

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40 238 Minor and major amputations were considered separately, whereas the disarticulation at the midtarsal joint
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42 239 (Chopart's amputation) was considered still to be minor. Wound size and wound tissue composition (percentage
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44 240 of granulation tissue, fibrin and necrosis) were monitored at each study visit. Quality of life (QoL) was measured
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46 241 using the questionnaire Euro Quol 5D (EQ5D) at inclusion, end of the maximum treatment time or end of the
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48 242 therapy and at the six-month follow-up visit. At each study visit participants were asked to provide their assessment
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50 243 of wound-associated pain on a numerical rating scale (0 to 10). The incidence of serious adverse events (SAEs)
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52 244 within six months and the incidence of device-related and wound-related adverse events occurring within 16 weeks
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54 245 or until wound closure confirmation were safety endpoints of this trial.

55 246

56 247 **Statistical analysis**

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58 248 Sample size calculation was performed using the expected difference between wound closure rates in both
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60 249 treatment arms based on information extracted from previously published studies by Armstrong and Lavery [16]

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3 250 and [17]. We assumed a complete wound closure rate of 45% for NPWT and 30% in the SMWC group, resulting
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5 251 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
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7 252 type two error of $\beta = 0.2$ (corresponding to a power of 80%) a total sample size of 162 patients per group was
8
9 253 calculated. The computer program of Dupont and Plummer was used for sample size calculation [26].

10 254 We performed all analyses based on a modified intention-to-treat (ITT) population that includes all randomized
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12 255 participants who have a valid baseline and at least one valid post baseline wound assessment. As a secondary
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14 256 approach a per-protocol (PP) analysis has been performed excluding patients with any serious protocol deviations,
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16 257 temporary changes from SMWC to NPWT, permanent wound treatment changes or without valid documentation
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18 258 until wound closure confirmation or end of maximum treatment time (EOMT). Safety data are presented on an 'as
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20 259 treated' basis. Subgroup analysis is presented for small vs big wound subpopulations. There was no interim
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22 260 analysis.

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24 261 The superiority hypothesis was tested in parallel for wound closure rate and time to wound closure within 16 weeks.
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26 262 Incidence of complete wound closure was analyzed using a chi-squared test (Fisher's exact test) comparing the
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28 263 two treatment arms. Time to complete wound closure was compared between the two treatment arms using a log-
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30 264 rank test. The method of Bonferroni-Holm was used for adjustment of the α -error for parallel confirmatory testing
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32 265 of both primary endpoints. Missing values have been incorporated as censored values.

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34 266 During study planning, the following concomitant diseases and therapeutic measures with a possible influence on
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36 267 the primary study outcome wound closure (confounders) were identified: presence of neuropathy (sensation loss
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38 268 according to the PEDIS classification system [27]); presence of diabetic neuropathic osteoarthropathy (DNOAP)
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40 269 (anatomical classification according to Sanders [28] and progression stages according to Levin [29]
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42 270), Wagner [30] grading of the ulcer; presence of peripheral arterial occlusive disease (Rutherford classification for
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44 271 chronic limb ischemia [31]), chronic venous insufficiency (CVI) (Widmer I-III [32]), presence of extreme foot
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46 272 deformities and malpositions of toes, foot or the entire limb; untreated or therapy-refractory inflammation in the
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48 273 wound area; chronic anemia; heel necrosis; presence of a lymphedema; infection; heightened glycated hemoglobin
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50 274 (HbA1c) level; dialysis; application of hyperbaric oxygen (HBO) or normothermal therapy, application of
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52 275 recombinant or autologous growth factors to the study wound, and application of skin or dermal substitutes and
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54 276 with living cells that produce growth factors. These covariates thought to influence wound closure were analyzed
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56 277 for their effect on the two primary endpoints. Covariates were excluded from the analysis if the number of missing
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58 278 values was too high. First, the relevant covariates were tested by means of a univariate analysis with regard to their
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60 279 effect on wound closure rate and time without consideration of the treatment arms. If there was a significant
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280 influence, the frequency of occurrence in the treatment arms was analyzed. Secondary, multivariate analyses were

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3 281 performed for both primary endpoints, taking into account treatment assignment and including all relevant
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5 282 covariates. The multivariate analysis of the primary endpoint wound closure rate was performed with binary
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7 283 logistic regression to describe the influence of the independent covariates (regressors) on the dependent
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9 284 dichotomous variable wound closure. The multivariate analysis of the primary endpoint time to wound closure
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11 285 was performed using a COX regression model.

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13 286 Safety and secondary endpoints were analyzed using conventional univariate testing.

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15 287 Within a priori planned subgroup analysis the ITT population was divided into a group of small wounds and a
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17 288 group of big wounds based on the wound surface area documented during the randomization visit. Wounds smaller
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19 289 than or equal to the total median wound surface (483 mm²) were assigned to the subgroup "small wounds". Patients
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21 290 with wound surface areas larger than the median value were assigned to the subgroup "large wounds". Since no
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23 291 citable scientific definition of a large wound was available at the time of study planning and the clinical experts
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25 292 involved could not make a decision, the median of all wounds was chosen as the criterion for the division into the
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27 293 two subgroups. Confirmatory analysis of primary and secondary endpoints was repeated for the subgroups.

28 294 Missing values for the following outcome parameters were replaced using the Last Observation Carried Forward
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30 295 (LOCF) method: wound closure rate, wound size and wound tissue quality, recurrence and amputation. The
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32 296 outcome parameters time to wound closure and time until optimal preparation of the wound bed did not require
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34 297 data replacement, since missing values are included in the analysis as right-censored values. If the wound closure
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36 298 is not confirmed to be closed after a minimum of 14 days, the wound is considered as an unsustained wound
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38 299 closure. All missing quality of life values (EQ-5D) were replaced with the overall quality of life assessment (visual
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40 300 analogue scale), if available. If there was no quality of life assessment, there was no replacement. For missing
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42 301 values of the demographic and baseline characteristics, which are necessary for the estimation of the regression
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44 302 coefficients, no replacement was performed. IBM SPSS Statistics (version 23) was used for all analyses.

45 303 This study is registered with ClinicalTrials.gov number NCT01480362 and in the German Clinical Trial Registry,
46
47 304 number DRKS00003347.

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49 305 A data monitoring committee was formed to oversee overall study performance and safety.

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51 306

52 53 307 **Role of the funding source**

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55 308 Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds,
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57 309 which provided integrated care contracts for all study participants and for up to 7000 patients with acute and
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59 310 chronic wounds in Germany; defined basic rules for study design based on the requirements of the German
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311 authorities; and provided a critical review of the study protocol and the final report. The study was funded by the

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3 312 manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the
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5 313 NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary
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7 314 support and information about the used material. The manufacturers had no role in study design, data collection,
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9 315 data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including
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11 316 statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.
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For peer review only

318 **Results**

319 Between Dec 23, 2011 and August 12, 2014 386 patients were enrolled and randomly assigned to receive NPWT
 320 (181) or SMWC (187) in the DiaFu-study (**Error! Reference source not found.**) in overall 40 study sites, which
 321 recruited minimum 1 patient and maximum 76 patients. A full list of investigators can be found in the appendix.
 322 13 clinical investigators randomized more than 10 patients. 23 study sites enrolled only between 1 and 4 patients.
 323 Most of these study sites refused further study participation due lack of time and staff for adequately performing
 324 the documentation. In the further course of the trial research nurses have been hired by the independent scientific
 325 institute overseeing the trial in order to support the documentation in the study sites whenever needed.
 326 Demographics and relevant baseline characteristics of the DFU are presented in Table 1 and the appendix. Baseline
 327 characteristics of the patients in the NPWT-and the SMWC-arm are similar in the ITT population without any
 328 relevant difference between the treatment arms.

329

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]

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

334
 335 The baseline of the identified factors possibly influencing wound closure is shown in Table 2.

336

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%) 225 (65.2%)	2 (1.2%) 110 (64.3%)	4 (2.3%) 115 (66.1%)
2 - Ulcers extend into tendon, bone, or capsule	85 (24.6%)	45 (26.3%)	40 (23%)
3 - Deep ulcer with osteomyelitis, or abscess	26 (7.5%)	13 (7.6%)	13 (7.5%)
4 - Gangrene of toes or forefoot	3 (0.9%)	1 (0.6%)	2 (1.1%)
5 - Midfoot or hindfoot gangrene			
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%)

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

340

341 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%)

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

346

347 Results for the primary outcomes in the ITT population

348 In the ITT population, the overall number of patients with wounds closed within 16 weeks was 46 of 345 (13·3%).

349 Wound closure rate was higher in the NPWT arm (14·6%) than in the SMWC arm (12·1%) but this was not
 350 significant (p 0·53) as the difference in healing rate between the two groups was only four patients (2·5%) (Table
 351 4). Wounds treated with NPWT were approximately at the same risk of remaining open like patients receiving
 352 SMWC (RR 0·97 [95% CI: 0·89-1·06]).

353

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 (F)
[95% CI]	[9.8 – 17.8]	[9.5 –21.6]	[7.5 – 18.4]	

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

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

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

393 No recurrences occurred during the study treatment time of 16 weeks. Between the end of the maximum study
 394 treatment time and the follow up at 6 months, 11 recurrences (6.4 %) occurred in the 171 patients in the NPWT
 395 arm. One patient had two recurrences. In the SMWC arm, five of 174 patients (2.9 %) had a recurrence. The
 396 difference is not significant (RR 2.24 [95%CI: 0.80-6.31]; $p=0.131$) but the overall number of 17 recurrences in
 397 16 patients was very low.

399 There was no significant difference in the number of patients with amputation or resection ($p=1.00$), the overall
 400 number of performed interventions ($p=0.89$), and the number of study participants with minor (0.79) and major
 401 amputations 0.25 between NPWT and SMWC arm (Table 6). Patients treated with NPWT were approximately at
 402 the same risk of undergoing an amputation or resection like patients treated with SMWC (RR: 0.99 [95%CI: 0.65-
 403 1.50]).

404

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

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

424 N=63 (36,8%); SMWC N=58 (33,3%); p 0·50) (Table 7). None of the SAEs in the NPWT arm was documented
 425 as definitely or possibly related to the medical device by investigators. For 9 of 244 AEs (6·1%) in the NPWT arm
 426 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%)	

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

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431

432 Secondary analyses and subgroups

433 The univariate analysis of predefined covariates potentially influencing wound closure in the ITT population
 434 showed that only the presence of an infection at the time of randomization was significantly associated with both
 435 the wound closure rate and time. The influencing factor "infection" was almost equally represented in both
 436 treatment arms (NPWT 35.1 [27.9 – 42.2] % N=60; SCWT 32.8 [25.8 – 39.7] % N= 57), so the treatment

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3 437 comparison was not influenced by this confounder. Of the a priori defined factors potentially influencing wound
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5 438 closure nine factors needed to be excluded because the number of missing values was too high or they were never
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7 439 documented by the investigators. The covariate peripheral arterial occlusive disease had significant influence on
8
9 440 the time until wound closure (p 0.026) and infection had a significant influence on the wound healing rate (p
10
11 441 0.012). However, both influencing factors were almost evenly distributed over both study arms by randomization.
12
13 442 Thus, the comparison of the treatment arms was also not influenced by these confounders.

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15 443 In the ITT population in 173 study participants the median wound surface area was smaller than 484 mm² and in
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17 444 172 study participants wounds were bigger than 484 mm². In the NPWT arm 48.5% (N=83) of patients had small
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19 445 wounds and 51.5% (N=88) of patients had large wounds. The SMWC arm had 51.7% (N=90) small wounds and
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21 446 48.3% (N=84) big wounds. The differences between the treatment arms were not significant.

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23 447 An overview of the measures for small and big wounds and detailed results for this subgroup analysis can be found
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25 448 in the appendix.

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27 449 In the subgroup of big wounds, wound closure rate was significantly higher in the NPWT arm within 16 weeks (p
28
29 450 0.08). Patients with big wounds have a lower risk of not achieving wound closure within 16 weeks when treated
30
31 451 with NPWT (RR 0.91 [95%CI: 0.82-1.0]). In the subgroup of big wounds, a significantly faster wound closure
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33 452 was achieved in the NPWT arm (p 0.027) (Figure 3). Time until complete, sustained and verified wound closure
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35 453 was not significantly different between the treatment arms in the subgroup of small wounds (Figure 4).

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37 454 In the subgroup of small wounds, the time to reach 95 % granulation tissue was significantly shorter for the patients
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39 455 treated with NPWT (p 0.005). Time until optimal wound bed preparation was shorter in the NPWT arm in the
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41 456 subgroup of big wounds, but did not significantly differ to the result of the SMWC arm (p 0.27). There are no
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43 457 relevant or significant differences in the overall number of patients with amputation or resection between the
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45 458 treatment arms in both subgroups. Both major amputations were performed in patients with big wounds treated
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47 459 with NPWT. Due to the low overall number of recurrences (N=16) we were not able to perform a subgroup analysis
48
49 460 for this outcome parameter.

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52 462 Results for the primary and secondary outcomes in the PP population

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54 463 In the PP-population study participants treated with NPWT showed a 14.5 % higher wound closure rate within 16
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56 464 weeks than those treated with SMWC (Appendix), but the difference was not significant (p 0.053). Wounds treated
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58 465 with NPWT had a lower risk of remaining open after 16 weeks (RR 0.82 [95%CI: 0.66-1.03]) than wounds treated
59
60 466 with SMWC. Time to wound closure in the NPWT arm was significantly shorter (p=0.004) (Figure 5). After 6
467 months, wound closure rate in the SMWC-arm was higher than in the NPWT-arm, but the difference was not

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3 468 significant (p 0·84). As in the ITT population, optimal wound bed preparation was achieved significantly faster in
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5 469 patients receiving NPWT (p<0·001). Patients receiving NPWT had a higher risk of recurrence than those in the
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7 470 control group (RR 1·50 [95%CI: 0·37-6·01]), however there was no significant difference between the treatment
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9 471 arms regarding the total number of recurrences (p 0·38) or the number of patients with recurrences (p 0·69). 9
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11 472 patients in the NPWT group and 21 (21·4%) patients in the SMWC group had an amputation or resection (NPWT
12
13 473 RR 1·07 [95%CI: 0·53-2·15]). Neither the number of patients with amputations or resections (NPWT 9 (20·5%)
14
15 474 SMWC 21 (21·4%) p 0·83) nor the number of amputations or resections performed (NPWT 11 SMWC 28 p 0·86)
16
17 475 differ significantly between the treatment arms. No major amputations were performed in the PP population. In
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19 476 the PP-population wound surface area started at smaller baseline levels and decreased faster than in the ITT-
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21 477 population whereas the measures were smaller in the NPWT arm than in the SMWC arm. Wound volume started
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23 478 higher in the NPWT arm and ended at similar levels for the treatment arms after decreasing continuously during
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25 479 the treatment period. This effect was stronger in the SMWC arm. Wound volume measures were lower in the PP-
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27 480 population than in the ITT-population. Wound tissues had a similar course over time like in the ITT population
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29 481 but showed higher values for granulation as well as lower values for fibrin and necrosis in the PP population. Like
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31 482 in the ITT population, pain levels were very low, showing no relevant difference between the treatment arms, and
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33 483 further decreased during the study treatment period. In the PP-population EQ5D values are higher than in the ITT
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35 484 population during screening, but still show that all patients have significant problems. In the NPWT arm QoL
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37 485 measures are similar to those of the SMWC arm for patients reaching end of maximum treatment time before end
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39 486 of therapy. EQ5D shows higher values for patients reaching the end of therapy during the study treatment time of
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41 487 16 weeks. Detailed results for the PP population can be found in the appendix.

