

## ORIGINAL ARTICLE

# A randomised, open-label, parallel-group, multicentre, comparative study to compare the efficacy and safety of Exufiber<sup>®</sup> with Aquacel<sup>®</sup> Extra<sup>™</sup> dressings in exuding venous and mixed aetiology leg ulcers

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## Abstract

The performance and safety of Exufiber<sup>®</sup> gelling fibre and Aquacel<sup>®</sup> Extra<sup>™</sup> Hydrofiber<sup>®</sup> wound dressings were compared for the management of chronic, exuding leg ulcers. The 6-week study ( $\leq 24$  weeks in a subgroup of subjects) was a randomised, open-label, parallel-group, multicentre, non-inferiority design. Adults ( $n = 248$ , 30–97 years of age) were randomised to either Exufiber<sup>®</sup> or Aquacel<sup>®</sup> Extra<sup>™</sup> dressing. The dressings were applied at baseline and evaluations of wound condition and performance of the dressing were recorded at 1, 2, 3, 4, and 6 weeks. The primary efficacy endpoint was the percentage reduction in wound area at 6 weeks relative to baseline, in the per protocol (PP) population. A median relative reduction of 50% for Exufiber<sup>®</sup> ( $n = 100$ ) vs 42% for Aquacel<sup>®</sup> Extra<sup>™</sup> ( $n = 107$ ) was demonstrated in the PP population ( $P = 0.093$ ) and confirmed in the intention-to-treat population. As the mean and 95% confidence interval for the difference in relative wound area reduction between groups at 6 weeks was  $-29.4\%$  ( $-63.5; 3.2$ ), and the lower limit did not exceed 12%, non-inferiority of Exufiber<sup>®</sup> was concluded. Both dressings were well tolerated and no safety concerns were identified in both groups. Clinicians' satisfaction with the dressings was higher for Exufiber<sup>®</sup> than for Aquacel<sup>®</sup> Extra<sup>™</sup> in terms of ease of use and management of exudate, slough, and blood.

## KEYWORDS

clinical trial, Exufiber<sup>®</sup>, gelling fibre dressings, leg ulcer, exudate

## Key Messages

- gelling fibre dressings are recommended for their ability to maintain a moist wound healing environment by absorbing wound exudate to form a cohesive gel and are particularly important in venous ulcers, which are very often exuding

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- the 6-week study was a randomised, open-label, parallel-group, multicentre, and non-inferiority design involving 248 adults with exuding leg ulcers
- Exufiber<sup>®</sup> was non-inferior to Aquacel<sup>®</sup> Extra<sup>™</sup> with regard to wound reduction at 6 weeks. A median relative reduction of 50% for Exufiber<sup>®</sup> (n = 100) vs 42% for Aquacel<sup>®</sup> Extra<sup>™</sup> (n = 107; *P* = 0.093) was reported (per protocol [PP] population). Although this difference was not statistically significant, a trend towards greater mean relative wound reduction was shown for Exufiber<sup>®</sup>
- clinicians' opinions were highly favourable towards Exufiber<sup>®</sup> in virtually every aspect of the dressing's features and technical performance, such as ease of removal, non-adherence to wound bed and periwound skin, ability to absorb and retain exudate, ability to retain slough and blood, and overall experience

## 1 | INTRODUCTION

Although wound exudate is commonly thought to be a negative feature of wound healing, it does, in fact, have a number of beneficial healing properties, including the maintenance of a moist wound bed (preventing the wound from drying out), helping the migration of skin cells, providing essential nutrients to the wound and encouraging autolysis.<sup>1</sup> Exudate does become an issue, however, when its volume becomes excessive and when its composition changes (e.g., when it becomes thick); steps must be taken to manage the exudate to prevent complications. Upstream all causes of exudates should have been researched and controlled. The main etiologies of exudates in venous ulcers are probably non-adherence to venous compression or insufficient compression pressure.

Poor management of exudate in chronic wounds can lead to a number of problems, including wound and periwound breakdown or maceration due to leakage and a delay in healing. In chronic wounds, excessive levels of exudate within the wound bed can lead to elevated proteolytic activity due to an imbalance in the levels of certain matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, resulting in tissue destruction and a delay in healing.<sup>2</sup>

The presence of excess exudate not only affects the clinical outcome of the wound (delay in healing, infection), but can also negatively impact patients, in terms of discomfort and pain, leakage, malodour, and increased frequency of dressing changes and soiling of clothes.<sup>3,4</sup> Furthermore, healthcare resources are likely to be increased, related to extended treatment periods, increased requirement for dressings, more staff time, and requirement for antimicrobials and other medication.<sup>3</sup> Therefore, when excess exudate is present in a wound, steps must be taken quickly to prevent wound deterioration, periwound skin damage (e.g., maceration), wound infection and delay in healing.

Dressing selection for chronic, exuding wounds is a key aspect of effective wound management and any dressing selected must be able to adapt to a changing wound environment, particularly in chronic wounds that do not necessarily follow the usual steps of healing. Although wound dressings are essential, dressing-associated complications are not uncommon and can lead to an increase in wound size as well as further hindering wound healing. Dressing-related issues include suboptimal moisture balance, adherence to the wound bed, mechanical stress and movement, presence of foreign bodies, suboptimal temperature and chemical imbalance and stress.<sup>5,6</sup> The ideal wound dressing for chronic, exuding wounds should be able to handle fluid (absorption and retention of exudate and its components, even under pressure), reduce the risk of leakage and spread of exudate onto the periwound area (reducing the risk of maceration) and provide a barrier against infection.<sup>7</sup> Other attributes are that the dressing should have conformability, be comfortable for patients to wear, be easy to use, provide optimal dressing change frequency, minimise unnecessary wound disturbance and be cost-effective.<sup>7</sup>

Gelling fibre and Hydrofiber dressings are recommended for their ability to maintain a moist wound healing environment by absorbing wound exudate to form a cohesive gel; the gelling action of the dressing facilitates debridement by autolysis.<sup>8</sup> Exufiber<sup>®</sup> (Mölnlycke Health Care AB, Gothenburg, Sweden) and Aquacel<sup>®</sup> Extra<sup>™</sup> (ConvaTec Group Plc, Reading, UK) are two dressings with these properties that are used to manage chronic, exuding wounds, such as venous leg ulcers (VLUs). It is well documented that venous ulcers are difficult to manage, not least because of the amount of pain they cause to patients.<sup>9</sup> A wealth of evidence supports the use of Aquacel<sup>®</sup> Extra<sup>™</sup> in wounds with elevated levels of exudate. The dressing was used effectively to manage moderate to high levels of exudate, resulting in a reduced need for

dressing change and resource use, as well as being scored positively on patient-recorded outcomes, such as pain and comfort.<sup>10</sup> Exufiber<sup>®</sup> is a next-generation gelling fibre dressing containing Hydrolock<sup>®</sup> Technology that both absorbs and locks away exudate within the fibres. It has been shown to lower the risk of leakage and maceration creating an optimal healing environment for highly exuding wounds such as VLU and cavity wounds.<sup>11</sup>

It is also important that the selected dressing is able to maintain its fluid management capacity even when exposed to the impact of real-world factors that can affect dressing performance. Dressings must maintain their mechanical strength and remain fully intact under the effect of any potential forces, including bodyweight forces, throughout the period of use.<sup>12</sup> Using a novel experimental approach and robotic computer-controlled phantom of an exuding sacral pressure ulcer, Lustig et al. (2020) demonstrated the consistent transfer of fluids from Exufiber to a secondary dressing when different simulated patient body postures were applied.<sup>12</sup> The authors highlighted how dressing structure interacts with the patient and individual wound characteristics, as well as environmental factors acting on the wound and that this type of laboratory method and the system allows for the investigation of dressing performance, with exposure of dressings to exudate-like fluids at the chemical, mechanical, thermodynamic and use conditions which replicate real-world settings.<sup>12</sup> Exufiber demonstrated a higher sorptivity (defined by the authors as the ability of dressings to transfer exudate away from the wound bed by capillary action) and better durability (defined by the authors as the capacity of dressings to maintain their [structural] integrity over time and during their removal), withstanding five times greater strain energy than the comparator product before failure occurred when tested in the supine configuration.<sup>12</sup>

The main aim of this study was to compare Exufiber<sup>®</sup> and Aquacel<sup>®</sup> Extra<sup>™</sup> in terms of their ability to reduce wound area, in moderate or highly exuding leg ulcers, over a period of 6 weeks. A subgroup of subjects was followed for up to 24 weeks. Secondary aims of the study were to compare wound status and progress as well as investigator- and patient-evaluated outcomes, such as ease of use, comfort, pain, ease of removal and tolerability.