488

489 Additional results on treatment compliance and documentation quality

490 29 (17·0%) patients in the NPWT group had a temporary therapy change to SMWC (mean duration 20·5 ± 21·6
491 days). In the SMWC group, 17 (9·8%) patients had a temporary therapy change to NPWT (mean duration 28·9 ±
492 21·6 days). For only 2 of the 29 NPWT patients (6·9%) with a temporary therapy change to SMWC the wound
493 closure was achieved within 16 weeks, whereas 16·2% (23 von 142) of the wounds of the NPWT patients without
494 therapy change were completely closed.

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

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3 498 duration until premature end of therapy was 28.5 days (SD 24.1), while a mean granulation area of 59.6% (SD 30.
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5 499 5) was achieved.
6
7 500 For 131 patients (76.6%) in the NPWT arm less than the required three dressing changes per week were
8
9 501 documented. 19 patients (14.5%) with this protocol violation achieved a complete wound closure. Six (15.4%)
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11 502 of the 39 NPWT patients who received at least 3 therapy changes per week achieved a complete wound closure.
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13 503 In the electronic Case Report Forms (eCRF) a wound closure was documented for 96 patients (NPWT 56 of 171;
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15 504 SMWC 40 of 174), but only for 46 patients (NPWT 25; SMWC 21) all criteria for a complete, verified and
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17 505 sustained wound closure have been met. For the wound closure visit seven wound photographs (NPWT 7; SMWC
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19 506 0) and for the wound closure confirmation visit four photographs (NPWT 3; SMWC 1) were missing. In addition,
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21 507 two of the existing wound photographs for the wound closure (NPWT 0; SMWC 2) and two photographs for the
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23 508 wound closure confirmation (NPWT 1, SMWC 3) were not assessable by the blinded observers due to serious
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25 509 quality issues. Furthermore 23 (NPWT 15; SMWC 8) existing and assessable wound photographs were not able
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27 510 to confirm the wound closure and 3 (NPWT 1; SMWC 2) photographs were not able to confirm the wound closure
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29 511 after 14 days.
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512 Discussion

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

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

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3 542 closure was significantly shorter with NPWT than with SMWC in the subgroup of big wounds, which indicates
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5 543 that NPWT has the potential to be a valuable treatment option for this kind of wounds.

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7 544 In the DiaFu-study methods against bias have been implemented whenever possible in order to avoid bias that
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9 545 have been described by several systematic reviews [18-22], but shortcomings in documentation quality and
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11 546 missing compliance to therapy guidelines negatively impact the results.

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13 547 Not addressing and analyzing all factors influencing the overall treatment outcome like targeted pressure relief,
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15 548 continuous infection control and adequate treatment of the underlying disease during the study treatment and
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17 549 observation period may be seen as a limitation of this health care research study. Study sites have been selected
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19 550 based on a self-disclosure by means of a qualification checklist and cross checks using quality reports. This ensured
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21 551 that all prerequisites were met for guideline-compliant patient care. Nevertheless, even in the application of NPWT
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23 552 there were deviations from the standards. Anyway, questioning the quality of investigators' treatment was not the
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25 553 main focus of this trial and evaluating the individual treatment quality within a single RCT is neither feasible nor
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27 554 effective.

28 555 In order to support the decision-making process of the German G-BA on general reimbursement of NPWT in
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30 556 German outpatient care the real-life clinical practice DiaFu-study included patients with chronic DFUs of
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32 557 neuropathic and angiopathic origin regardless of whether a simple wound cleansing, tissue debridement or even
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34 558 amputation was necessary prior to application of wound therapy targeted to achieve complete wound closure. The
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36 559 study was performed without excluding concomitant diseases negatively impacting wound healing; with therapy
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38 560 application in the discretion of the attending physician; and with evaluation of patient relevant outcome. Thus,
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40 561 results can easy be generalized and applied in clinical practice settings. Anyway, shortcomings in data quality
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42 562 negatively impacted the study results and statements about specific patient groups were not possible.

43 563

44 564 **Conclusions**

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47 565 NPWT was not superior to SMWC when evaluated in German real-life clinical practice. Missing compliance with
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49 566 therapy guidelines and poor documentation quality led to restrictions in achieving the patient-relevant endpoint
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51 567 complete wound closure and prevents a clear proof of effectiveness. The question if NPWT is superior to SMWC
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53 568 for treating diabetic foot wounds remains unanswered due to the limitations of the DiaFu-study. An overall low
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55 569 number of wound closures indicate problems with the overall treatment quality. Despite all limitations NPWT
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57 570 showed a significant superiority in optimal wound bed preparation. This indicates that NPWT works according to
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59 571 its intended use and has at least a potential to be a valuable treatment option.

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3 572 Furthermore, the results of the PP population suggest that without the negative impact of premature treatment
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5 573 cessation, temporary changes of the randomized therapy and partly incomplete documentation, NPWT may be
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7 574 more effective for treating diabetic foot wounds than SMWC.
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9 575 In Germany, NPWT should be evaluated again after implementation of a sufficient, well-considered and widely-
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11 576 accepted concept for quality control. In a future health care research study, the treatment outcome before and after
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13 577 the implementation of these quality measures should be evaluated, for which the results of this trial may serve as
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15 578 a basis. Practitioners worldwide should review their processes with regard to the problems described here.
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For peer review only

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3 **580 Ethics approval and consent to participate**
4

5 581 Ethical approval of the main ethical committee (EC): Ethical Committee of the University of Witten-Herdecke,
6
7 582 has been fully granted without any conditions. Due to performing the trial according to § 23b MPG (German
8
9 583 Medical Device Act), participating study sites in Germany only received a consultation for the main clinical
10
11 584 investigator according to professional law by the respective EC. All investigators have been fully approved by the
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13 585 respective ECs. An evaluation of the study's content by ECs of participating study sites in Germany was not
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15 586 applicable. All study participants gave written informed consent prior to randomization and any trial related
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17 587 procedure.
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20 **589 Data sharing**
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22 590 The datasets used and/or analyzed during the current study are available from the corresponding author on
23
24 591 reasonable request. Datasets are available in German language.
25

26 592

27
28 **593 Competing interests**
29

30 594 All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare:
31
32 595 The German statutory health insurance companies commissioned the Witten/Herdecke University (UW/H) to plan,
33
34 596 conduct, analyze and publish the study. Dörthe Seidel is an employee of the UW/H. The study has been financed
35
36 597 by the manufacturers KCI (Acelity) and Smith&Nephew. Dörthe Seidel received a consulting fee for the
37
38 598 presentation of the study during an event organized by the manufacturer Hartmann. During study planning and
39
40 599 conduct Edmund Neugebauer was an employee of the UW/H. He was the director of the IFOM.

41 600 The clinical investigators Martin Storck, Holger Lawall, Gernold Wozniak, Peter Maukner, Dirk Hochlenert,
42
43 601 Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink
44
45 602 received a case fee of 1000 € for each patient included in the DiaFu-study in order to compensate for the additional
46
47 603 organizational and especially the documentation effort during trial conduct. Furthermore all investigators received
48
49 604 compensation for travelling to the investigator meetings. The institutions of the investigators used integrated care
50
51 605 contracts for NPWT during study conduct in order to provide best practice for the study participants during
52
53 606 outpatient care.

54 607 Gernold Wozniak and Walter Wetzel-Roth are members of the scientific advisory board of the manufacturer
55
56 608 Kinetic Concepts Incorporated (KCI) (now Acelity).
57

58 609

59
60 **610 Funding**

1
2
3 611 Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds,
4
5 612 which provided integrated care contracts for all study participants and for up to 7000 patients with acute and
6
7 613 chronic wounds in Germany; defined basic rules for study design based on the requirements of the German
8
9 614 authorities; and provided a critical review of the study protocol and the final report. The study was funded by the
10
11 615 manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the
12
13 616 NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary
14
15 617 support and information about the used material. The manufacturers had no role in study design, data collection,
16
17 618 data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including
18
19 619 statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

620

621 **Authors' contributions**

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

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

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

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

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

635 All authors approved the final version of the report.

636

637 **Acknowledgements**

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

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

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13 678 GmbH Hohenzollernring 70 48145 Münster.

14 679 The study was initiated by a consortium of 19 statutory German health insurance funds represented by the AOK
15
16 680 federal association (AOK-Bundesverband – AOK-BV), the association of alternative health insurance funds
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18 681 (Verband der Ersatzkrankenkassen – vdek) and the minors (Knappschaft). In order to guarantee outpatient care for
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20 682 all study participants without any restrictions, the contracting health insurance companies provided integrated care
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22 683 contracts for outpatient negative pressure wound therapy.

23
24 684 A project advisory board was implemented to coordinate all processes and project partners. The board comprised
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26 685 two representatives each from the statutory health insurance funds, the management company and the sponsor as
27
28 686 well as one representative each from the participating medical device manufacturers (KCI and smith & nephew).
29
30 687 Representing the contracting authority (statutory German health insurance funds) Dr. Gerhard Schillinger (AOK-
31
32 688 BV) and Ute Leonhard (vdek) acted as contact persons for all aspects of the project.

33
34 689 The management company “Gesundheitsforen Leipzig” has been entirely responsible for the logistics of the study.
35
36 690 Central tasks of the management company included the recruitment of study sites and patients, the development
37
38 691 of the IT infrastructure including the documentation, communication and invoicing software as well as the
39
40 692 processing of all payments.

41 693 The manufacturers Kinetic Concepts Incorporated (KCI) (Acelity) and smith & nephew provided the NPWT
42
43 694 devices as well as support and training for the investigators and financed the study.

44
45 695 The Private University of Witten/Herdecke gGmbH acted as the Sponsor of the trial and the Institute for Research
46
47 696 in Operative Medicine with its former director Prof. E.A.M. Neugebauer, the current interim head Prof. Rolf
48
49 697 Lefering and the head of the division for clinical research Dörthe Seidel was responsible for the scientific
50
51 698 conception, the evaluation as well as the reporting and publication of the study. Prof. Dr. Rolf Lefering was
52
53 699 responsible for the statistical planning and analysis. PD Dr. Peter Krüger was responsible for the data management
54
55 700 of the study. Special thanks are going to Stefan Bauer, who supported the data management as well as the statistical
56
57 701 analysis and reporting.

58 702 We would like to thank Sophie Thorn, who checked the article as a native English speaker with regard to spelling
59
60 703 and grammar.

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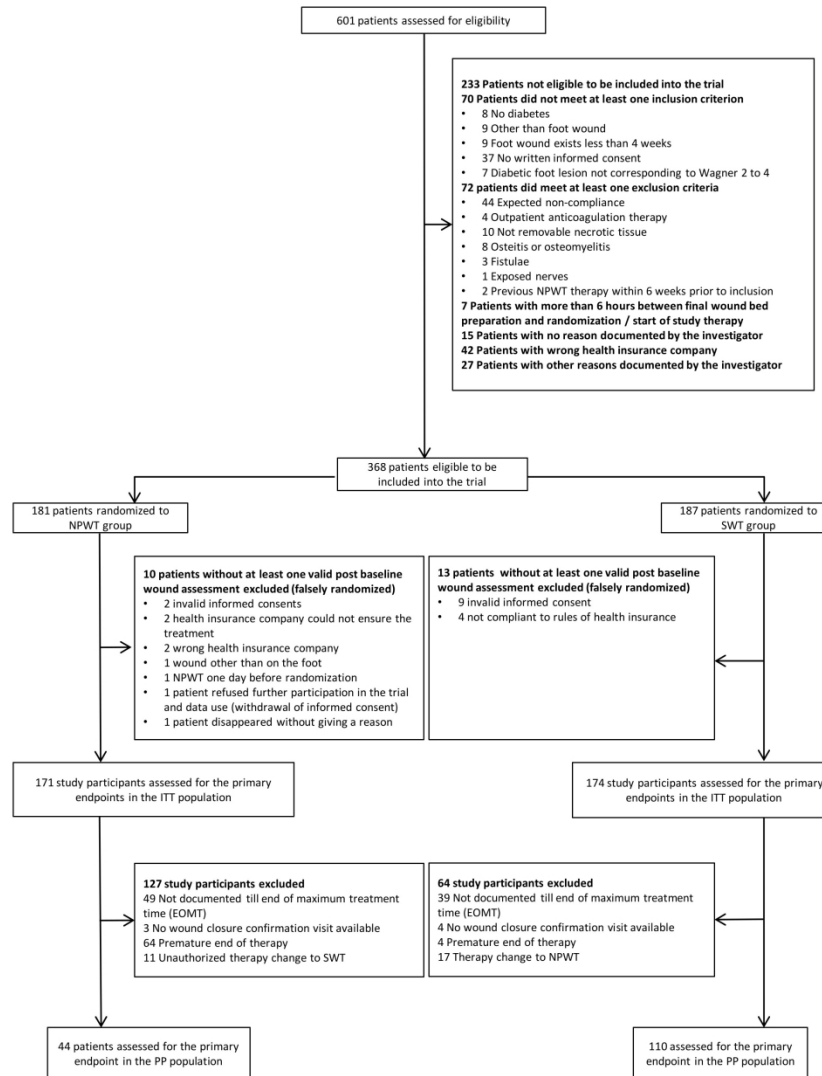


Figure 1: Trial profile (CONSORT Flow Diagram)

190x275mm (300 x 300 DPI)

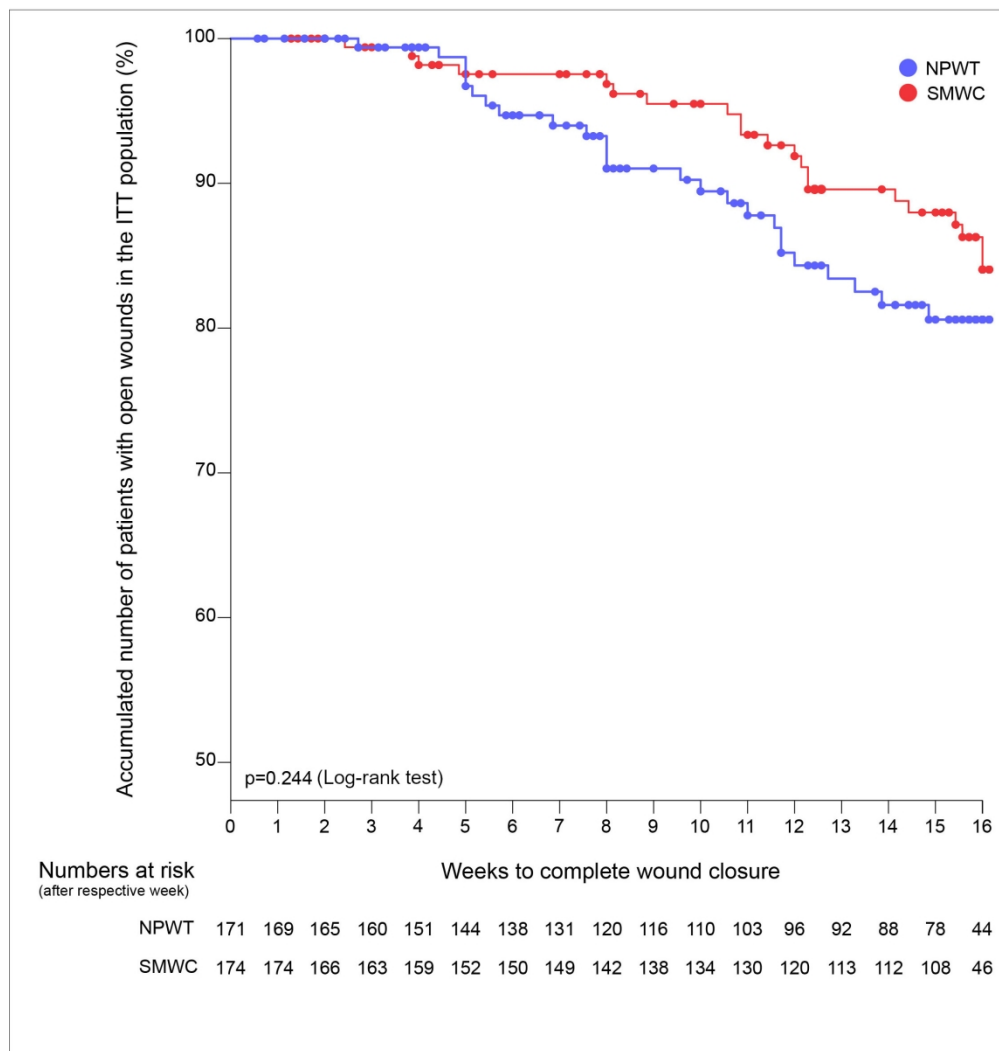


Figure 2: Time until complete, sustained and verified wound closure in the ITT population

189x198mm (300 x 300 DPI)

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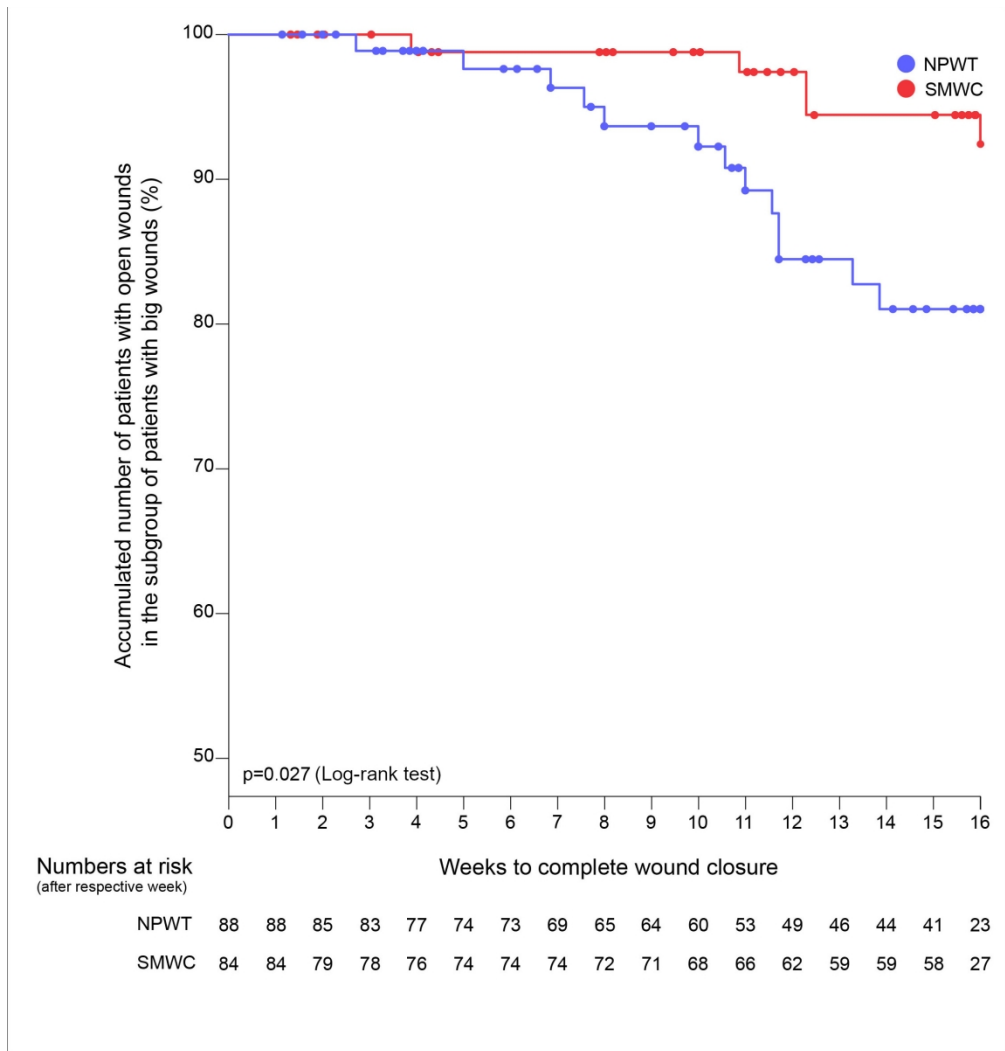


Figure 3: Time until complete, sustained and verified wound closure for the subgroup of big wounds

189x198mm (300 x 300 DPI)

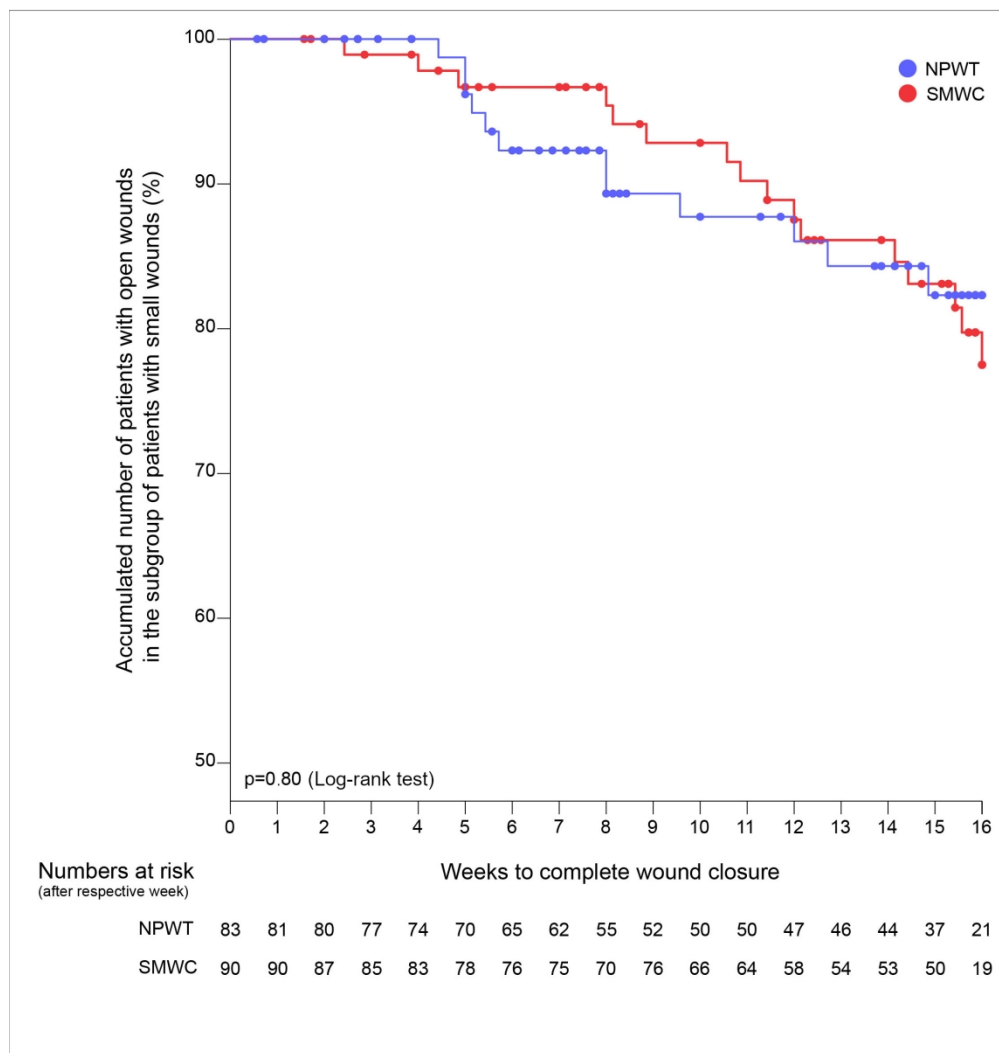


Figure 4: Time until complete, sustained and verified wound closure for the subgroup of small wounds

189x198mm (300 x 300 DPI)

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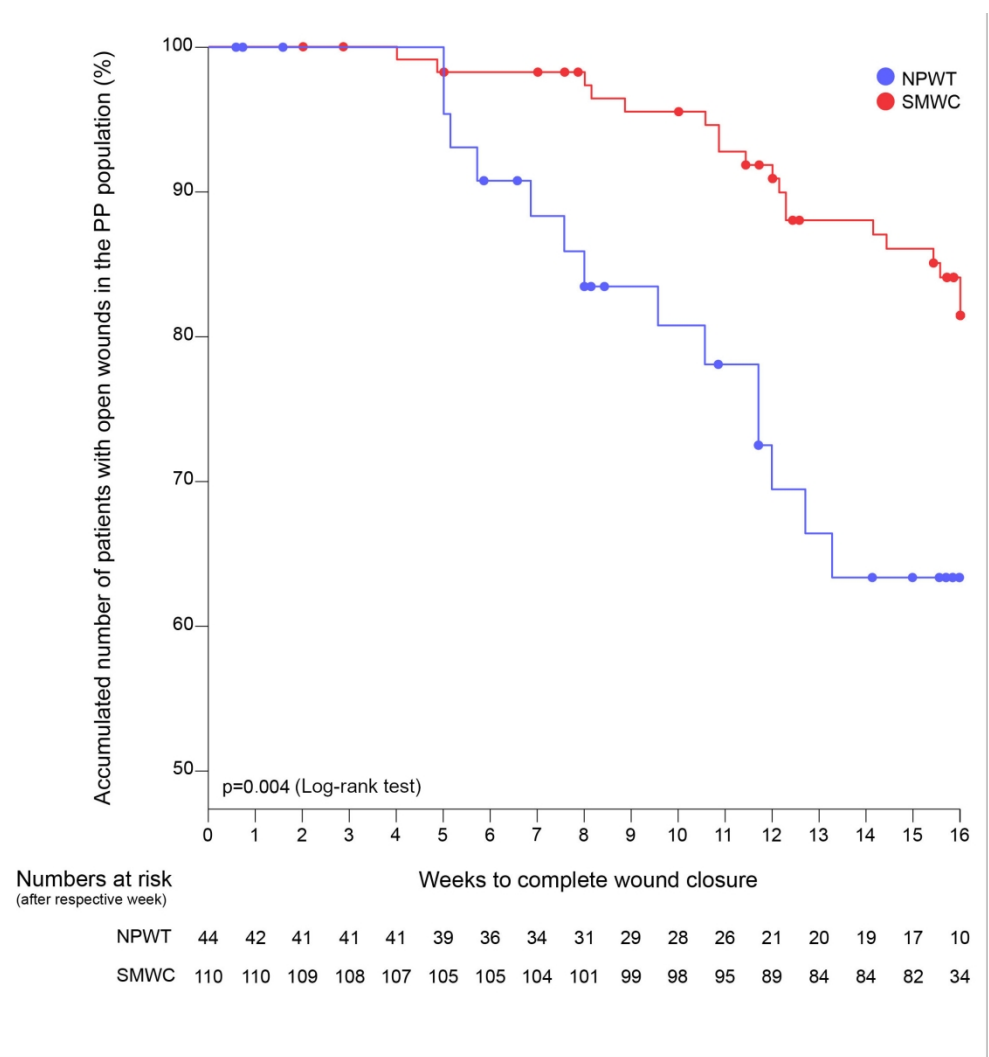


Figure 5: Time until complete, sustained and verified wound closure in the PP-population
189x198mm (300 x 300 DPI)

Supplementary Appendix

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- Supplementary result tables
- Supplementary discussion

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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%)
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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	N=154	N=44	N=110
Mean (SD)	67.4 (10.6)	66.5 (11.0)	67.8 (10.4)
Height in cm	N=153	N=43	N=110
Mean (SD)	173.8 (12.9)	173.5 (17.4)	174.0 (10.7)
Weight in kg	N=150	N=42	N=108
Mean (SD)	95.4 (23.3)	96.2 (21.6)	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