## 2 | METHODS

### 2.1 | Study design

This was a randomised, open-label, parallel-group, multicentre, non-inferiority study comparing the efficacy

and safety of two dressings (Exufiber<sup>®</sup> and Aquacel<sup>®</sup> Extra<sup>™</sup>) in the management of chronic, moderately or highly exuding venous or mixed aetiology leg ulcers of predominantly venous origin. Inpatients and outpatients presenting with an exuding leg ulcer were assessed according to study inclusion and exclusion criteria and eligible patients were asked to provide written informed consent. The study was conducted in 31 clinics throughout six European countries (Czech Republic, Denmark, France, Germany, Poland, and Sweden) between October 2016 and November 2019. The clinics were located within hospitals and private settings including dermatology, surgery, vascular medicine and vascular surgery units, as well as specialised wound care units/clinics. The clinical study protocol was approved by an independent ethics committee and the investigation was performed in accordance with the ethical principles outlined in the Declaration of Helsinki and applicable regulatory requirements. The duration of the main study was 6 weeks, although a subgroup of subjects was followed for up to 24 weeks.

### 2.2 | Subjects and recruitment

The study recruited adults (30–97 years of age) with leg ulcers that were moderately or highly exudative justifying the use of an absorbent dressing and whose ankle-brachial-pressure index (ABPI) by Doppler was  $\geq 0.7$  and  $< 1.3$ . The ulcer had to have been present for between 6 weeks and 60 months, with a surface area between 3 cm<sup>2</sup> and 100 cm<sup>2</sup> and located at least 3 cm away from any other lesion. All subjects were treated with a recognised compression system and relevant concomitant medications, including antibiotics and analgesics at the discretion of the investigator.

Exclusion criteria included a known allergy/hypersensitivity to the dressings, pregnancy, or breastfeeding, dry or circumferential wounds (entire wound had to be captured on a single image/photo), malignant wound degeneration, a clinically infected wound (as evaluated by the investigator), a systemic infection that was not controlled by antibiotics or a wound covered with black necrosis. Also excluded were subjects who would have had difficulty following the study protocol or who were currently involved (or had been within the last 30 days) in other ongoing clinical wound dressing evaluations or who were undergoing radiotherapy, chemotherapy, immunosuppressant therapy, were receiving high doses of oral corticosteroids, who had experienced deep vein thrombosis within 3 months prior to inclusion or who had withdrawn their consent.

## 2.3 | Wound dressings

The two wound dressings under evaluation were Exufiber<sup>®</sup> and Aquacel<sup>®</sup> Extra<sup>™</sup>. Exufiber<sup>®</sup> is a sterile, non-woven dressing, made from highly absorbent polyvinyl alcohol fibres, while Aquacel<sup>®</sup> Extra<sup>™</sup> is a sterile, non-woven pad dressing, composed of sodium carboxymethylcellulose, and regenerated cellulose fibre. The study sites were provided with 10 × 10 cm size dressings for both Exufiber<sup>®</sup> and Aquacel<sup>®</sup> Extra<sup>™</sup> at no cost.

Wound dressings were applied at baseline (Week 0) and changed at each study visit. However, dressings could also be changed between visits, if necessary (e.g., if they were saturated), following normal practice and intended dressing use. The number of dressing changes between scheduled visits was recorded at each visit. No active dressings, such as antimicrobial dressings, were permitted; simple gauze dressings and compresses were recommended for use as secondary dressings.

## 2.4 | Study procedures and evaluations

Wound debridement including mechanical was permitted during the study. After wound cleansing/debridement, subjects were randomised to either Exufiber<sup>®</sup> or Aquacel<sup>®</sup> Extra<sup>™</sup> using an electronic centralised system using the minimisation technique and balancing for the following prognostic factors: wound duration (6 weeks–12 months; >12 months), wound area (<10 cm<sup>2</sup>, ≥10 cm<sup>2</sup>), ABPI (0.7–0.9, >0.9), compression at inclusion (yes, no).<sup>13</sup> Although unscheduled visits were allowed at the clinic when deemed necessary for dressing changes or other reasons, subjects were asked to visit the clinic at baseline (Week 0) and at Weeks 1, 2, 3, 4, and 6 (or until wound healing, if earlier) after initial placement of the dressing, that is, 6 visits in total. Those subjects who were followed for up to 24 weeks also attended the clinic at Weeks 8, 12, 16, 20, and 24 after the initial dressing placement (or until wound healing, if earlier), that is, up to 11 visits in total.

At each visit, evaluations by the study doctor or nurse (“clinician”) were performed to assess the condition and performance of the wound dressing, wound status, condition of the periwound skin, signs of local infection, wound pain, and patient comfort. Any medication which was considered necessary for the subject’s safety and well-being could be used. Subjects were treated with a recognised efficient compression system, for example, multi-component such as a two-, three- or four-layer bandage or a short stretch bandage. The number of dressing changes between visits was reported at each scheduled visit. Safety data were collected throughout the study.

## 2.5 | Study endpoints

The primary efficacy endpoint was the percentage reduction in wound area at Week 6 relative to baseline, as measured by a blinded assessor and the validated digital photo planimetry software (PictZar<sup>®</sup> Digital Planimetry, Program Software, BioVisual Technologies, LLC, Elmwood Park, NJ, USA).<sup>14</sup> Photos were taken in line with standard procedures and analysed using PictZar. A second supportive blind review was conducted by independent experts.

Blind assessment by PictZar Digital Planimetry was also used to measure a number of secondary efficacy endpoints: absolute reduction in wound area from baseline to Week 6; linear advance of the wound margin according to Gilman’s equation,<sup>15</sup> baseline to Week 6; percentage reduction of fibrin/sloughy tissue at 6 weeks (or when the wound was dry/healed) relative to baseline (also assessed by a clinical evaluation); and proportion of debrided wounds at 6 weeks (defined as ≥70% of the wound area covered with granulation tissue).

Other secondary efficacy endpoints were: change from baseline in periwound skin condition (maceration, redness/irritation, blistering, skin stripping, trauma to wound edges); level of pain (prior to dressing assessment, during dressing removal/change and during debridement, as measured by visual analogue scale [VAS], 0–100 mm); analgesia use within 3 h prior to assessment, number of dressing changes/week and over the whole treatment period; wound status (reflected by exudate amount and nature); appearance of wound bed before and after cleansing/debridement (percentages of fibrin/sloughy tissue, granulation tissue, epithelialisation, other); dressing technical performance (residual material in the wound after dressing removal, ability to absorb and retain exudate and blood/slough); clinician’s evaluation of dressing performance in relation to ease of application/removal, adherence (or not) to wound bed or to periwound skin at dressing removal, dressing flexibility and conformability, and overall perception.

Subjects’ opinion of the dressing was sought in relation to the level of anxiety they experienced during a dressing change, ease of movement and comfort while wearing the dressing, stinging or burning during wear, and ability of the dressing to remain in place during wear. At the last visit, subjects were asked whether they would use the dressing again.

In order to support that wound area reduction at week 6 was a clinically relevant parameter to predict long-term wound healing, a subgroup of at least 50 subjects was assessed at 24 weeks (or to wound healing). Favourable trajectory was defined by an area regression, compared to baseline, of ≥80% at week 24. Additionally,

wound closure (100% re-epithelialisation confirmed by photo) was evaluated. All these parameters were centrally measured on photos according to previously described procedures.

Safety data were collected in the form of adverse events (AEs), adverse device-related events (ADEs), serious adverse events (SAEs), serious adverse device-related events (SADEs) and device deficiencies. In addition, signs of local infection as evaluated by the clinician were recorded based on: pain since last dressing change, perilesional skin erythema, oedema, malodour, and high level of exudate. Furthermore, health-related quality of life was measured using EQ-5D-3L.

## 2.6 | Data management

Viedoc, a web-based electronic case report form (eCRF) system (<https://www.viedoc.com>), was used to capture data (including photographic data). The eCRF system complied with FDA Title 21 CFR part 11 (ER/ES) requirement and training in its use was given to personnel at the investigational sites before or at study initiation. Data entry was performed by investigators (or other authorised personnel); online checks were applied in Viedoc to ensure data entry consistency and validation.