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

Table S4: 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) [$(\pi / 4) \times \text{length} \times \text{width} = \text{area}$]. 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)	22 (25)	21 (28)	71 (27)	3 (10)	7 (15)	34 (37)	24 (26)	22 (29)	69 (28)	2 (9)	7 (14)
	20 (70)	12 (37)	10 (30)	79 (46)	0 (0)	0 (5)	20 (71)	14 (39)	10 (40)	79 (44)	0 (0)	0 (8)
	171 (2)	118 (8)	170 (4)	118 (8)	169 (5)	118 (8)	174 (3)	129 (12)	174 (1)	129 (12)	172 (2)	129 (12)
Week 1	58 (35)	21 (25)	19 (22)	73 (27)	5 (13)	6 (12)	49 (35)	21 (25)	24 (27)	74 (26)	6 (15)	5 (9)
	70 (70)	10 (36)	10 (30)	81 (47)	0 (2)	0 (5)	50 (70)	10 (36)	15 (31)	85 (40)	0 (5)	0 (5)
	171 (16)	118 (32)	71 (19)	118 (32)	169 (23)	118 (32)	174 (28)	129 (36)	174 (27)	129 (36)	172 (30)	129 (36)
Week 3	67 (31)	16 (23)	18 (22)	80 (25)	5 (13)	4 (11)	57 (32)	21 (25)	25 (26)	77 (25)	5 (13)	3 (7)
	80 (55)	5 (25)	10 (30)	91 (30)	0 (0)	0 (1)	60 (60)	10 (36)	20 (35)	85 (36)	0 (3)	0 (1)
	171 (26)	118 (27)	171 (30)	118 (27)	169 (28)	118 (27)	174 (24)	129 (35)	174 (25)	129 (35)	172 (30)	129 (35)
Week 5	70 (30)	15 (22)	18 (24)	83 (22)	4 (13)	2 (8)	62 (31)	18 (26)	23 (25)	80 (26)	4 (12)	3 (10)
	80 (45)	6 (21)	10 (25)	91 (26)	0 (0)	0 (1)	63 (50)	4 (32)	10 (39)	93 834	0 (0)	0 (0)
	171 (36)	118 (43)	171 (38)	118 (43)	169 (42)	118 (43)	174 (44)	129 (36)	174 (47)	129 (36)	172 (46)	129 (36)
Week 8	74 (30)	16 (23)	17 (24)	82 (24)	4 (13)	2 (6)	70 (29)	17 (24)	17 (21)	80 (25)	5 (13)	3 (11)
	90 (40)	4 (27)	10 (20)	93 (33)	0 (0)	0 (0)	80 (40)	3 (33)	10 (20)	92 (36)	0 (0)	0 (0)
	171 (53)	118 (48)	171 (56)	118 (48)	171 (59)	118 (48)	174 (44)	129 (43)	174 (49)	129 (43)	174 (52)	129 (43)
Week 12	75 (30)	15 (23)	17 (25)	83 (24)	4 (13)	1 (5)	73 (29)	16 (23)	16 (20)	82 (23)	5 (13)	2 (6)
	90 (40)	4 (22)	5 (20)	96 (23)	0 (0)	0 (0)	80 (38)	3 (29)	10 (20)	93 (32)	0 (0)	0 (0)
	171(115)	118 (89)	171(118)	118 (89)	171(119)	118 (89)	174(124)	129(102)	174(125)	129(102)	172(126)	129(102)
Week 16	77 (30)	13 (22)	14 (22)	86 (24)	3 (10)	1 (6)	76 (30)	17 (24)	15 (24)	81 (24)	3 (13)	2 (6)
	90 (40)	1 (17)	2 (20)	98 (19)	0 (0)	0 (0)	90 (40)	4 (31)	5 (20)	93 (35)	0 (0)	0 (0)
	171 (78)	118 (66)	171 (79)	118 (66)	171 (82)	118 (66)	174 (62)	129 (576)	174 (65)	129 (56)	174 (66)	129 (56)

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2 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
3 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
4 (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).
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For peer review only

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)	0,61 (0,25)
	0,66 (0,28)	0,63 (0,24)
	N=63 (2)	N=95 (2)
Follow up after 6 months	0,69 (0,26)	0,67 (0,23)
	0,77 (0,35)	0,63 (0,39)
	N=93 (3)	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				
	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	0.232	0	0	0	0.193
Mean (SD)	213	212	213			1995	1860	2135	
Median (IQR)	(136)	(138)	(135)			(3377)	(1805)	(4474)	
Min - Max	188 (220)	176 (220)	196 (222)			1276 (1482)	1364 (1242)	1242 (1708)	
	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	NPWT (N=171)	SMWC (N=174)	p
Small wounds	N=83	N=90	
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	NPWT (N=171)	SMWC (N=174)	P
Big wounds	N=88	N=84	
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	Total	NPWT	SMWC	p
Small wounds	N=173	N=83	N=90	
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	Total	NPWT	SMWC	p
Big wounds	N=172	N=88	N=84	
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.

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

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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).

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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

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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%)
<u>Alcohol</u>	<u>N=341</u>	<u>N=169</u>	<u>N=172</u>
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%)
<u>Smoking</u>	<u>N=342</u>	<u>N=169</u>	<u>N=173</u>
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
<u>Drugs</u>	<u>N=341</u>	<u>N=169</u>	<u>N=172</u>
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%)
<u>Allergies</u>	<u>N=343</u>	<u>N=170</u>	<u>N=173</u>
Yes	37 (10·7%)	16 (9·4%)	21 (12·0%)
No	306 (88·4%)	154 (90·1%)	152 (86·9%)
<u>Subjective assessment of nutritional condition</u>	<u>N=342</u>	<u>N=169</u>	<u>N=173</u>
Well-nourished	325 (94·2%)	162 (94·7%)	163 (93·7%)
Moderately malnourished or suspected malnutrition	11 (3·2%)	4 (2·3%)	7 (4%)

<u>Malnourished</u>	<u>0 (0%)</u>	<u>0 (0%)</u>	<u>0 (0%)</u>
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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	N=154	N=44	N=110
Mean (SD)	67.4 (10.6)	66.5 (11.0)	67.8 (10.4)
Height in cm	N=153	N=43	N=110
Mean (SD)	173.8 (12.9)	173.5 (17.4)	174.0 (10.7)
Weight in kg	N=150	N=42	N=108
Mean (SD)	95.4 (23.3)	96.2 (21.6)	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 S34: 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

Observation time point	Wound surface NPWT		Wound surface SMWC	
	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)	5465 (14874)
	141 (1890)	200 (1587)
	N=171 (83)	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).

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

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2 | Table [S4S6](#): 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)
3 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
4 (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).
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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 SSS7: 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)	0,61 (0,25)
	0,66 (0,28)	0,63 (0,24)
	N=63 (2)	N=95 (2)
Follow up after 6 months	0,69 (0,26)	0,67 (0,23)
	0,77 (0,35)	0,63 (0,39)
	N=93 (3)	N=97 (2)

Table S6S8: 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).

<u>Adverse Events (AE)</u>	<u>Total</u> <u>N=269</u>	<u>NPWT</u> <u>N=167</u>	<u>SMWC</u> <u>N=102</u>
<u>Day of occurrence (N_{available})</u>	<u>269</u>	<u>167</u>	<u>102</u>
<u>Mean (SD)</u>	<u>39.5 (28.9)</u>	<u>37.5 (28.6)</u>	<u>42.7 (29.2)</u>
<u>Median (IQR)</u>	<u>34.0 (42)</u>	<u>30.0 (40.0)</u>	<u>38.0 (50.0)</u>
<u>Duration in days (N_{available})</u>	<u>254</u>	<u>157</u>	<u>97</u>
<u>Mean (SD)</u>	<u>21.9 (33.0)</u>	<u>19.7 (29.0)</u>	<u>25.3 (38.6)</u>
<u>Median (IQR)</u>	<u>11.0 (21)</u>	<u>10.0 (20.0)</u>	<u>13.0 (22.0)</u>
<u>Severity (N_{available})</u>	<u>263</u>	<u>161</u>	<u>102</u>
<u>Mild</u>	<u>88 (33.5%)</u>	<u>64 (39.8%)</u>	<u>24 (23.5%)</u>
<u>Moderate</u>	<u>92 (35.0%)</u>	<u>54 (33.5%)</u>	<u>38 (37.3%)</u>
<u>Severe</u>	<u>83 (31.6%)</u>	<u>43 (26.7%)</u>	<u>40 (39.2%)</u>
<u>AE expected / unexpected (N_{available})</u>	<u>259</u>	<u>159</u>	<u>100</u>
<u>Expected</u>	<u>79 (30.5%)</u>	<u>52 (32.7%)</u>	<u>27 (27.0%)</u>
<u>Unexpected</u>	<u>180 (69.5%)</u>	<u>107 (67.3%)</u>	<u>73 (73.0%)</u>
<u>Action taken (N_{available})</u>	<u>240</u>	<u>146</u>	<u>94</u>
<u>No</u>	<u>46 (19.2%)</u>	<u>23 (15.8%)</u>	<u>23 (24.5%)</u>
<u>Yes</u>	<u>194 (80.8%)</u>	<u>123 (84.2%)</u>	<u>71 (75.5%)</u>
<u>Cessation of therapy</u>	<u>10 of 194 (5.2%)</u>	<u>10 of 123 (8.1%)</u>	<u>0 of 71 (0%)</u>
<u>Temporary interruption of therapy</u>	<u>30 of 194 (15.5%)</u>	<u>28 of 123 (22.8%)</u>	<u>2 of 71 (2.8%)</u>
<u>Adaptation of therapy / treatment</u>	<u>100 of 194 (51.5%)</u>	<u>52 of 123 (42.3%)</u>	<u>48 of 71 (67.6%)</u>
<u>Other</u>	<u>54 of 194 (27.8%)</u>	<u>33 of 123 (26.8%)</u>	<u>21 of 71 (29.6%)</u>
<u>Outcome (N_{available})</u>	<u>244</u>	<u>148</u>	<u>96</u>
<u>Fixed without consequences</u>	<u>115 (47.1%)</u>	<u>72 (48.6%)</u>	<u>43 (44.8%)</u>
<u>Condition improved</u>	<u>58 (23.8%)</u>	<u>32 (21.6%)</u>	<u>26 (27.1%)</u>
<u>Fixed with consequences</u>	<u>34 (13.9%)</u>	<u>22 (14.9%)</u>	<u>12 (12.5%)</u>
<u>Not fixed</u>	<u>7 (2.9%)</u>	<u>4 (2.7%)</u>	<u>3 (3.1%)</u>
<u>Death</u>	<u>15 (6.1%)</u>	<u>9 (6.1%)</u>	<u>6 (6.3%)</u>
<u>Unknown</u>	<u>15 (6.1%)</u>	<u>9 (6.1%)</u>	<u>6 (6.3%)</u>

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 mm ²	Small wounds				Big wounds			
	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 S7S10: 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 S118: 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 S9S12: 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 S10S13: 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-1414: 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 S12S15: 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 S13S16: 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 S14S17: 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 S15S18: 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 S16S19: 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 S17S20: 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 S1821: 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)

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2 | 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
3 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
4 PP population (number (N) of values substituted by the last observation carried forward (LOCF) method).
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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 S2424: 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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026345.R3
Article Type:	Original research
Date Submitted by the Author:	15-Jan-2020
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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

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3 1 **Negative Pressure Wound Therapy compared with standard moist wound care on**
4 **diabetic foot ulcers in real-life clinical practice – Results of the German DiaFu-RCT**

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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

71 **Strengths and limitations of this study**

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

90 **Background**

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

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3 101 wound healing [7]. The first use of vacuum sealing was described in 1993 by Fleischmann et al. [8] and the
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5 102 commercially available product was developed later in the 1990s [9, 10]. Positive effects of NPWT on wound
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7 103 healing have been suggested in various basic studies [10, 11]. At the time of planning the DiaFu-study, the clinical
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9 104 evidence largely consisted of clinician perception, case reports and series, small cohort studies, and weakly-
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11 105 powered or low-quality randomized trials that documented broad use of NPWT in various clinical settings and
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13 106 constituted a substantial number of publications but an overall small amount of evidence [12-15]. Two randomized
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15 107 controlled trials (RCTs) performed by Armstrong 2005 [16] and Blume 2008 [17] provided a solid basis for
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17 108 planning a study.

18 109 In the recent years, a specific review for the use of NPWT in diabetic foot wounds performed by Dumville et al in
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20 110 2013 [18], an assessment in the home setting by Rhee et al. in 2014 [19] and a health technology assessment
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22 111 particularly issued for the evaluation of NPWT for managing diabetic foot ulcers [20] in 2014, as well as the most
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24 112 recent work of Liu et al in 2017 [21, 22] all concluded that although NPWT may have a positive effect, the trials
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26 113 that have been performed have methodological flaws and sufficient, unbiased evidence of whether wounds heal
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28 114 better or worse with NPWT than with conventional treatment is still missing.

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30 115 In Germany, the issue of evidence for efficacy and safety of NPWT in acute and chronic wounds was first
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32 116 addressed in 2002 when the German Federal Joint Committee (German: Gemeinsamer Bundesausschuss [G-BA])
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34 117 needed to decide whether NPWT could be reimbursed without restrictions in outpatient care.

35 118 Finally, in 2007 taking into account all available evidence the G-BA decided that the benefits of the treatment
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37 119 method NPWT should be evaluated in a so-called model project. This included the conduct of clinical studies for
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39 120 which the G-BA defined basic requirements. This essentially concerned the formulation of a study hypothesis that
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41 121 supports G-BA's overall question if NPWT can be reimbursed in German outpatient care without any limitation;
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43 122 the selection of a comparator that represents the current treatment standard in Germany; and implementation of all
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45 123 measures to ensure a sufficient certainty of the results.

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47 124 Following the announcement of the G-BA, the German statutory health insurance funds initiated an overall project
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49 125 through a European tender. The DFU has been chosen to be the representative for chronic wounds in a RCT
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51 126 comparing NPWT and standard moist wound care (SMWC) in clinical practice.

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54 128 **Methods**

55 129 **Aim of the study**

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57 130 The aim of the DiaFu-study was to evaluate whether the effectiveness and safety of NPWT is superior to SMWC
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59 131 in German real-life clinical practice.
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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.

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3 163 Patients estimated to be at risk of non-compliance with study requirements, with wounds with necrotic tissue
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5 164 present that could not be removed by debridement or amputation, with exposed blood vessels within or directly
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7 165 surrounding the wound not possible to be sufficiently covered or with an increased risk of bleeding with
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9 166 hemodynamic consequences (mainly relevant for posterior tibial artery dorsalis pedis artery), and outpatients
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11 167 receiving anticoagulation therapy or suffering from a high-grade impaired clotting function with a heightened risk
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13 168 of bleeding with hemodynamic consequences were excluded from the DiaFu-study. The use of NPWT devices on
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15 169 the study wound within six weeks prior to study start represented an exclusion criterion in order to demonstrate a
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17 170 clear therapeutic effect of each treatment arm.

18 171 Written informed consent was obtained from every participant after being informed about all aspects of the trial
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20 172 and before randomization and any trial-related procedure. As the statutory health insurance funds provided
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22 173 integrated care contracts for outpatient NPWT, it was only possible to include patients in the study who were
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24 174 members of a participating health insurance fund.

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27 28 176 **Randomization and masking**

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30 177 Patients were randomly allocated to the treatment arms in a 1:1 ratio using a computer-generated list located on a
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32 178 centralized web-based tool. The randomization list consisted of permuted blocks of variable length (4, 6) which
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34 179 were randomly arranged. Patients were stratified by study site and by Wagner-Armstrong stage within each site
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36 180 (<Wagner-Armstrong stage 2C and \geq Wagner-Armstrong stage 2C). The randomization lists were generated with
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38 181 the help of a self-created Java program and integrated into the study database. Each registered investigator received
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40 182 individual access to the randomization tool via the study website, but without knowledge of future treatment
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42 183 assignment, which provided adequate allocation concealment. The investigators were responsible for adequately
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44 184 implementing the assigned therapy. Due to the physical differences between the treatment regimens it was not
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46 185 possible to blind either participant or physician to the treatment assignment. Verification of complete wound
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48 186 closure was performed by independent, blinded assessment of wound photographs. Determination of wound size
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50 187 and percentage wound tissue quality was also performed by central, blinded outcome assessors based on the wound
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52 188 photographs using the Wound Healing Analyzing Tool (W.H.A.T.). The determination of sufficient wound bed
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54 189 conditioning and the indication for surgical closure was carried out by the treating physician, as in clinical practice.
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56 190 The treating physician was not blinded to treatment allocation.

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58 192 **Procedures**

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3 193 Basic data were collected for all patients considered for study participation during screening and have been updated
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5 194 during the randomization visit. Patients received an extensive examination of overall health status, specific
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7 195 diabetes associated disorders, and relevant influence factors on wound healing during screening with an update at
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9 196 the randomization visit. Neuropathy and vascular diagnostics were performed according to the German National
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11 197 Health Care Guidelines for Type 2 Diabetes Foot Complications [24]. After anamnesis and general diagnostics
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13 198 (physical examination) this care guideline recommends the following further vascular diagnostics: ankle-arm index
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15 199 (ABI, "Ankle-Brachial-Index") and additional assessment of the Doppler frequency spectrum (due to the possible
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17 200 falsifying of the results by Media sclerosis) and, if necessary, additional hydrostatic toe pressure measurement
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19 201 (pole test) or a transcutaneous oxygen partial pressure measurement (tcPO₂); duplex sonography to determine the
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21 202 extent and distribution pattern of PADK (including the lower leg arteries if necessary). In case of inconclusive
22
23 203 findings contrast-agent-enhanced MR angiography (MRA) and intra-arterial digital subtraction angiography
24
25 204 (DSA) were considered. No detailed examination results of the vascular diagnostics but the final diagnosis of
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27 205 peripheral artery occlusive disease (PAOD) and critical limb ischemia (CLI) were to be documented in the eCRF
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29 206 by the clinical investigators. Infection diagnosis comprised clinical evaluation and laboratory testing. In case of
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31 207 suspected diabetic foot osteomyelitis (DFO) a probe to bone test and a stepwise approach to imaging modalities
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33 208 were applied in order to confirm the clinical diagnosis and to determine the best treatment regimen for the study
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35 209 participants.

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37 210 Before randomization and start of study treatment all patients underwent one or more of the following no longer
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39 211 than six hours before randomization: amputation, debridement or thorough wound cleansing. Study therapy was
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41 212 allowed to be started either in-hospital or as outpatient and was intended to be continued in outpatient care
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43 213 whenever possible.

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45 214 In the intervention arm commercially available CE-marked NPWT devices of the manufacturers Kinetic Concepts
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47 215 Incorporated (KCI) and Smith & Nephew were used in the discretion of the clinical investigator according to
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49 216 clinical routine and manufacturer's instructions [23]. Intermittent and continuous NPWT was allowed to be used
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51 217 with the negative pressure to be adapted as recommended for the dressing applied (V.A.C.-Granufoam®black or
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53 218 Silver®; V.A.C.-White Foam®; Renassys™ -F/P; Renassys™ -G) and adapted to the wound needs.
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55 219 Recommendations for use can be found on the manufacturers' websites. As part of the European tender for the
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57 220 overall project, the German statutory health insurance funds awarded lots for the provision of the medical products
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59 221 by the respective manufacturers. Germany was divided into 4 supply areas. During the award procedure, Smith &
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222 Nephew received 1 lot and KCI 3 lots. Thus, devices and consumables of Smith & Nephew were used for the north

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

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

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

240 **Outcomes**

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

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

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3 253 Minor and major amputations were considered separately, whereas the disarticulation at the midtarsal joint
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5 254 (Chopart's amputation) was considered still to be minor. Wound size and wound tissue composition (percentage
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7 255 of granulation tissue, fibrin and necrosis) were monitored at each study visit. Quality of life (QoL) was measured
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9 256 using the questionnaire Euro Quol 5D (EQ5D) at inclusion, end of the maximum treatment time or end of the
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11 257 therapy and at the six-month follow-up visit. At each study visit participants were asked to provide their assessment
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13 258 of wound-associated pain on a numerical rating scale (0 to 10). The incidence of serious adverse events (SAEs)
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15 259 within six months and the incidence of device-related and wound-related adverse events occurring within 16 weeks
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17 260 or until wound closure confirmation were safety endpoints of this trial.

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20 262 **Statistical analysis**

22 263 Sample size calculation was performed using the expected difference between wound closure rates in both
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24 264 treatment arms based on information extracted from previously published studies by Armstrong and Lavery [16]
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26 265 and Blume [17]. We assumed a complete wound closure rate of 45% for NPWT and 30% in the SMWC group,
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28 266 resulting in a minimum difference of 15% after a treatment time of 16 weeks. Based on a type one error of $\alpha = 0.05$
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30 267 and a type two error of $\beta = 0.2$ (corresponding to a power of 80%) a total sample size of 162 patients per group
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32 268 was calculated. The computer program of Dupont and Plummer was used for sample size calculation [27].

33
34 269 We performed all analyses based on a modified intention-to-treat (ITT) population that includes all randomized
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36 270 participants who have a valid baseline and at least one valid post baseline wound assessment. As a secondary
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38 271 approach a per-protocol (PP) analysis has been performed excluding patients with any serious protocol deviations,
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40 272 like temporary changes from SMWC to NPWT, permanent wound treatment changes or without valid
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42 273 documentation until wound closure confirmation or end of maximum treatment time (EOMT). Safety data are
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44 274 presented on an 'as treated' basis. Subgroup analysis is presented for small vs big wound subpopulations. There
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46 275 was no interim analysis.

47 276 The superiority hypothesis was tested in parallel for wound closure rate and time to wound closure within 16 weeks.
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49 277 Incidence of complete wound closure was analyzed using a chi-squared test (Fisher's exact test) comparing the
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51 278 two treatment arms. Time to complete wound closure was compared between the two treatment arms using a Log-
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53 279 rank test. The method of Bonferroni-Holm was used for adjustment of the α -error for parallel confirmatory testing
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55 280 of both primary endpoints. Missing values have been incorporated as censored values.

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57 281 During study planning, the following concomitant diseases and therapeutic measures with a possible influence on
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59 282 the primary study outcome wound closure (confounders) were identified: presence of neuropathy (sensation loss
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283 according to the PEDIS classification system [28]); presence of diabetic neuropathic osteoarthropathy (DNOAP)

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3 284 (anatomical classification according to Sanders [29] and progression stages according to Levin [30]), Wagner [31]
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5 285 grading of the ulcer; presence of peripheral arterial occlusive disease (Rutherford classification for chronic limb
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7 286 ischemia [32]), chronic venous insufficiency (CVI) (Widmer I-III [33]), presence of extreme foot deformities and
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9 287 malpositions of toes, foot or the entire limb; untreated or therapy-refractory inflammation in the wound area;
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11 288 chronic anemia; heel necrosis; presence of a lymphedema; infection; heightened glycated hemoglobin (HbA1c)
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13 289 level; dialysis; application of hyperbaric oxygen (HBO) or normothermal therapy, application of recombinant or
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15 290 autologous growth factors to the study wound, and application of skin or dermal substitutes and with living cells
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17 291 that produce growth factors. These covariates thought to influence wound closure were analyzed for their effect
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19 292 on the two primary endpoints. Covariates were excluded from the analysis if the number of missing values was
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21 293 too high. First, the relevant covariates were tested by means of a univariate analysis with regard to their effect on
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23 294 wound closure rate and time without consideration of the treatment arms. If there was a significant influence, the
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25 295 frequency of occurrence in the treatment arms was analyzed. Secondary, multivariate analyses were performed for
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27 296 both primary endpoints, taking into account treatment assignment and including all relevant covariates. The
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29 297 multivariate analysis of the primary endpoint wound closure rate was performed with binary logistic regression to
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31 298 describe the influence of the independent covariates (regressors) on the dependent dichotomous variable wound
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33 299 closure. The multivariate analysis of the primary endpoint time to wound closure was performed using a COX
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35 300 regression model.
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37 301 Safety and secondary endpoints were analyzed using conventional univariate testing.
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39 302 Within a priori planned subgroup analysis the ITT population was divided into a group of small wounds and a
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41 303 group of big wounds based on the wound surface area documented during the randomization visit. Wounds smaller
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43 304 than or equal to the total median wound surface (483 mm²) were assigned to the subgroup "small wounds". Patients
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45 305 with wound surface areas larger than the median value were assigned to the subgroup "large wounds". Since no
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47 306 citable scientific definition of a large wound was available at the time of study planning and the clinical experts
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49 307 involved could not make a decision, the median of all wounds was chosen as the criterion for the division into the
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51 308 two subgroups. Confirmatory analysis of primary and secondary endpoints was repeated for the subgroups.
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53 309 Missing values for the following outcome parameters were replaced using the Last Observation Carried Forward
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55 310 (LOCF) method: wound closure rate, wound size and wound tissue quality, recurrence and amputation. The
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57 311 outcome parameters time to wound closure and time until optimal preparation of the wound bed did not require
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59 312 data replacement, since missing values are included in the analysis as right-censored values. If the wound closure
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313 was not confirmed to be closed after a minimum of 14 days, the wound was considered as an unsustained wound
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closure. All missing quality of life values (EQ-5D) were replaced with the overall quality of life assessment (visual

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3 315 analogue scale), if available. If there was no quality of life assessment, there was no replacement. For missing
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5 316 values of the demographic and baseline characteristics, which are necessary for the estimation of the regression
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7 317 coefficients, no replacement was performed. IBM SPSS Statistics (version 23) was used for all analyses.

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9 318 This study is registered with ClinicalTrials.gov. Number NCT01480362 and in the German Clinical Trial Registry,
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11 319 number DRKS00003347.

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13 320 A data monitoring committee was formed to oversee overall study performance and safety.

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16 322 **Role of the funding source**

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18 323 Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds,
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20 324 which provided integrated care contracts for all study participants and for up to 7000 patients with acute and
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22 325 chronic wounds in Germany; defined basic rules for study design based on the requirements of the German
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24 326 authorities; and provided a critical review of the study protocol and the final report. The study was funded by the
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26 327 manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the
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28 328 NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary
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30 329 support and information about the used material. The manufacturers had no role in study design, data collection,
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32 330 data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including
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34 331 statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

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36 332

37 333 **Results**

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39 334 Between Dec 23, 2011 and August 12, 2014 386 patients were enrolled and randomly assigned to receive NPWT
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41 335 (181) or SMWC (187) in the DiaFu-study (**Error! Reference source not found.**) in overall 40 study sites, which
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43 336 recruited minimum 1 patient and maximum 76 patients. 13 clinical investigators randomized more than 10 patients.
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45 337 23 study sites enrolled only between 1 and 4 patients. Most of these study sites refused further study participation
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47 338 due lack of time and staff for adequately performing the documentation. In the further course of the trial research
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49 339 nurses have been hired by the independent scientific institute overseeing the trial in order to support the
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51 340 documentation in the study sites whenever needed.

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55 342 Demographics and relevant baseline characteristics of the DFU are presented in Table 1 and Supplement Table 1.

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57 343 Baseline characteristics of the patients in the NPWT-and the SMWC-arm are similar in the ITT population without
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59 344 any relevant difference between the treatment arms.

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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 (mm²)			
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 (mm²)			

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 \leq 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%) 225 (65.2%)	2 (1.2%) 110 (64.3%)	4 (2.3%) 115 (66.1%)
2 - Ulcers extend into tendon, bone, or capsule	85 (24.6%)	45 (26.3%)	40 (23%)
3 - Deep ulcer with osteomyelitis, or abscess	26 (7.5%)	13 (7.6%)	13 (7.5%)
4 - Gangrene of toes or forefoot	3 (0.9%)	1 (0.6%)	2 (1.1%)
5 - Midfoot or hindfoot gangrene			
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 tcPO₂ < 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%)

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

357

358 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%)

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

364 Results for the primary outcome wound closure in the ITT population

365 In the ITT population, there was no significant difference between the treatment arms for either wound closure
 366 rate (Table 4) or time to complete wound closure ($p=0.244$, Log-Rank test; Figure 2) within 16 weeks. Beginning
 367 in week five the number of study participants with open wounds in the NPWT-arm was lower than in the SMWC-
 368 arm (Figure 2). However, after 16 weeks, the difference between the treatment arms was only 2.5% [-4.7 - 9.7]
 369 (Table 4). Wounds treated with NPWT were approximately at the same risk of remaining open as wounds treated
 370 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

372 Table 4: The table shows the number of patients with wound closure (wound closure rate) and the number of patients with
 373 recurrences (recurrence rate) in the ITT population. Data show the number (N) of participants available for the analysis in
 374 total and for both treatment arms. Wound closures within the maximum study treatment time of 16 weeks and recurrences
 375 during the Follow up of 6 months are shown with the number (N), the percentage (%) of patients, and the 95% Confidence
 376 Interval (CI). *F=Fisher's Exact Test.

377
 378 Since the cumulative number of patients with open wounds was more than 70% after 16 weeks, we could not
 379 calculate medians for the time to wound closure.

380 381 Results for the secondary outcomes in the ITT population

382 Only one recurrence of the foot wound after complete, sustained and confirmed closure was documented for one
 383 study participant in the NPWT arm (Table 4). Study participants treated with NPWT were at higher risk for a
 384 recurrence than participants treated with SMWC 0.96 [0.87-1.04].

385 After 6 months the number of study participants with closed wounds was higher in the SMWC- than in the NPWT-
 386 arm (36 of 174 [20.7 %] vs 24 of 171 [14.0 %]), but the difference was not significant (p 0.12).

387 The time until optimal preparation of the wound for further treatment to achieve a complete epithelization (min 95
 388 % granulation tissue) was significantly shorter for patients treated with NPWT (p 0.021) (Table 5).