## 3 | STATISTICAL PLAN

### 3.1 | Sample size

The study was designed to confirm the non-inferiority of Exufiber<sup>®</sup> compared with Aquacel<sup>®</sup> Extra<sup>™</sup> on the relative reduction/change in wound size from baseline to 6 weeks. Applying a non-inferiority margin of 12%, in accordance with Meaume et al. (2014)<sup>16</sup> and a standard deviation (SD) of 35%, 106 subjects were deemed to be necessary in each group (ie, 212 subjects in total) with a power level of 80%.

### 3.2 | Statistical populations

The intention-to-treat (ITT) population was defined as all randomised subjects who had initiated treatment with one of the test dressings. Subjects were excluded from the ITT population if they dropped out at/after baseline and before the first formal assessment. The per protocol (PP) population comprised all subjects following the clinical protocol and who had a wound area measurement at baseline and at 6 weeks follow-up (or at a time point prior to this if their wound had healed). Individuals were

excluded from the PP population if they had a significant protocol deviation. The safety population consisted of all subjects who had initiated treatment with a test dressing, whether or not they dropped out before the first formal assessment.

The primary efficacy analysis was conducted on the PP population and confirmed in the ITT population. Secondary efficacy analyses were conducted on the ITT population and confirmed in the PP population. Safety analyses were conducted on the safety population.

## 3.3 | Statistical evaluation

In this non-inferiority study, for the primary efficacy analysis, a two-sided 95% confidence interval (CI) was constructed using Fisher's non-parametric permutation test for between-treatment differences in the mean percentage wound area change from baseline to 6 weeks. This means that if the lower limit of the CI was >12%, non-inferiority would be established. However, the study design could establish superiority, should the lower limit of a two-sided 95% CI not exceed 0% for between-treatment differences in the mean percentage wound area change from baseline to 6 weeks.

For secondary variables, Fisher's exact test for dichotomous variables, Mantel-Haenszel Chi-square test for ordered categorical variables and Pearson Chi-square test for non-ordered categorical variables and Fisher's non-parametric permutation were used for continuous variables.

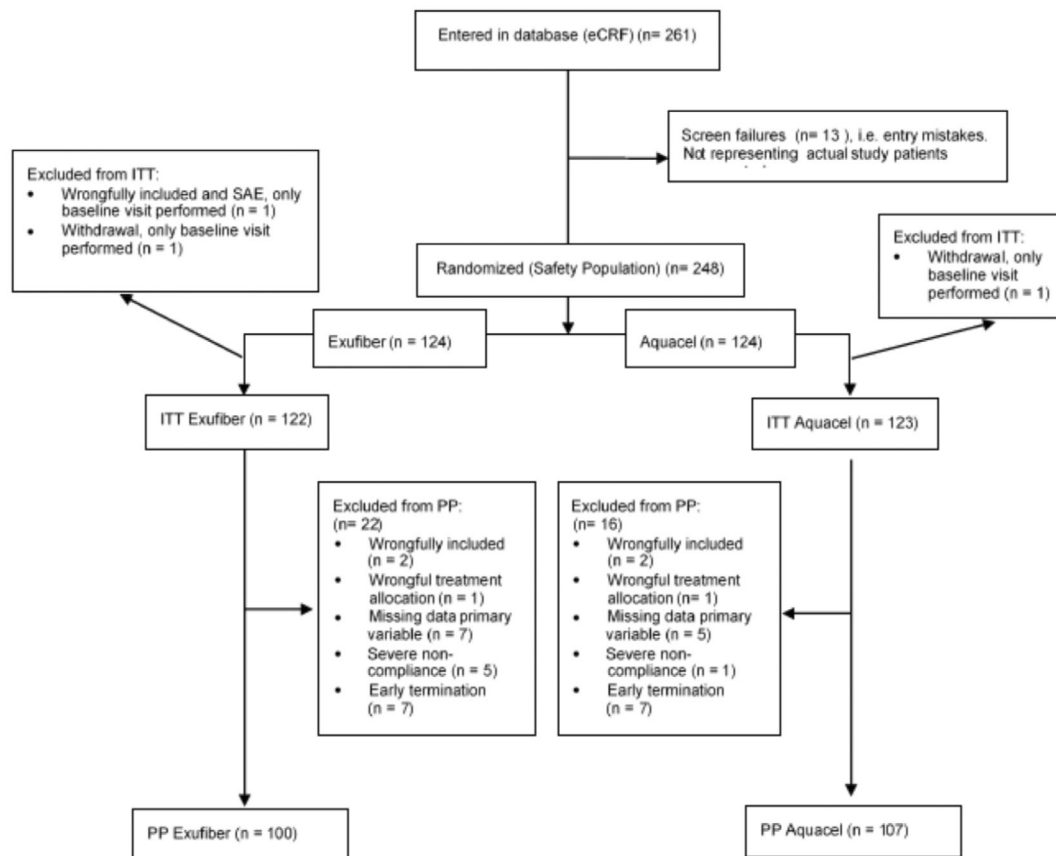
All statistical tests were two-sided and conducted at the 5% significance level. Changes in continuous variables were presented as mean, SD, median, minimum and maximum, and as numbers and percentages for categorical variables. Other endpoints were summarised using descriptive statistics only. All analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

## 4 | RESULTS

### 4.1 | Subject disposition

Entries of a total of 261 subjects were made into the eCRF database; of which 13 subjects were immediately excluded due to screening failures. Among the 248 subjects remaining (the safety population), 124 were randomised into each of the two dressing groups (Figure 1). The ITT population comprised 245 patients (Exufiber<sup>®</sup>, n = 122 and Aquacel<sup>®</sup> Extra<sup>™</sup>, n = 123); three subjects were excluded from the ITT population (Figure 1).





**FIGURE 1** Patient flow diagram. ITT populations included those patients followed up for 24 weeks ( $n = 35$  for Exufiber<sup>®</sup> and  $n = 40$  for Aquacel). PP populations included those patients followed up for 24 weeks ( $n = 29$  for Exufiber<sup>®</sup> and  $n = 36$  for Aquacel)

The PP population comprised 207 subjects who completed the 6-week study or achieved wound healing (Exufiber<sup>®</sup>,  $n = 100$  and Aquacel<sup>®</sup> Extra<sup>™</sup>,  $n = 107$ ). A total of 38 subjects were excluded from the PP population (Figure 1).

Regarding the subgroup of subjects who were followed for up to 24 weeks, 75 subjects comprised the ITT population (Exufiber<sup>®</sup>,  $n = 35$  and Aquacel<sup>®</sup> Extra<sup>™</sup>,  $n = 40$ ), while the PP population comprised 65 subjects (Exufiber<sup>®</sup>,  $n = 29$  and Aquacel<sup>®</sup> Extra<sup>™</sup>,  $n = 36$ ). A total of 31 subjects completed the 24-week treatment period (Exufiber<sup>®</sup>,  $n = 15$  and Aquacel<sup>®</sup> Extra<sup>™</sup>,  $n = 16$ ). Early study termination among subjects was mainly related to ulcer healing prior to the scheduled 24-week visit, in 12 Exufiber<sup>®</sup> subjects (86%) and 17 Aquacel<sup>®</sup> Extra<sup>™</sup> subjects (85%).

## 4.2 | Demographic and baseline characteristics

The two treatment groups were well balanced and comparable with regard to demographic variables and baseline characteristics, including predictive factors for

wound healing/reduction (Table 1). Subjects were elderly (mean, 70 years of age) with a mean body mass index (BMI) of around  $30 \text{ kg/m}^2$  and were generally mobile (95%). Just one subject (in the Aquacel<sup>®</sup> Extra<sup>™</sup> group) was bedridden. There was a difference in mean height between the two groups, with subjects tending to be taller in the Exufiber<sup>®</sup> group (171 cm vs 169 cm,  $P = 0.03$ ) (Table 1). This was not, however, judged to be clinically relevant or likely to impact outcomes. Furthermore, such a difference was not noted in the PP population. Most subjects ( $> 90\%$ ) had a comorbid condition that was relevant to wound healing (ie, diabetes, arterial hypertension, cardiovascular disease, or deep vein thrombosis) and this was comparable between groups.