389

Time until optimal preparation of the wound bed (min 95 % granulation tissue) within 16 weeks (days) in the ITT population N_{available}	Total N=183	NPWT N=100	SMWC N=83	Mean difference [95% CI] p*
values				
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

390 Table 5: The table shows time until optimal preparation of the wound for further treatment (min 95 % granulation tissue for
 391 the ITT population. Data show the number (N) of participants available for the analysis in total and for both treatment arms.
 392 Time until optimal preparation of the wound is described with Mean and Standard Deviation (SD); Median and Inter Quartile
 393 Range (IQR); and Minimum (Min) and Maximum (Max). *Student's t-test

394
 395 In the ITT population, wound surface area and wound volume were similar at baseline (Table 1) and decreased
 396 continuously during the study treatment time of 16 weeks in both treatment arms (Supplement Tables 2 and 3).
 397 The values are largely scattered. Measurements derived from the blinded photo analysis using the Wound Healing
 398 Analyzing Tool (W.H.A.T.) were smaller than the values documented by the clinical investigators.
 399 Wound tissue composition (Supplement Table 4) was similar in both treatment arms at baseline. Granulation tissue
 400 values increased during the study treatment period of 16 weeks and fibrin values decreased, with clinically
 401 documented values showing only minor differences between treatment arms. The values for necrotic tissue were
 402 very low and did not differ relevantly between the treatment arms. The results of the W.H.A.T. evaluation for
 403 granulation and fibrin deviate markedly from the values documented by the clinical investigators.
 404 Patients treated with NPWT were approximately at the same risk of undergoing an amputation or resection like
 405 patients treated with SMWC (RR: 0.99 [95%CI: 0.65-1.50]) (Table 6).

406

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%)	0 (0%)	1 (0.6%)	1 (0.6%)
	1 (0.3%)	0 (0%)		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)

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

411
412 Overall, pain levels were very low and decreased further during the study treatment time (Supplement Table 5).
413 The values hardly differ between the treatment arms at any observation time point.

414 At baseline, Quality of life (EQ5D) was significantly limited in both treatment arms (Supplement Table 6). EQ5D
415 levels were improved in both study participants reaching end of therapy as well as end of maximum treatment
416 time. On follow-up after 6-months, all patients still showed increased EQ5D levels in both treatment arms.

417 Safety results

418
419 The number of study participants with AEs was significantly higher in the NPWT arm (96 (56.1%)) than in the
420 SMWC arm (72 (41.4%)) (p=0.007) but only 16 (10.2%) of the AEs in the NPWT arm were decided by the
421 investigators to have a definite relation to the medical device (Table 7). The number of study participants with at
422 least one AE documented to be serious (SAE) was not significantly different between the treatment arms (NPWT
423 N=63 (36.8%); SMWC N=58 (33.3%); p=0.50) (Table 7). None of the SAEs in the NPWT-arm was documented
424 as definitely or possibly related to the medical device by the investigators. 9 of 171 (5.3%) study participants in
425 the NPWT arm and 6 of 174 (3.5%) study participants in the SMWC-arm died during the study.

426

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 (%)	168 (48.7%)	96 (56.1%)	72 (41.4%)	24 (14.7%)
[95% CI]	[43,4 -54,0]	[48,7 - 63,6]	[34,1 - 48,7]	[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 (%)	121 (35.1%)	63 (36.8%)	58 (33.3%)	5 (3.5%)
[95% CI]	[30,0 – 40,1]	[29,6 – 44,1]	[26,3 – 40,3]	[-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).

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3 442 In the subgroup of large wounds (wound surface area at randomization shown in Table 1), wound closure rate
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5 443 within 16 weeks was significantly higher in the NPWT-arm (13 of 88 (14.8 [7.4 – 22.2] %)) than in the SMWC-
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7 444 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
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9 445 wounds had a lower risk of not achieving wound closure within 16 weeks when treated with NPWT (RR 0.91
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11 446 [95% CI: 0.82-1.0]) and achieved wound closure significantly faster in the NPWT-arm than in the SMWC-arm (p
12
13 447 0.027) (Figure 3). The only recurrence occurred in the subgroup of large wounds. Both major amputations were
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15 448 performed in study participants with large wounds treated with NPWT.

16 449 In the subgroup of small wounds (wound surface area at randomization shown in Table 1), the time to reach 95 %
17
18 450 granulation tissue was significantly shorter for the patients treated with NPWT than for those treated with SMWC
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20 451 (p 0.005), but wound closure rate and time until wound closure within 16 weeks were not significantly different
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22 452 between the treatment arms (Figure 4). Further details of the subgroup analyses are presented in the Supplement
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24 453 Tables 7 and 8.

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27 28 455 Results for the primary and secondary outcomes in the PP population

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30 456 Demographics, relevant baseline characteristics and the results of the revascularization before study start of the PP
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32 457 population are presented in Supplement Table 9. In the PP population, 14 of 44 study participants (31.8% [95%CI
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34 458 18.1 -45.6]) treated with NPWT and 19 of 110 participants (17.3% [95%CI 10.2 – 24.3]) .treated with SMWC
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36 459 achieved complete, sustained and verified wound closure within 16 weeks, but the difference was not significant
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38 460 (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
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40 461 weeks (RR 0.82 [95%CI: 0.66-1.03]) than wounds treated with SMWC. Time to wound closure in the NPWT arm
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42 462 was significantly shorter than in the SMWC-arm (p=0.004) (Figure 5). After 6 months, wound closure rate in the
43
44 463 SMWC-arm (30 of 110 (27.3% [95%CI 18.9 – 35.6]) was higher than in the NPWT-arm 11 of 44 (25.0% [95%CI
45
46 464 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,
47
48 465 optimal wound bed preparation was achieved significantly faster in patients receiving NPWT (p<0.001). No
49
50 466 recurrences occurred after complete, sustained and confirmed wound closure in the PP population. Neither the
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52 467 number of patients with amputations or resections nor the number of amputations or resections performed .differed
53
54 468 significantly between the treatment arms. No major amputations were performed in the PP population. Further
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56 469 details on the results for the PP population are presented in the Supplement Tables 10 – 16.

57 470

58 471 Treatment compliance

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2
3 472 29 (17.0%) patients in the NPWT-arm had a temporary therapy change to SMWC (mean duration 20.5 ± 21.6
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5 473 days). In the SMWC group, 17 (9.8%) patients had a temporary therapy change to NPWT (mean duration $28.9 \pm$
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7 474 21.6 days). For only 2 of the 29 NPWT patients (6.9%) with a temporary therapy change to SMWC the wound
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9 475 closure was achieved within 16 weeks, whereas 16.2% (23 von 142) of the wounds of the NPWT patients without
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11 476 therapy change were completely closed.

12
13 477 A total of 57.3% (98 of 171) of the patients randomized to NPWT completed treatment before achieving a
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15 478 granulation surface of the wound of at least 95%. Fewer patients with this premature end of NPWT (4.7%, N=8)
16
17 479 achieved a complete wound closure than patients with no premature end of therapy (9.9, N=17). Mean NPWT-
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19 480 duration until premature end of therapy was 28.5 days (SD 24.1), while a mean granulation area of 59.6% (SD 30.
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21 481 5) was achieved. For 131 patients (76.6%) in the NPWT arm less than the required three dressing changes per
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23 482 week were documented. 19 patients (14.5%) with this protocol violation achieved a complete wound closure. Six
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25 483 (15.4%) of the 39 NPWT patients who received at least 3 therapy changes per week achieved a complete wound
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27 484 closure.

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29 486 Documentation quality

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32 487 In the NPWT-arm 52 study participants and in the SMWC-arm 43 participants were excluded from the PP
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34 488 population due to missing documentation until the end of maximum treatment time or at wound closure
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36 489 confirmation (Figure 1). In the electronic Case Report Forms (eCRF) a wound closure was documented for 96
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38 490 patients (NPWT 56 of 171; SMWC 40 of 174), but only for 46 participants (NPWT 25; SMWC 21) all criteria for
39
40 491 a complete, verified and sustained wound closure have been met. For the wound closure visit seven wound
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42 492 photographs (NPWT 7; SMWC 0) and for the wound closure confirmation visit four photographs (NPWT 3;
43
44 493 SMWC 1) were missing. In addition, two of the existing wound photographs for wound closure (NPWT 0; SMWC
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46 494 2) and two photographs for wound closure confirmation (NPWT 1; SMWC 3) were not assessable by the blinded
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48 495 observers due to serious quality issues. Furthermore 23 (NPWT 15; SMWC 8) existing and assessable wound
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50 496 photographs were not able to confirm the wound closure and 3 (NPWT 1; SMWC 2) photographs were not able
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52 497 to confirm the wound closure after 14 days.

53 498

54 499 **Discussion**

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56
57 500 The DiaFu-study did not demonstrate significant superiority in wound closure rate or time to complete wound
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59 501 closure for neither NPWT nor SMWC. Wound closure rates were higher in the NPWT arm but did not significantly
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502 differ from those in the SMWC arm. Time to wound healing in the NPWT group was lower than in the SMWC

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3 503 arm while the difference between the treatment arms becomes statistically significant only in the PP population.
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5 504 Thus, with this study we were not able to confirm our hypothesis that wound closure can be achieved more often
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7 505 and faster with NPWT than with SMWC when used in German real-life clinical practice. Previous RCTs, which
8
9 506 were the basis for sample size calculation, showed a higher rate and a significant superiority in healing when using
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11 507 NPWT on amputation and chronic wounds [16, 17], but the populations of these studies were different. Other than
12
13 508 the Armstrong-study, the DiaFu-study did not exclude patients with venous insufficiency and included more than
14
15 509 twice as many patients. The studies of Armstrong and Blume excluded patients with Wagner stage four; active
16
17 510 Charcot; uncontrolled hyperglycemia and therapy with glucocorticoids, immunosuppressants or chemotherapy;
18
19 511 and required proof of adequate perfusion. The DiaFu-study, did not exclude patients with impaired perfusion, but
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21 512 required adequate therapy of the circulatory disorder according to clinical practice guidelines. In the DiaFu-study,
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23 513 we were able to show that the presence of PAOD at randomization had a significant influence on the time to wound
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25 514 closure but not on the overall wound closure rate within the maximum study treatment time. The number of patients
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27 515 with critical limb ischemia at baseline was low and differed only slightly between the treatment arms. As in clinical
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29 516 practice, in the DiaFu-study adequate treatment of concomitant diseases was mandatory. Invasive therapy of
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31 517 POAD could be performed before initiation of wound therapy as well as during the study treatment period, if the
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33 518 wound needed pretreatment as a basis for the revascularization procedure or if new or recurrent critical ischemia.
34
35 519 The presence of clinical signs of inflammation (suspected infection) at randomization had a significant effect on
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37 520 both, time to wound closure and wound closure rate within 16 weeks. Both covariates were equally represented in
38
39 521 the treatment arms, thus the differences in time until wound closure and wound closure rate were not affected by
40
41 522 these confounders.
42
43 523 However, the probably most serious factors negatively influencing treatment and outcome are documentation
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45 524 deficiencies and deviations from treatment guidelines. Temporary therapy changes and premature therapy
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47 525 cessation negatively impacted the patient relevant treatment outcome wound closure in study participants treated
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49 526 with NPWT. Missing study visits resulting in low numbers of complete endpoint documentations strongly affected
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51 527 the proof of the outcome wound closure in both, the NPWT- and the SMWC-arm.
52
53 528 Optimal preparation of the wound bed (95% granulation tissue) was achieved significantly earlier when using
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55 529 NPWT in the ITT and the PP population, but the overall rate of wound closures was low. Wound bed preparation
56
57 530 and granulation tissue formation are important prerequisites for wound healing, but are not a proof of treatment
58
59 531 effectiveness and cannot serve as a basis for benefit assessment.
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532 Although significantly more AEs were documented in the NPWT-arm only a small number of these events were
533 related to the medical device according to the investigator's assessment. Mortality rates were very low in both

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3 534 treatment arms and there was no significant difference between the treatment arms regarding amputations and
4
5 535 resections performed during the study. Only two major amputations have been performed in patients with big
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7 536 wounds treated with NPWT. None of the treatments resulted in an additional impairment of the patients' quality
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9 537 of life during study treatment time or follow up. Time until complete wound closure was significantly shorter with
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11 538 NPWT than with SMWC in the subgroup of big wounds, which indicates that NPWT has the potential to be a
12
13 539 valuable treatment option for this kind of wounds.

14
15 540 In the DiaFu-study methods against bias have been implemented whenever possible in order to avoid bias that
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17 541 have been described by several systematic reviews [18-22], but blinding of study participants as well as attending
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19 542 physicians and nurses was not possible due to the nature of NPWT..

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21 543 Not addressing and analyzing all factors influencing the overall treatment outcome like targeted pressure relief,
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23 544 continuous infection control and adequate treatment of the underlying disease during the study treatment and
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25 545 observation period may be seen as a limitation of this health care research study. Study sites have been selected
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27 546 based on a self-disclosure by means of a qualification checklist and cross checks using quality reports. This ensured
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29 547 that all prerequisites were met for guideline-compliant patient care. Nevertheless, even in the application of NPWT
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31 548 there were deviations from the standards.

32
33 549 In order to support the decision-making process of the German G-BA on general reimbursement of NPWT in
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35 550 German outpatient care the real-life clinical practice DiaFu-study included patients with chronic DFUs of
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37 551 neuropathic and angiopathic origin regardless of whether a simple wound cleansing, tissue debridement or even
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39 552 amputation was necessary prior to application of wound therapy targeted to achieve complete wound closure. The
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41 553 study was performed without excluding concomitant diseases negatively impacting wound healing; with therapy
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43 554 application in the discretion of the attending physician; and with evaluation of patient relevant outcome. Thus,
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45 555 results can easy be generalized and applied in clinical practice settings. Anyway, shortcomings in data quality
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47 556 negatively impacted the study results and statements about specific patient groups were not possible. A high
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49 557 number of study participants needed to be excluded from the PP population (NPWT 127 of 171 (74%), SMWC
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51 558 arm 64 of 174 (37%). For most of these participants, documentation was lacking until the end of the maximum
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53 559 treatment period (Total=88, NPWT=49, SMWC=39) (Figure 1). In the primary analysis based on the ITT
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55 560 population it was assumed that these patients did not achieve wound closure within 16 weeks study treatment and
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57 561 observation time (using the last observation carried forward (LOCF) method, the open wound status was "carried
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59 562 forward" until the end of the maximum treatment period. This may have led to a false negative bias in the outcome
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563 wound closure in the ITT population. Due to the high loss of patients and the difference in the number of
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564 participants excluded from the treatment arms, the validity of the PP analysis is very limited.

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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.

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3 **581 Ethics approval and consent to participate**
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5 582 Ethical approval of the main ethical committee (EC): Ethical Committee of the University of Witten-Herdecke,
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7 583 has been fully granted without any conditions. Due to performing the trial according to § 23b MPG (German
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9 584 Medical Device Act), participating study sites in Germany only received a consultation for the main clinical
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11 585 investigator according to professional law by the respective EC. All investigators have been fully approved by the
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13 586 respective ECs. An evaluation of the study's content by ECs of participating study sites in Germany was not
14
15 587 applicable. All study participants gave written informed consent prior to randomization and any trial related
16
17 588 procedure.
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19 589

20 **590 Data sharing**
21

22 591 The datasets analyzed for the results presented in this article are available from the corresponding author on
23
24 592 reasonable request. Datasets are available in German language.
25

26 593

27
28 **594 Competing interests**
29

30 595 All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare:
31
32 596 The German statutory health insurance companies commissioned the Witten/Herdecke University (UW/H) to plan,
33
34 597 conduct, analyze and publish the study. Dörthe Seidel is an employee of the UW/H. The study has been financed
35
36 598 by the manufacturers KCI (Acelity) and Smith&Nephew. Dörthe Seidel received a consulting fee for the
37
38 599 presentation of the study during an event organized by the manufacturer Hartmann. During study planning and
39
40 600 conduct Edmund Neugebauer was an employee of the UW/H. He was the director of the IFOM.

41 601 The clinical investigators Martin Storck, Holger Lawall, Gernold Wozniak, Peter Maukner, Dirk Hochlenert,
42
43 602 Walter Wetzel-Roth, Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink
44
45 603 received a case fee of 1000 € for each patient included in the DiaFu-study in order to compensate for the additional
46
47 604 organizational and especially the documentation effort during trial conduct. Furthermore all investigators received
48
49 605 compensation for travelling to the investigator meetings. The institutions of the investigators used integrated care
50
51 606 contracts for NPWT during study conduct in order to provide best practice for the study participants during
52
53 607 outpatient care.

54
55 608 Gernold Wozniak and Walter Wetzel-Roth are members of the scientific advisory board of the manufacturer
56
57 609 Kinetic Concepts Incorporated (KCI) (now Acelity).
58

59 610

60 **611 Funding**

1
2
3 612 Through a European tender the study was initiated by a consortium of 19 statutory German health insurance funds,
4
5 613 which provided integrated care contracts for all study participants and for up to 7000 patients with acute and
6
7 614 chronic wounds in Germany; defined basic rules for study design based on the requirements of the German
8
9 615 authorities; and provided a critical review of the study protocol and the final report. The study was funded by the
10
11 616 manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew (S&N). Both companies provided the
12
13 617 NPWT devices and associated consumable supplies in the assigned regions of Germany as well as all necessary
14
15 618 support and information about the used material. The manufacturers had no role in study design, data collection,
16
17 619 data analysis, data interpretation, or writing of the report. All authors had full access to all of the data (including
18
19 620 statistical reports and tables) in the study and take full responsibility for the accuracy of the data analysis.

20 621

22 622 **Authors' contributions**

23
24 623 Dörthe Seidel was the principal coordinating investigator. She conceived the study, reviewed the scientific
25
26 624 literature, and was responsible for study design, data analysis, data interpretation, writing and reviewing of the
27
28 625 report. She is the lead author and takes overall responsibility for this report. She affirms that the manuscript is an
29
30 626 honest, accurate, and transparent account of the study being reported; that no important aspects of the study have
31
32 627 been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have
33
34 628 been explained.

35
36 629 Martin Storck and Holger Lawall were study investigators and contributed to study design, data collection and
37
38 630 interpretation, and reviewed the report.

39
40 631 Gernold Wozniak, Peter Maukner, Walter Wetzels-Roth and Dirk Hochlenert were study investigators and
41
42 632 contributed to data collection and data interpretation and reviewed the report.

43
44 633 Klemens Sondern, Matthias Hahn, Gerhard Rothenaicher, Thomas Krönert and Karl Zink were study investigators
45
46 634 and contributed to data collection and reviewed the report.

47 635 Edmund Neugebauer contributed to study design and data interpretation and reviewed the report.

48
49 636 All authors approved the final version of the report.

51 637

53 638 **Acknowledgements**

54
55 639 The authors thank all investigators, nurses, patients and partners for supporting the study.

56
57 640 At least one patient was included in the following facilities: HSK - Dr. Horst Schmidt Kliniken GmbH Klinik für
58
59 641 Gefäßchirurgie Ludwig-Erhard-Straße 100 65199 Wiesbaden; Asklepios Westklinikum Hamburg Zentrum für
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33 658 Dorothea Christiane Erxleben GmbH Klinik für Allgemein-, Viszeral- und Gefäßchirurgie Ditfurter Weg 24 06484
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37 660 Hegau-Bodensee Klinikum Radolfzell (HBK) Klinik für Innere Medizin Hausherrenstraße 12 78315 Radolfzell;
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39 661 Diabetologische Schwerpunktpraxis Dr. med. Hansjörg Mühlen & Partner Ruhrorter Straße 195 47119 Duisburg;
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9 677 Ludwigshafen; Mariannen-Hospital Werl Abt. für Chirurgie Unnaer Straße 15 59457 Werl; Diabetes Klinik GmbH
10
11 678 & Co KG Theodor-Klotzbücher-Straße 12 97980 Bad Mergentheim; Institut für Diabetesforschung Münster
12
13 679 GmbH Hohenzollernring 70 48145 Münster.

14 680 The study was initiated by a consortium of 19 statutory German health insurance funds represented by the AOK
15
16 681 federal association (AOK-Bundesverband – AOK-BV), the association of alternative health insurance funds
17
18 682 (Verband der Ersatzkrankenkassen – vdek) and the minors (Knappschaft). In order to guarantee outpatient care for
19
20 683 all study participants without any restrictions, the contracting health insurance companies provided integrated care
21
22 684 contracts for outpatient negative pressure wound therapy.

23
24 685 A project advisory board was implemented to coordinate all processes and project partners. The board comprised
25
26 686 two representatives each from the statutory health insurance funds, the management company and the sponsor as
27
28 687 well as one representative each from the participating medical device manufacturers (KCI and smith & nephew).
29
30 688 Representing the contracting authority (statutory German health insurance funds) Dr. Gerhard Schillinger (AOK-
31
32 689 BV) and Ute Leonhard (vdek) acted as contact persons for all aspects of the project.

33
34 690 The management company “Gesundheitsforen Leipzig” has been entirely responsible for the logistics of the study.
35
36 691 Central tasks of the management company included the recruitment of study sites and patients, the development
37
38 692 of the IT infrastructure including the documentation, communication and invoicing software as well as the
39
40 693 processing of all payments.

41 694 The manufacturers Kinetic Concepts Incorporated (KCI) (Acelity) and smith & nephew provided the NPWT
42
43 695 devices as well as support and training for the investigators and financed the study.

44
45 696 The Private University of Witten/Herdecke gGmbH acted as the Sponsor of the trial and the Institute for Research
46
47 697 in Operative Medicine with its former director Prof. E.A.M. Neugebauer, the current interim head Prof. Rolf
48
49 698 Lefering and the head of the division for clinical research Dörthe Seidel was responsible for the scientific
50
51 699 conception, the evaluation as well as the reporting and publication of the study. Prof. Dr. Rolf Lefering was
52
53 700 responsible for the statistical planning and analysis. PD Dr. Peter Krüger was responsible for the data management
54
55 701 of the study. Special thanks are going to Stefan Bauer, who supported the data management as well as the statistical
56
57 702 analysis and reporting.

58 703 We would like to thank Sophie Thorn, who checked the article as a native English speaker with regard to spelling
59
60 704 and grammar.

705 **List of figures:**

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Figure 1: Trial profile (CONSORT)

190x275mm (300 x 300 DPI)

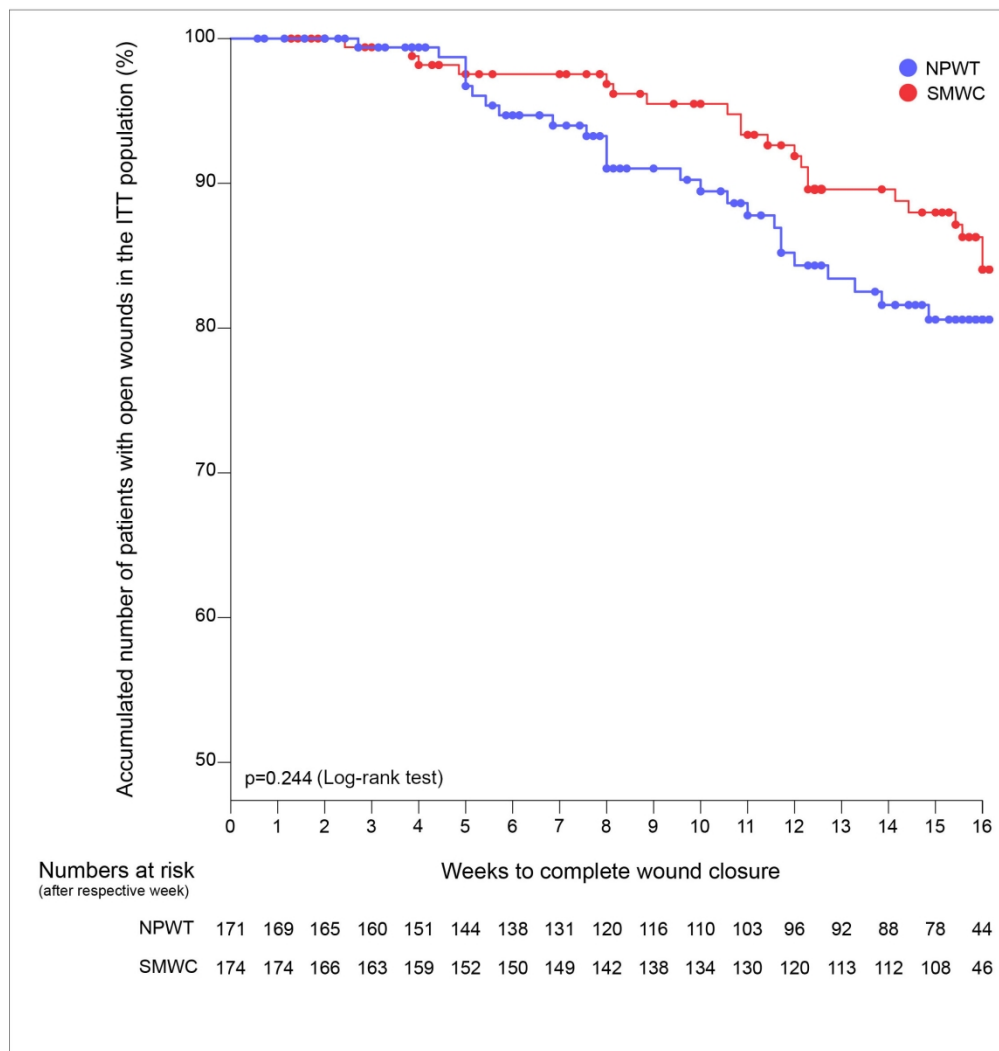


Figure 2: Time until complete, sustained and verified wound closure in the ITT population

189x198mm (300 x 300 DPI)

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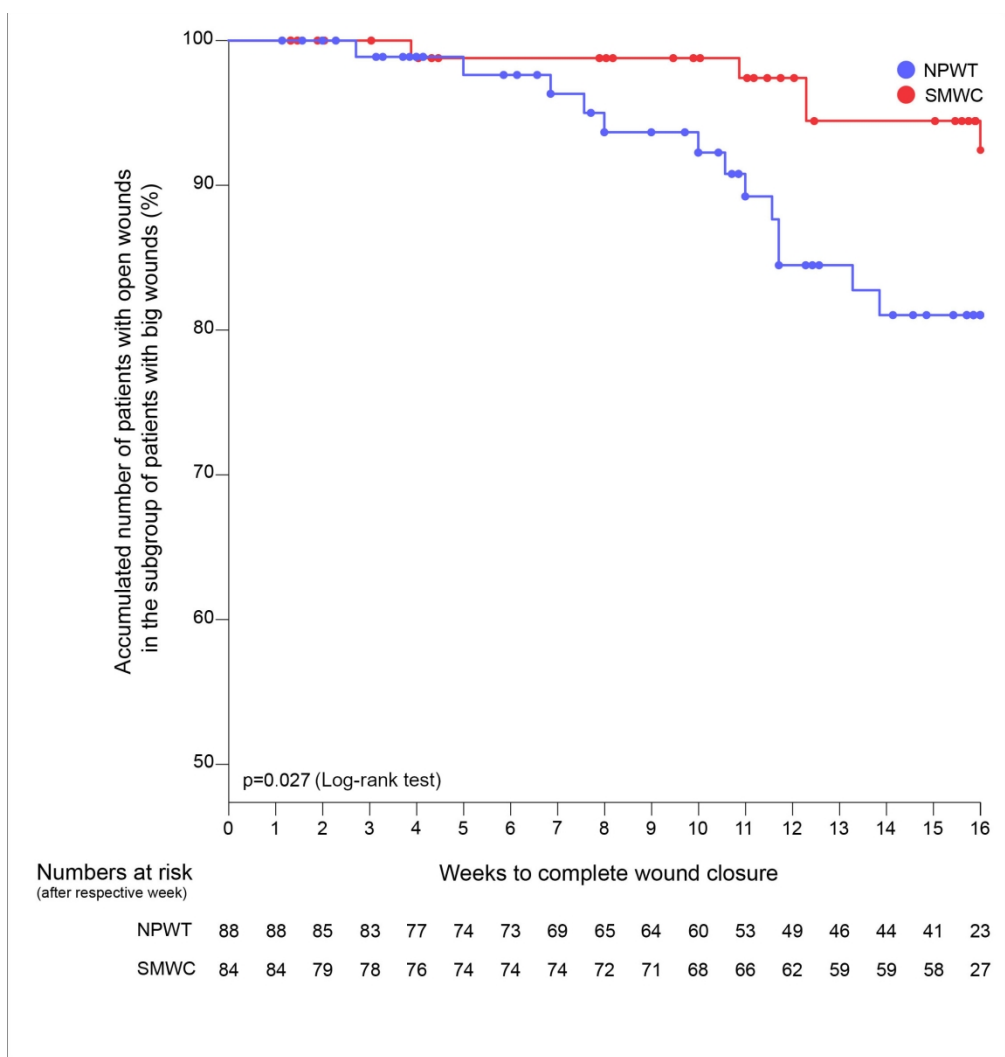