## 4.3 | Wound characteristics

Wound characteristics at baseline (prior to the initiation of the study treatment) for subjects in the ITT population are presented in Table 2. Most (70.5% in the Exufiber<sup>®</sup> group, 71.5% in the Aquacel<sup>®</sup> Extra<sup>™</sup>) of the leg ulcers had been present for between 6 weeks and 1 year, were located below the knee and were recurrent in around

**TABLE 1** Demographic and baseline characteristics of patients in the ITT population (n = 245)

Variable	Exufiber® (n = 122)	Aquacel® Extra™ (n = 123)
Gender (n, %)		
Male	60 (49.2)	54 (43.9)
Female	62 (50.8)	69 (56.1)
Mean age (± SD) (years)	70.0 (12.3)	69.0 (15.0)
min, max, median	34.0, 97.0 72.0	30.0, 92.0 70.0
Mean height (cm) (± SD)	171.4 (10.5)	168.7 (8.9)*
min, max, median	150.0, 197.0 170.0	148.0, 192.0 168.0
Mean weight (kg) (± SD)	90.6 (26.8)	87.7 (24.1)*
min, max, median	40.0, 195.0 85.0	48.0, 160.0 82.0
BMI (kg/m <sup>2</sup> ) (± SD)	30.6 (7.5)	30.7 (7.6)*
min, max, median	16.3, 52.4 29.6	18.3, 56.0 28.9
Mobility, n (%)		
Bedridden	0 (0)	1 (0.8)
Chair bound	7 (5.7)	3 (2.4)
Ambulant	115 (94.3)	119 (96.8)

Note: \*n = 122.

Abbreviations: BMI, body mass index; SD, standard deviation.

50% of subjects (42.6% and 50.4% in the Exufiber® and Aquacel® Extra™ groups, respectively; no statistically significant difference between groups). At baseline, prior to the initiation of the study treatment, most wounds (70.5% in the Exufiber® group, 71.5% in the Aquacel® Extra™ group) were under compression and covered with around 60% of sloughy tissue (before debridement). Most wounds produced moderate to copious amounts of exudate, with more wounds in the Aquacel® Extra™ group producing copious amounts of exudate (Exufiber® = 14% vs Aquacel® Extra™ = 23%). The proportion of sloughy tissue, as evaluated by clinicians, was slightly higher in the Exufiber® group (65.3% vs 57.7%,  $P = 0.039$ ), however, when this factor was analysed using PictZar, the difference between the Exufiber® group and the Aquacel® Extra™ group (61.3% vs 58.3%) was not statistically significant ( $P = 0.51$ ).

#### 4.4 | Compliance with compression during the study period (ITT population)

At the baseline visit (initiation of treatment), the majority of subjects (90.2% in the Exufiber® group, 89.4% in the Aquacel® Extra™ group) received efficient compression

(only 1 subject received a four-layer bandage; this subject was in the Aquacel® Extra™ group), with no statistically significant difference between groups. In the eCRF, however, the option of “other” could be selected for the type of compression which also allowed for free text entries for the type of compression used. As such, for two subjects in the Exufiber group, it was reported that no compression was used; for one subject in the Exufiber group, it was recorded that “compresses” were used. These three subjects did not change the type of compression during the study period. If the remaining free text answers for the “other” type of compression are assumed to be efficient compression, then 99% of the subjects received efficient compression at baseline (ie, at the start of the study period).

Any changes in compression type used in between visits, or at visits, were recorded at each follow-up visit. Few changes in the type of compression were reported during the follow-up visits. Two subjects, one in each group, were changed from efficient compression to no compression during the study, the former due to peri-wound skin irritation and blistering, and the latter due to too much pain.

## 4.5 | Efficacy outcomes

### 4.5.1 | Primary efficacy analysis

The primary efficacy analysis (percentage reduction in wound area at 6 weeks relative to baseline) was conducted on the PP population. A median relative reduction of 50% for Exufiber® vs 42% for Aquacel® Extra™ was recorded, though no statistically significant difference between groups was identified (Table 3; Figures 2, 3). Nevertheless, a consistent trend of greater mean relative wound reduction was observed for Exufiber® compared with Aquacel® Extra™ (Figures 3, 4). As the mean and 95% CI for the difference in relative wound area reduction between groups at 6 weeks was  $-29.4$  ( $-63.5$ ;  $3.2$ ), and the lower limit did not exceed 12%, non-inferiority of Exufiber® to Aquacel® Extra™ was concluded (Table 3). This conclusion of non-inferiority was confirmed in the ITT population (data not shown).

### 4.5.2 | Secondary efficacy endpoints

In both treatment groups, wound area fell progressively over time; mean absolute reductions at Week 4 relative to baseline were  $-3.4$  cm<sup>2</sup> (Exufiber®) and  $-2.3$  cm<sup>2</sup> (Aquacel® Extra™) and, at Week 6,  $-4.6$  cm<sup>2</sup> (Exufiber®) and  $-3.5$  cm<sup>2</sup> (Aquacel® Extra™). In both groups (ITT

TABLE 2 Wound characteristics at baseline for patients in the ITT population (n = 245)

Variable	Exufiber® (n = 122)	Aquacel® Extra™ (n = 123)
Leg ulcer duration category (stratification factor), n (%)		
6 weeks to 12 months	86 (70.5)	88 (71.5)
>12 months	36 (29.5)	35 (28.5)
Leg ulcer duration, mean ( $\pm$ SD)	10.8 (10.7)	12.5 (13.4)
min, max, median (months)	1.4, 48, 6.0	1.4, 72.0, 7.0
Latest ABPI value category (stratification factor), n (%)		
0.7 to 0.9	37 (30.3)	39 (31.7)
>0.9	85 (69.7)	84 (68.3)
Latest ABPI value, mean ( $\pm$ SD)	1.01 (0.13)	1.01 (0.13)
min, max, median	0.7, 1.29, 1.0	0.7, 1.29, 1.0
Estimated wound area category, n (%)		
$\leq 10$ cm <sup>2</sup>	66 (54.1)	67 (54.5)
>10 cm <sup>2</sup>	56 (45.9)	56 (45.5)
Estimated wound area, mean ( $\pm$ SD)	16.2 (17.8)	18.3 (21.2)
min, max, median (cm <sup>2</sup> )	3.0, 98.0, 9.0	3.1, 100, 10.0
Current compression (stratification factor), n (%)		
Yes	86 (70.5)	88 (71.5)
No	36 (29.5)	35 (28.5)
Wound location, n (%)		
Right thigh	2 (1.6)	1 (0.8)
Right knee	0 (0)	2 (1.6)
Right lower leg	29 (23.8)	38 (26.6)
Left lower leg	39 (32.0)	33 (26.8)
Right ankle (inner/outer)	27 (22.1)	19 (15.4)
Left ankle (inner/outer)	22 (18.0)	29 (23.6)
Other	3 (2.5)	1 (0.8)
Recurrent ulcer? n (%)		
Yes	52 (42.6)	62 (50.4)
No	70 (57.4)	61 (49.6)
Exudate amount, n (%)		
None	1 (0.8)	0 (0)
Low	3 (2.5)	0 (0)
Moderate	101 (82.8)	95 (77.2)
Copious	17 (13.9)	28 (22.8)*
Level of fibrin/sloughy tissue before debridement (clinician judged), mean ( $\pm$ SD)	65.3 (26.5)	57.7 (30.0)**
min, max, median (%)	0, 100, 75.2	0, 100, 70.0
Amount of fibrin/sloughy tissue before debridement (PictZar), mean ( $\pm$ SD)	61.3 (34.5)	58.3 (33.4)
min, max, median (%)	0, 100, 75.2 (n = 113)	0, 100, 60.8 (n = 116)

Note: \* $P = 0.019$ ; \*\* $P = 0.039$ .

Abbreviations: ABPI, ankle brachial pressure index; SD, standard deviation.



**TABLE 3** Wound area, absolute change in wound area, and relative percentage change in wound area, from baseline to 6 weeks for Exufiber® vs Aquacel® Extra™ (PP population and Pictzar digital planimetry)

Visit	Variable	Exufiber® (n = 100)	Aquacel® Extra™ (n = 107)	P value	Between-group difference mean (95% CI)
Baseline	Total area post-debridement (cm <sup>2</sup> )	10.8 (11.9)	9.85 (10.48)	0.53	0.982 (−2.082, 4.036)
		0.7, 52.8	0.4, 56.5		
		5.8 (n = 98)	6.49 (n = 106)		
Week 4	Total area post-debridement (cm <sup>2</sup> )	7.44 (9.07)	7.86 (8.35)	0.74	−0.413 (−2.875, 2.046)
		0.11, 46.12	0, 42.06		
		4.5 (n = 95)	5.25 (n = 101)		
	Change in area post-debridement (cm <sup>2</sup> )	−3.44 (5.78)	−2.33 (6.82)	0.23	−1.11 (−2.86, 0.66)
		−28.19, 8.43	−36.7, 21.64		
		−1.7 (n = 95)	−1.3 (n = 101)		
Relative percentage change in area post-debridement (cm <sup>2</sup> ) <sup>a</sup>	−28.4 (41.9)	−1.91 (140.39)	0.057	−26.5 (−54.8, 0.5)	
	−94.8, 109	−100, 1113.87			
	−27.7 (n = 95)	−25.66 (n = 101)			
Week 6	Total area post-debridement (cm <sup>2</sup> )	6.53 (8.71)	6.71 (7.38)	0.87	−0.180 (−2.460, 2.081)
		0, 52.4	0, 32.01		
		3.53 (n = 93)	3.94 (n = 98)		
Change in area post-debridement (cm <sup>2</sup> )	−4.64 (7.73)	−3.48 (7.59)	0.31	−1.16 (−3.32, 1.02)	
	−30.52, 11.25	−42.34, 19.97			
	−2.77 (n = 93)	−1.92 (n = 98)			
Primary efficacy variable	Relative percentage change in area post-debridement (cm <sup>2</sup> )	−37.5 (56.1) −100, 191.2 −49.7 (n = 93)	−8.06 (177.85) −100, 1538.44 −42.39 (n = 98)	0.093	−29.4 (−63.5, 3.2)

Note: NB Varying numbers reported due to missing post-debridement values and/or healing. Values shown are mean (SD), min, max, and median. For comparisons between groups (including mean difference) for continuous variables, Fisher's non-parametric permutation test was used.

<sup>a</sup>Negative value indicates reduction in wound area over time.

population), the linear advance of the wound margin based on measurements of the photos by PictZar digital planimetry, advanced inwards over time (ie, reduction in perimeter) and mean values were around 0.008 cm/day (Exufiber®) vs 0.006 cm/day (Aquacel® Extra™) at Week 4, and 0.008 cm/day (Exufiber®) vs 0.007 cm/day (Aquacel® Extra™) at Week 6. Even though no statistically significant difference was found between the groups, a trend of greater wound margin advance was observed for Exufiber®, in line with the favourable trend seen with Exufiber® in the primary efficacy analysis. Wound healing was also assessed by clinicians and no statistically significant differences were observed between Exufiber® and Aquacel® Extra™. In total, 19/245 wounds (7.7%) healed during the 6-week follow-up, 7/122 for

Exufiber® (5.7%) vs 12/123 for Aquacel® Extra™ (9.8%) ( $P = 0.35$ ).

Wound status was analysed by the relative reduction of fibrin/sloughy tissue from baseline to 6 weeks and was measured on the photos using PictZar and also by clinical evaluation. For PictZar, the tissue types were categorised as either granulation/viable or slough/non-viable tissue. Clinicians evaluated the tissue types in the wound bed as fibrin/slough, granulation, epithelialisation, and others. Thus, the tissue type categories were not aligned so the two analyses could not be compared.

There was a reduction in the percentage of sloughy tissue over time (before debridement) in both groups, as evaluated by the clinician and by PictZar (ITT population, Table 4). At Week 4, the mean percentage of

sloughy tissue, assessed by the clinician, was 48.6% (Exufiber®) vs 39.5% (Aquacel® Extra™) ( $P = 0.031$ ), and at Week 6 it was 46.3% (Exufiber®) vs 35.2% (Aquacel® Extra™) ( $P = 0.0087$ ). At Week 6, the mean percentage

of sloughy tissue, analysed by PictZar, was also significantly higher in Exufiber® treated wounds (56.1% vs 46.1%) ( $P = 0.047$ ) (Table 4).

In both groups, changes in tissue types, assessed by the clinician after debridement, seem to reflect an improved wound status over time although a significant amount of variability was observed. Debridement was used for almost all wounds (> 90%) at the follow-up visits. For both groups, there was an increase in both granulation and epithelial tissue over time, with no difference between treatment groups.

Clinician-assessed exudate amount and nature were also evaluated as part of wound status (Figure 5). At baseline, patients treated with Exufiber® compared with those in the Aquacel® Extra™ group had fewer wounds with moderate to copious amounts of exudate (96.7% vs 100%) and there was a significant difference in exudate distribution between the groups ( $P = 0.019$ ). Thereafter, no statistically significant differences in exudate amount were seen between groups at any of the follow-up visits. The

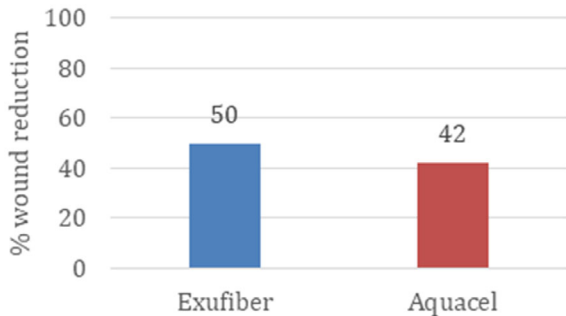


FIGURE 2 Primary efficacy endpoint—percentage reduction in median wound area at 6 weeks relative to baseline (post debridement and Pictzar digital planimetry) (Exufiber®,  $n = 100$ ; Aquacel® Extra™,  $n = 107$ , per protocol [(PP)] population)

FIGURE 3 Non-inferiority—95% confidence interval includes zero but not the non-inferiority margin which indicates non-inferiority of Exufiber® compared to Aquacel® Extra™ with respect to the primary efficacy endpoint

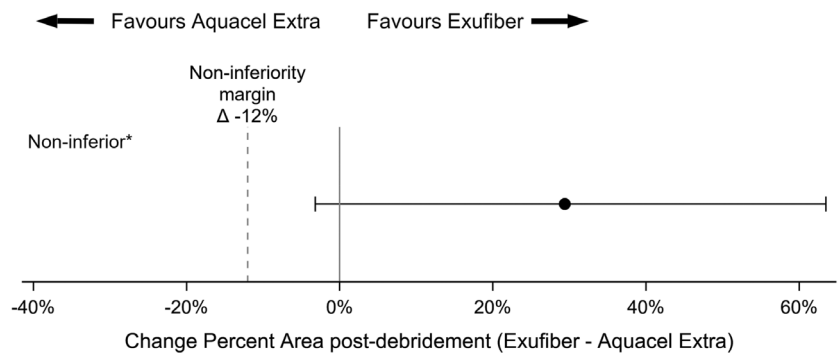
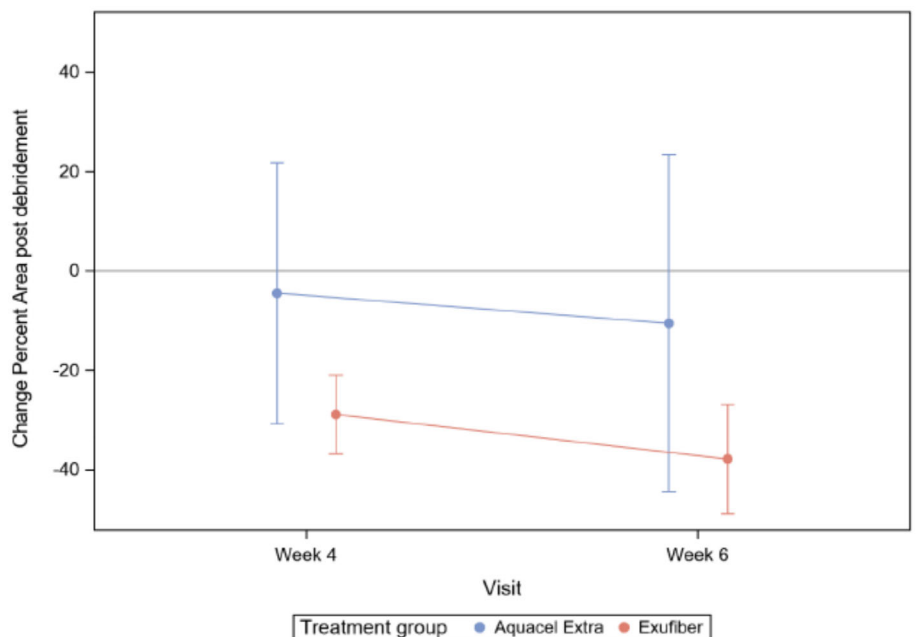