Figure 3: Time until complete, sustained and verified wound closure for the subgroup of big wounds

189x198mm (300 x 300 DPI)

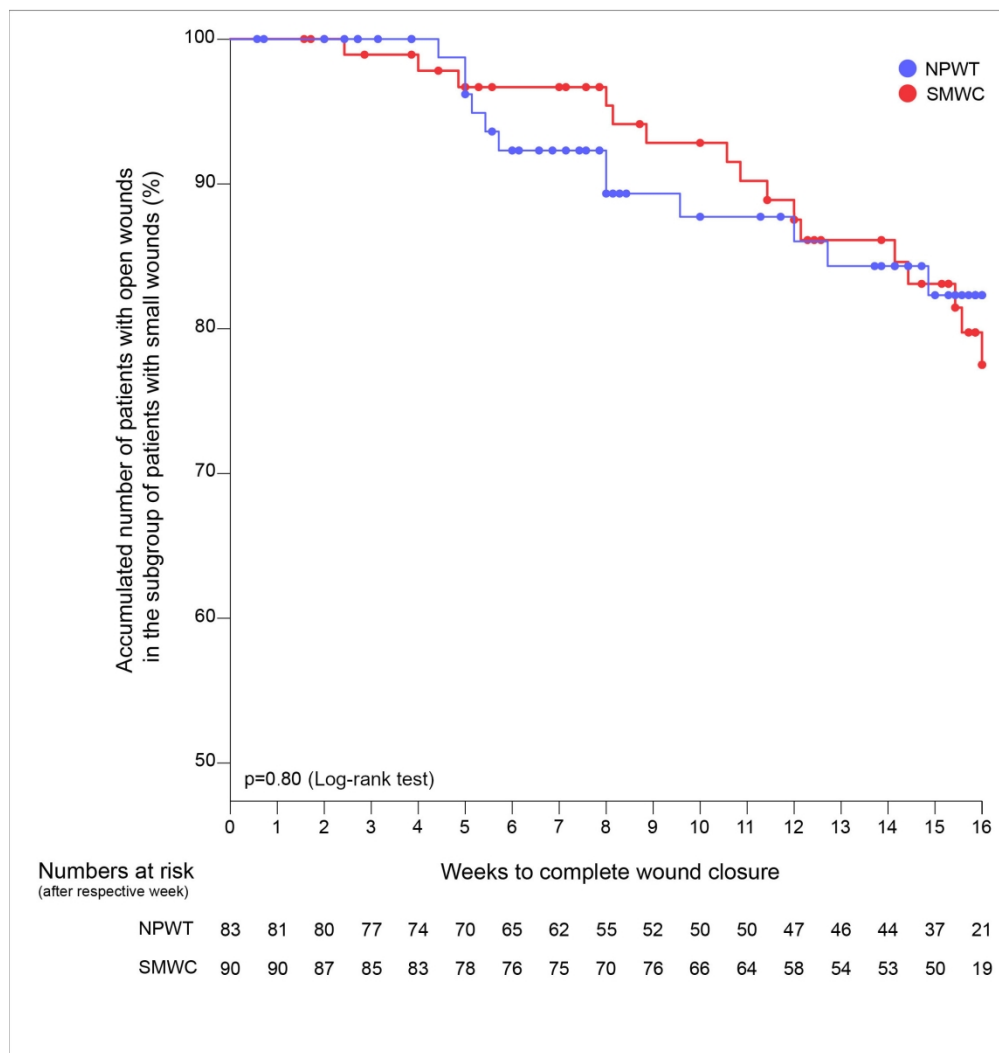


Figure 4: Time until complete, sustained and verified wound closure for the subgroup of small wounds

189x198mm (300 x 300 DPI)

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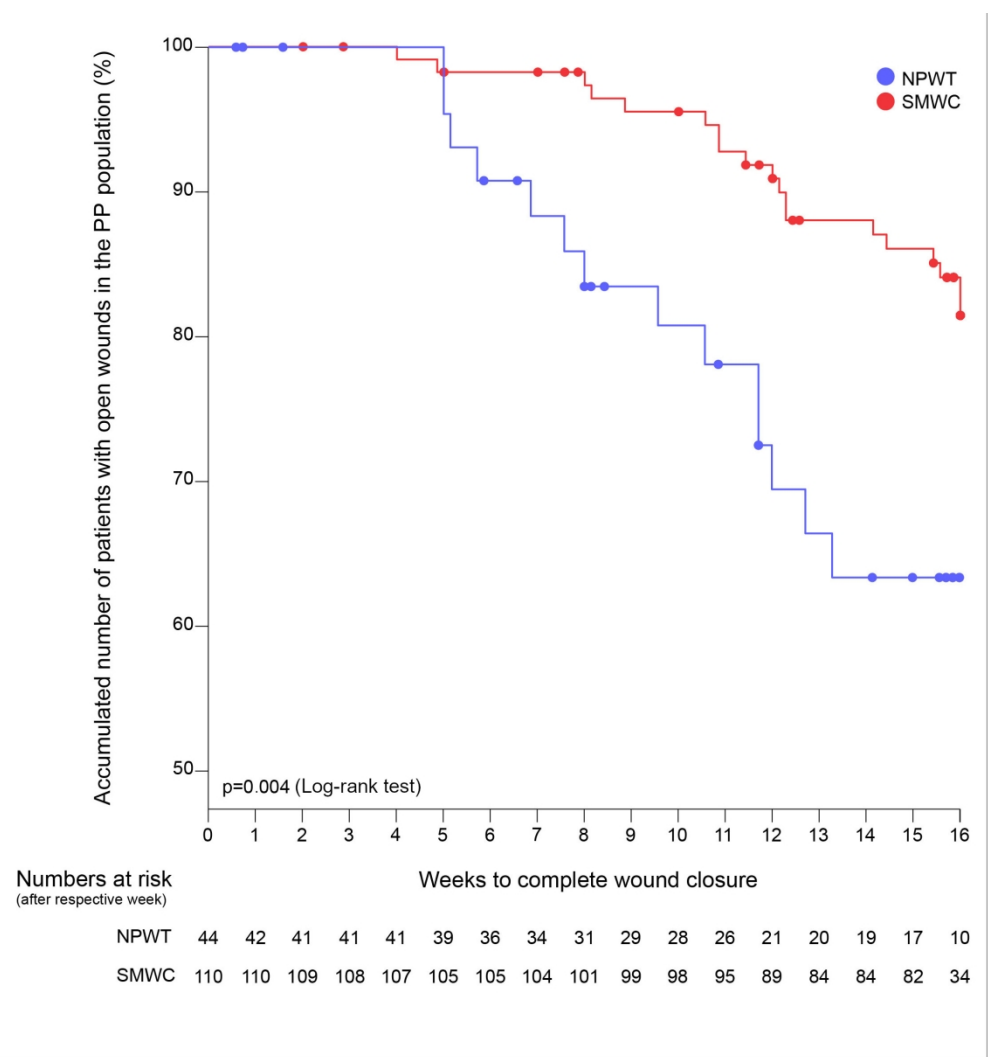


Figure 5: Time until complete, sustained and verified wound closure in the PP-population
189x198mm (300 x 300 DPI)

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) $[(\pi / 4) \times \text{length} \times \text{width} = \text{area}]$. 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 number of values substituted by the last observation carried forward (LOCF) method (in brackets).

Wound volume (mm³) 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)	22 (25)	21 (28)	71 (27)	3 (10)	7 (15)	34 (37)	24 (26)	22 (29)	69 (28)	2 (9)	7 (14)
	20 (70)	12 (37)	10 (30)	79 (46)	0 (0)	0 (5)	20 (71)	14 (39)	10 (40)	79 (44)	0 (0)	0 (8)
	171 (2)	118 (8)	170 (4)	118 (8)	169 (5)	118 (8)	174 (3)	129 (12)	174 (1)	129 (12)	172 (2)	129 (12)
Week 1	58 (35)	21 (25)	19 (22)	73 (27)	5 (13)	6 (12)	49 (35)	21 (25)	24 (27)	74 (26)	6 (15)	5 (9)
	70 (70)	10 (36)	10 (30)	81 (47)	0 (2)	0 (5)	50 (70)	10 (36)	15 (31)	85 (40)	0 (5)	0 (5)
	171 (16)	118 (32)	71 (19)	118 (32)	169 (23)	118 (32)	174 (28)	129 (36)	174 (27)	129 (36)	172 (30)	129 (36)
Week 3	67 (31)	16 (23)	18 (22)	80 (25)	5 (13)	4 (11)	57 (32)	21 (25)	25 (26)	77 (25)	5 (13)	3 (7)
	80 (55)	5 (25)	10 (30)	91 (30)	0 (0)	0 (1)	60 (60)	10 (36)	20 (35)	85 (36)	0 (3)	0 (1)
	171 (26)	118 (27)	171 (30)	118 (27)	169 (28)	118 (27)	174 (24)	129 (35)	174 (25)	129 (35)	172 (30)	129 (35)
Week 5	70 (30)	15 (22)	18 (24)	83 (22)	4 (13)	2 (8)	62 (31)	18 (26)	23 (25)	80 (26)	4 (12)	3 (10)
	80 (45)	6 (21)	10 (25)	91 (26)	0 (0)	0 (1)	63 (50)	4 (32)	10 (39)	93 834	0 (0)	0 (0)
	171 (36)	118 (43)	171 (38)	118 (43)	169 (42)	118 (43)	174 (44)	129 (36)	174 (47)	129 (36)	172 (46)	129 (36)
Week 8	74 (30)	16 (23)	17 (24)	82 (24)	4 (13)	2 (6)	70 (29)	17 (24)	17 (21)	80 (25)	5 (13)	3 (11)
	90 (40)	4 (27)	10 (20)	93 (33)	0 (0)	0 (0)	80 (40)	3 (33)	10 (20)	92 (36)	0 (0)	0 (0)
	171 (53)	118 (48)	171 (56)	118 (48)	171 (59)	118 (48)	174 (44)	129 (43)	174 (49)	129 (43)	174 (52)	129 (43)
Week 12	75 (30)	15 (23)	17 (25)	83 (24)	4 (13)	1 (5)	73 (29)	16 (23)	16 (20)	82 (23)	5 (13)	2 (6)
	90 (40)	4 (22)	5 (20)	96 (23)	0 (0)	0 (0)	80 (38)	3 (29)	10 (20)	93 (32)	0 (0)	0 (0)
	171(115)	118 (89)	171(118)	118 (89)	171(119)	118 (89)	174(124)	129(102)	174(125)	129(102)	172(126)	129(102)
Week 16	77 (30)	13 (22)	14 (22)	86 (24)	3 (10)	1 (6)	76 (30)	17 (24)	15 (24)	81 (24)	3 (13)	2 (6)
	90 (40)	1 (17)	2 (20)	98 (19)	0 (0)	0 (0)	90 (40)	4 (31)	5 (20)	93 (35)	0 (0)	0 (0)
	171 (78)	118 (66)	171 (79)	118 (66)	171 (82)	118 (66)	174 (62)	129 (576)	174 (65)	129 (56)	174 (66)	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	28 of 173	12 of 83	16 of 90	4
%	16.2%	14.5%	17.8%	3.3%
[95%CI]	[10.7 – 21.7]%	[6.9 – 22.0]	[9.9 – 25.7]	[-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}	100	52	48	
Mean (SD)	38.6 (37.4)	28.5 (30.0)	49.5 (41.6)	21.0 (11.0)
Median (IQR)	26.5 (50.0)	20.0 (28.0)	48.0 (79.0)	[6.9 – 35.1]
Min-Max	0-114	0-113	0-114	
				0.005*
No. of study participants with amputations or resections within 16 weeks N	35 of 173	19 of 83	16 of 90	3
%	20.2%	22.9%	17.8%	5.1%
[95%CI]	[14.2 - 26.2]	[13.9 - 31.9]	[9.9 - 25.7]	[-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	37 von 173	13 of 83	24 of 90	11
%	21,4%	15.7%	26.7%	11%
[95%CI]	[15.3 – 27.5]	[7.8 – 23.5] .	[17.5 – 35.8] .	[-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	NPWT	SMWC	Difference
	172 of 345	N=88 of 171	N=84 of 174	[95%CI]
				p
Wound closure rate within 16 weeks N				
%	18 of 172	13 of 88	5 of 84	8
[95%CI]	10,5% [5.9 – 15.0]	14.8% [7.4 – 22,2]	6.0% [0.9 – 11.0] .	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}	80	47	33	
Mean (SD)	47.8 (40.8)	43.4 (37.9)	54.0 (44.6)	10.6 (6.7)
Median (IQR)	36.5 (70.0)	35.0 (61.0)	56.0 (105.0)	[-7.6 – 28.8]
Min-Max	0 - 127	0 - 127	0 -115	0.27*

No. of patients with amputations or resections within 16 weeks				
N	36 of 172	16 of 88	20 of 84	4
%	20.9	18.2%	23.8%	5.6%
[95%CI]	[14.9 – 27.0] %	[10.1 – 26.2]	[14.7 – 32.9]	[-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
%	13.4%	12.5%	14.3%	-1.8%
[95%CI]	[8.3 – 18.5]	[5.6 – 19.4]	[6.8 – 21.8]	[-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	N=154	N=44	N=110
Mean (SD)	67.4 (10.6)	66.5 (11.0)	67.8 (10.4)
Height in cm	N=153	N=43	N=110
Mean (SD)	173.8 (12.9)	173.5 (17.4)	174.0 (10.7)
Weight in kg	N=150	N=42	N=108
Mean (SD)	95.4 (23.3)	96.2 (21.6)	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	30 of 154	9 of 44	21 of 110	12
N (%)	19.5 %	20.5 %	19.1 %	1.4%
[95%CI]	[13,2 – 25,7]	[8,5 - 32,4]	[11,7 – 26,4]	[-12.6 – 15.4]
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 (mm²) 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) $[(\pi / 4) \times \text{length} \times \text{width} = \text{area}]$. 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 number of values substituted by the last observation carried forward (LOCF) method (in brackets).

Wound volume (mm³) 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)	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)

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)	0.65 (0.20)	0.81 (0.14)
	0.76 (0.26)	0.78 (0.20)	0.87 (0.26)
	N=34 (2)	N=26 (2)	N=8 (0)
End of maximum study treatment time	0.66 (0.22)	0.65 (0.25)	0.66 (0.21)
	0.63 (0.28)	0.66 (0.43)	0.63 (0.28)
	N=92 (2)	N=19 (0)	N=73 (2)
Follow up after 6 months	0.71 (0.23)	0.75 (0.22)	0.70 (0.23)
	0.77 (0.34)	0.78 (0.30)	0.77 (0.34)
	N=99 (2)	N=26 (0)	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.