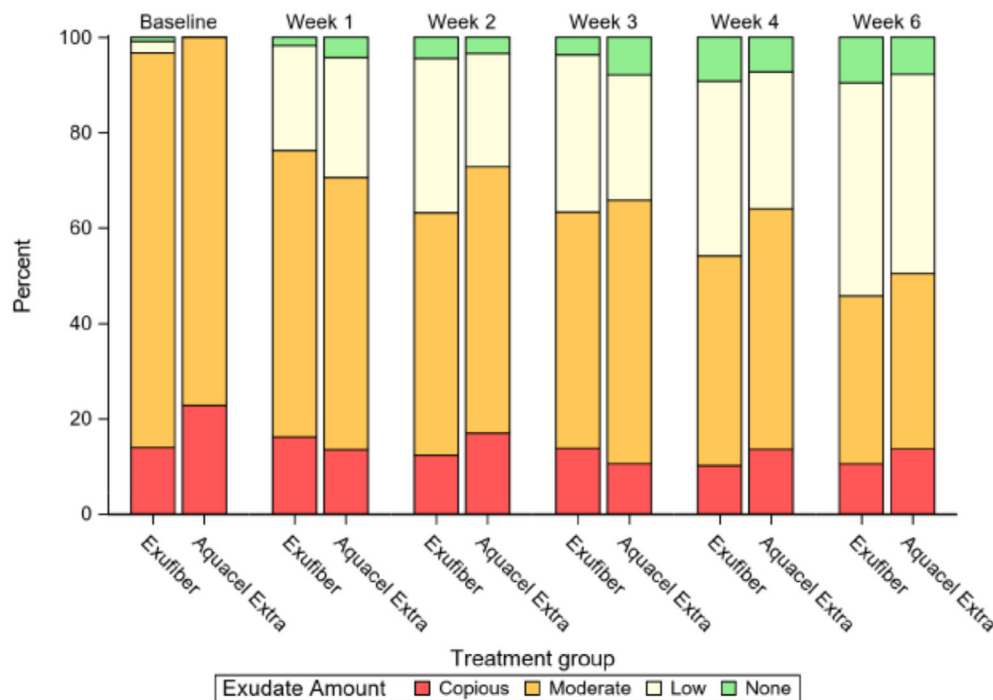
FIGURE 4 Percentage change in wound area at weeks 4 and 6 relative to baseline for Exufiber® and Aquacel® Extra™ (per protocol (PP) population). Values shown are mean and 95% confidence intervals



**TABLE 4** Changes in proportions of wound sloughy tissue for Exufiber® and Aquacel® Extra™ from baseline to 6 weeks, assessed by the clinician and analysed by PictZar (ITT population)

Visit	Variable	Exufiber® (n = 122)	Aquacel® Extra™ (n = 123)	P value	Between-group difference mean (95% CI)
Baseline	Percentage of fibrin/sloughy tissue before debridement (clinician)	65.3 (26.5) 72.5 (n = 122)	57.7 (30.0) 70.0 (n = 123)	0.039	7.58 (0.43, 14.77)
	Percentage of fibrin/sloughy tissue before debridement (PictZar)	61.3 (34.5) 75.2 (n = 113)	58.3 (33.4) 60.8 (n = 116)	0.51	3.00 (−5.88, 11.82)
Week 4	Percentage of fibrin/sloughy tissue before debridement (clinician)	48.6 (30.8) 50.0 (n = 109)	39.5 (31.0) 30.0 (n = 111)	0.031	9.04 (0.76, 17.24)
	Percentage of fibrin/sloughy tissue before debridement (PictZar)	58.1 (32.6) 59.0 (n = 105)	54.6 (35.6) 57.2 (n = 107)	0.46	3.49 (−5.69, 12.84)
Week 6	Percentage of fibrin/sloughy tissue before debridement (clinician)	46.3 (32.5) 50.0 (n = 105)	35.2 (28.9) 30.0 (n = 103)	0.0087	11.2 (2.8, 19.5)
	Percentage of fibrin/sloughy tissue before debridement (PictZar)	56.1 (35.6) 63.8 (n = 104)	46.1 (36.6) 41.0 (n = 105)	0.047	10.0 (0.1, 19.8)

Note: Values shown are mean (SD), median. For comparisons between groups (including mean difference) for continuous variables, Fisher's non-parametric permutation test was used.



**FIGURE 5** Exudate amount produced by the wounds over the 6-week study (ITT population, Exufiber®, n = 122; Aquacel® Extra™ n = 123)

number of patients with moderate or copious levels of exudate, however, reduced over time in both groups, from Week 4 (Exufiber® = 54.1% vs Aquacel® Extra™ = 64%) to Week 6 (Exufiber® = 45.7% vs Aquacel® Extra™ = 50.5%) (Figure 5). At Week 6, 9.5% in the

Exufiber® group and 7.8% of the wounds in the Aquacel® Extra™ group had no exudate indicating that the dressings were no longer needed. Irrespective of the treatment group, the proportion of purulent thick exudate remained at a low level throughout the study (Exufiber® vs

**TABLE 5** Clinicians' opinion on the various features of the two test dressings, Exufiber® (n = 122) and Aquacel® Extra™ (n = 123). All follow-up visits aggregated (ITT population)

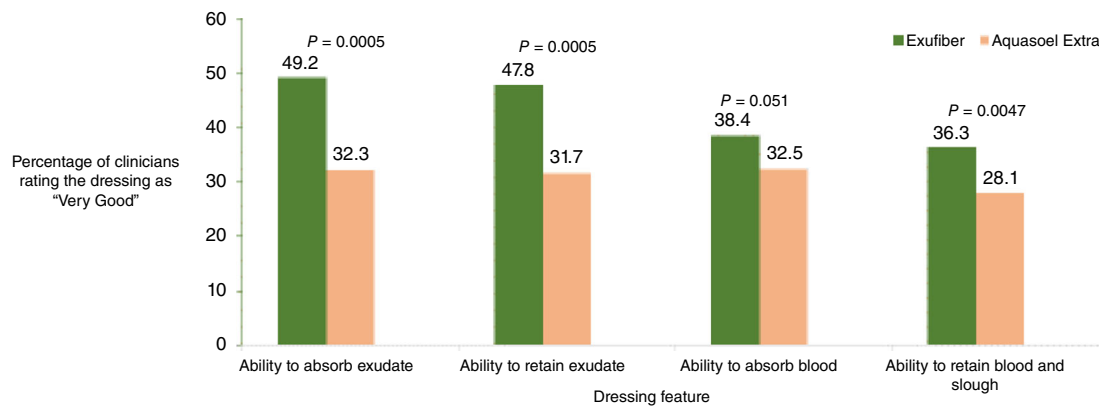
Variable	Exufiber (n = 587)	Aquacel Extra (n = 592)	P-value
Ease of application of dressing			
Very poor	2 (0.4%)	3 (0.7%)	
Poor	8 (1.8%)	2 (0.4%)	
Good	175 (39.3%)	188 (41.4%)	
Very good	260 (58.4%)	261 (57.5%)	0.74
Ease of removal of dressing			
Very poor	6 (1.1%)	16 (2.8%)	
Poor	39 (7.1%)	57 (10.1%)	
Good	237 (43.1%)	269 (51.2%)	
Very good	266 (48.7%)	203 (35.9%)	0.0024
Flexibility of dressing			
Very poor	2 (0.4%)	1 (0.2%)	
Poor	22 (4.0%)	56 (9.9%)	
Good	264 (47.7%)	279 (49.1%)	
Very good	266 (48.0%)	232 (40.8%)	0.16
Overall experience of dressing			
Very poor	3 (0.5%)	2 (0.4%)	
Poor	12 (2.2%)	19 (3.4%)	
Good	284 (51.3%)	362 (63.8%)	
Very good	255 (46.0%)	184 (32.5%)	0.017
Conformability to the wound			
Very poor	1 (0.2%)	6 (1.1%)	
Poor	11 (2.0%)	41 (7.2%)	
Good	319 (57.9%)	314 (55.5%)	
Very good	220 (39.9%)	205 (36.2%)	0.15
Non-adherence to wound bed at removal of primary dressing			
Does not adhere	241 (44.2%)	175 (31.1%)	
Adhere a little	196 (36.0%)	259 (46.0%)	
Adhere a lot	108 (19.8%)	129 (22.9%)	0.013
Non-adherence to peri-wound skin at removal of primary dressing			
Does not adhere	390 (72.0%)	293 (52.1%)	
Adhere a little	128 (23.6%)	206 (36.7%)	
Adhere a lot	24 (4.4%)	63 (11.2%)	<.0001

Aquacel® Extra™: 0.9% vs 3.4% at baseline, 2.1% vs 4.9% at Week 4, and 4.3% vs 1.1% at Week 6).

There was no statistically significant difference between groups in the extent to which a wound was debrided at the end of the study (defined as coverage of  $\geq 70\%$  granulation tissue) according to the clinician ( $P = 0.40$ ) or PictZar ( $P = 0.49$ ). Irrespective of the treatment group, the percentage of wounds covered with  $\geq 70\%$  of granulation tissue, assessed by the clinician, increased over time. At baseline, the proportions were, Exufiber® vs Aquacel® Extra™: 10.7% vs 20.3%, 21.1% vs

24.3% at Week 4, and 23.8% vs 30.1% at Week 6. Corresponding percentages measured by PictZar for Exufiber® vs Aquacel® Extra™ were: 28.3% vs 27.6% at baseline, 25.7% vs 29.9% at Week 4, and 27.9% vs 35.2% at Week 6.

There was a trend in the periwound skin becoming healthier over time in both treatment groups. For the ITT population, the periwound skin was evaluated as healthy at baseline for 43.4% (Exufiber®) vs 40.7% (Aquacel® Extra™) of wounds, 48.6% (Exufiber®) vs 53.6% (Aquacel® Extra™) of wounds at Week 4, and 49.5% (Exufiber®) vs 51.4% (Aquacel® Extra™) of wounds at



**FIGURE 6** Technical performance of the two dressings rated by clinicians. Data aggregated for all follow-up visits (ITT population, Exufiber<sup>®</sup>, n = 122; Aquacel<sup>®</sup> Extra<sup>™</sup>, n = 123)

Week 6. The most common factor contributing to the periwound skin being reported as “not healthy” was redness/irritation.

Wound pain at baseline, before any study-related dressing assessments were conducted, was similar in the two groups: 30.0 mm for Exufiber<sup>®</sup> and 27.4 mm for Aquacel<sup>®</sup> Extra<sup>™</sup>. Irrespective of the treatment group, mean pain during debridement fell slightly over time, possibly correlating with the greater ease of debridement over the study period. At Week 4, relative to baseline, a statistically significant reduction in pain level during debridement was recorded for the Exufiber<sup>®</sup> group (mean change on VAS scale = −19.4 mm) vs the Aquacel<sup>®</sup> Extra<sup>™</sup> group (mean change on VAS scale = −11.5 mm). At Week 6, relative to baseline, the mean reduction in pain during debridement was −21.7 mm for Exufiber<sup>®</sup> and −14.4 mm for Aquacel<sup>®</sup> Extra<sup>™</sup>. Irrespective of the treatment group, mean pain during dressing removal reduced over time. At Week 4, pain at dressing removal was 14.3 mm for Exufiber<sup>®</sup> and 16.9 mm for Aquacel<sup>®</sup> Extra<sup>™</sup>; the corresponding changes from baseline were −5.2 mm for Exufiber<sup>®</sup> and −4.0 mm for Aquacel<sup>®</sup> Extra<sup>™</sup>. At Week 6, pain at dressing removal was 15.2 mm for Exufiber<sup>®</sup> and 14.6 mm for Aquacel<sup>®</sup> Extra<sup>™</sup>, corresponding to a −4.1 mm reduction from baseline for Exufiber<sup>®</sup> and −6.9 mm reduction from baseline for Aquacel<sup>®</sup> Extra<sup>™</sup>. Prior to dressing change, throughout the study, analgesics were used at a consistent level, resulting in a similar level of pain reduction in both groups.

For the ITT population, as a whole, the mean number of dressing changes per week remained at a constant level of 2.5 to 2.7 throughout the 6-week follow-up period. The mean total number of dressing changes during the study was 12.

Clinicians' evaluations regarding specific dressing features were also reported (Table 5). When answers from

all follow-up visits were aggregated (ITT population), statistically significant differences in favour of Exufiber<sup>®</sup> were demonstrated for ease of removal ( $P = 0.0024$ ), overall experience ( $P = 0.017$ ), non-adherence to wound bed at dressing removal ( $P = 0.013$ ), and for non-adherence to periwound skin at dressing removal ( $P < 0.001$ ), compared with Aquacel<sup>®</sup> Extra<sup>™</sup> (Table 5). These data were confirmed in the PP population.

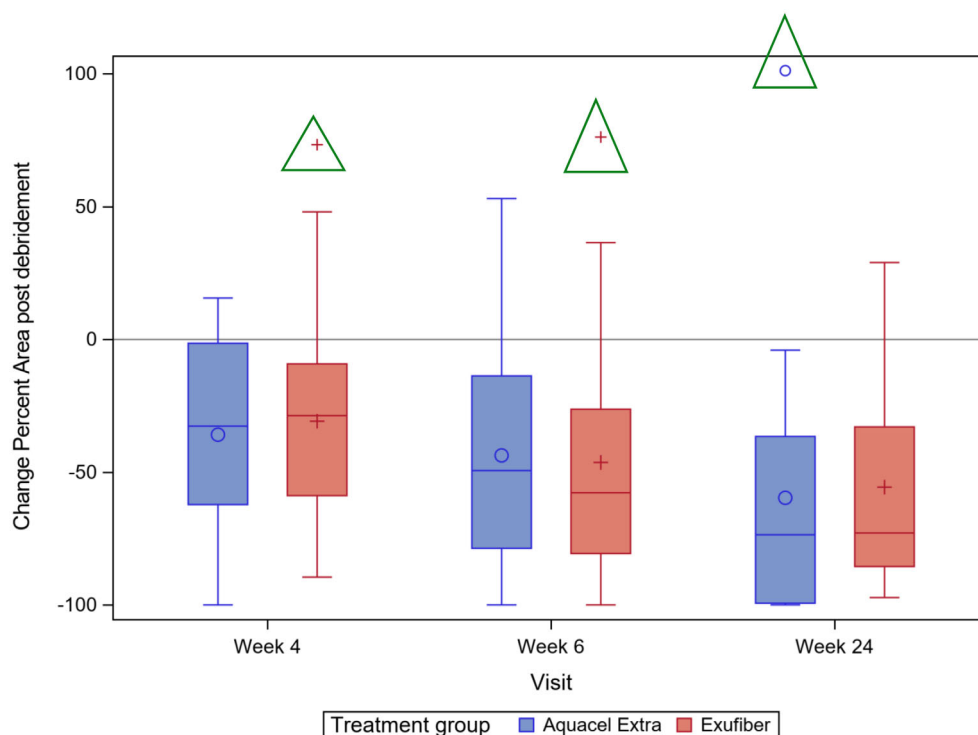
Clinicians were also asked to rate the technical performance of the dressings at each follow-up visit. When data from all follow-up visits for the ITT population were aggregated, there were statistically significant differences in favour of Exufiber<sup>®</sup> for the ability to absorb exudate ( $P = 0.0006$ ), ability to retain exudate ( $P = 0.0005$ ) and ability to retain slough and blood ( $P = 0.0047$ ) compared with Aquacel<sup>®</sup> Extra<sup>™</sup> (Figure 6). Analysis of the PP population confirmed the ITT analysis. Just over 10% of wounds, in both groups, contained residual material after dressing removal.

Subjects were also asked for their opinion about the dressings throughout the study. For the ITT population, results showed no statistically significant differences between Exufiber<sup>®</sup> and Aquacel<sup>®</sup> Extra<sup>™</sup>, whether data from the follow-up visits were aggregated or evaluated individually. “Ease of movement” was reported as “good” or “very good” by >95% of patients in both groups; “remained in place” was reported as “good” or “very good” by 93% and 96% of those receiving Exufiber<sup>®</sup> and Aquacel<sup>®</sup> Extra<sup>™</sup>, respectively, and “comfort” was reported as “good” or “very good” for approximately 95% of patients in both groups. Most patients (> 70% in each group) did not experience anxiety during dressing change and almost half of all patients did not experience stinging or burning. Overall, > 90% of patients would choose to use their allocated dressing again.

Health-related quality of life measured by EQ-5D-3L improved over time in both treatment groups but no



**FIGURE 7** Relative percentage change in wound area from baseline for the subgroup of patients (Exufiber<sup>®</sup>, n = 35; Aquacel<sup>®</sup> Extra<sup>™</sup>, n = 40) followed for up to 24 weeks or to healing, whichever came first (ITT population). Marker inside the box (o or +) indicates the mean value, and the line inside the box the median. Marker inside the triangle (o or +) indicates the maximum change at each time point.



**TABLE 6** Adverse events summarised for both treatment groups (n = 248, safety population)

	Exufiber <sup>®</sup> (n = 124)		Aquacel <sup>®</sup> Extra <sup>™</sup> (n = 124)	
	Events, n	Patients with events, n (%)	Events, n	Patients with events, n (%)
Adverse event	24	23 (18.5)	30	27 (21.8)
Adverse device event	4	4 (3.2)	2	2 (1.6)
Serious adverse event	5	5 (4.0)	8	8 (6.5)
Device deficiency	1	1 (0.8)	7	1 (0.8)

statistically significant differences between groups were observed.

#### 4.5.3 | Ancillary endpoints

Ancillary endpoints were: wound area reduction, wound healing/closure and linear advance of the wound. These were assessed in a subgroup of patients who were followed up for up to 24 weeks after baseline (or until wound healing). There were no statistically significant differences detected for any of these variables when comparing Exufiber<sup>®</sup> with Aquacel<sup>®</sup> Extra<sup>™</sup>. The wound areas progressively reduced in size over time, with a mean (percentage) change from baseline to Week 4 of  $-4.54 \text{ cm}^2$  ( $-30.8\%$  for Exufiber<sup>®</sup>) and  $-3.76 \text{ cm}^2$  ( $-35.9\%$  for Aquacel<sup>®</sup> Extra<sup>™</sup>), from baseline to Week 6 of  $-6.33 \text{ cm}^2$  ( $-46.3\%$  for Exufiber<sup>®</sup>) and  $-5.02 \text{ cm}^2$  ( $-43.7\%$  for Aquacel<sup>®</sup> Extra<sup>™</sup>), and from baseline to

Week 24 of  $-9.7 \text{ cm}^2$  ( $-55.6\%$  for Exufiber<sup>®</sup>) and  $-8.89 \text{ cm}^2$  ( $-59.6\%$  for Aquacel<sup>®</sup> Extra<sup>™</sup>) observed. At Week 24, 41% of wounds in both groups had a reduction of  $\geq 80\%$  in wound area (Figure 7). In total, 33/75 wounds healed (44%) during the 24 weeks, mostly after Week 6. Irrespective of the treatment group, the wound margin advanced inwards over time, and mean values (ITT population, both groups) of wound perimeter reduction were between 0.008 and 0.009 cm/day at Week 4 and Week 6, reducing to 0.004 cm/day at Week 24 in both groups.

## 4.6 | Safety and tolerability

### 4.6.1 | Signs of local infection

For Exufiber<sup>®</sup> and Aquacel<sup>®</sup> Extra<sup>™</sup>, respectively, at baseline, signs of local infection were noted in 27.0% and 30.9% of wounds. Signs of local infection continued to be

present at Week 4 (27.9% for Exufiber<sup>®</sup> and 26.8% for Aquacel<sup>®</sup> Extra<sup>™</sup>) and at Week 6 (31.2% for Exufiber<sup>®</sup> and 28.8% for Aquacel<sup>®</sup> Extra<sup>™</sup>) suggesting that local infection was ongoing. The most common sign of infection was perilesional skin erythema followed by pain between dressing changes.

#### 4.6.2 | Adverse events

A summary of AEs, in each group, device-related or otherwise, is shown in Table 6. Two subjects died during the study (one in each group) but neither of these deaths (acute renal failure and unknown cause) were considered to be related to the dressings nor study participation.

ADEs occurred in four subjects in the Exufiber<sup>®</sup> group, including periwound skin irritation and blistering ( $n = 1$ , the patient continued treatment with Aquacel<sup>®</sup> Extra<sup>™</sup>), periwound skin redness and irritation ( $n = 1$ , event resolved and the patient continued), stinging or burning while wearing the dressing ( $n = 1$ , ADE continued but the patient completed the 6-week study) and pain and itching under the dressing ( $n = 1$ , patient received analgesia but withdrew consent and discontinued). There were two ADEs in the Aquacel<sup>®</sup> Extra<sup>™</sup> group: severe irritation around the wound ( $n = 1$ ) and dressing intolerance (burning and redness,  $n = 1$ ); both of which were assessed as related to Aquacel<sup>®</sup> Extra<sup>™</sup> and led to discontinuation of the patients from the study.

A total of 13 SAEs in 13 subjects (Exufiber<sup>®</sup>,  $n = 5$ ; Aquacel<sup>®</sup> Extra<sup>™</sup>,  $n = 8$ ) were reported during the study (Table 6). None of the SAEs was considered to be related to study participation or to wound dressings.

## 5 | DISCUSSION

Although wound dressings are more sophisticated than ever, the management of wounds producing excess exudate continues to present a significant challenge for clinicians. Excessive exudate in chronic wounds can lead to complications such as maceration of the surrounding skin, which in turn may increase the risk of infection, a delay in wound healing and distress for the patient due to associated pain and discomfort.<sup>3,4</sup> It is therefore important that excess wound exudate is accurately assessed and managed promptly using the most appropriate fluid-absorbing wound dressing.<sup>17</sup> In this randomised, open-label, parallel-group, non-inferiority study, the performance and safety of two gelling fibre dressings (Exufiber<sup>®</sup> and Aquacel<sup>®</sup> Extra<sup>™</sup>) were compared in the management of moderately or highly exuding venous and mixed aetiology leg

ulcers. Wound characteristics were comparable between the two treatment groups and most wounds ( $\geq 95\%$ ) produced moderate or copious amounts of exudate, which reduced over the study period.

Exufiber<sup>®</sup> demonstrated non-inferiority to Aquacel<sup>®</sup> Extra<sup>™</sup> in terms of wound area reduction and no relevant differences could be shown in wound healing and wound status. For the primary outcome, the percentage reduction in wound area at 6 weeks relative to baseline in the PP population, Exufiber<sup>®</sup> demonstrated that it was at least as effective as Aquacel<sup>®</sup> Extra<sup>™</sup>. The result was robust and of high validity and applicable to both the short-term (6 weeks) and long-term (24 weeks). Consistent data was delivered confirming non-inferiority in both the PP and ITT populations throughout all sensitivity analyses, in the secondary blind assessment review, and for the subgroup of patients with up to 24 weeks' follow-up. Whilst there was no statistical difference between the two groups for the primary efficacy endpoint, there was a consistent trend throughout the study in favour of Exufiber<sup>®</sup> resulting in a greater percentage reduction in wound area. At Week 6, wounds treated with Exufiber<sup>®</sup> had a median relative wound area reduction of 50% (PP population).

There was also a trend towards greater wound margin advance observed for Exufiber<sup>®</sup>. Irrespective of the treatment group, there was a reduction in the percentage of sloughy tissue over time (as reported by both the clinician and demonstrated by PictZar) and an increase in both granulation and epithelial tissue over time. In both groups, the number of dressing changes/week remained at a constant level of 2.5 to 2.7 throughout the 6-week study (Exufiber<sup>®</sup> = 2.5, Aquacel<sup>®</sup> Extra<sup>™</sup> = 2.7). This dressing change frequency appeared to reflect normal clinical practice.<sup>18</sup>

Generally, pain levels were low in both groups. Pain during debridement and during dressing removal decreased over the study period for both groups.

The opinions of clinicians were highly favourable towards Exufiber<sup>®</sup> in practically all aspects of the dressing's performance. When clinicians were asked about specific dressing features and technical performance, there were statistical differences between groups in favour of Exufiber<sup>®</sup> in relation to ease of removal ( $P = 0.0024$ ), overall experience ( $P = 0.017$ ), non-adherence to wound bed at dressing removal ( $P = 0.013$ ), non-adherence to periwound skin at dressing removal ( $P < 0.001$ ), ability to absorb and retain exudate ( $P = 0.0006$  and  $P = 0.0005$ , respectively), and ability to retain slough and blood ( $P = 0.0047$ ). Patients found the two dressings to be equally acceptable in relation to comfort, conformability, and their ability to carry out daily activities. More than 90% of patients said they would be willing to use the dressing again. Whether or not this

study population can be considered to be a true representation of patients requiring this type of dressing may need further clarification, as it is possible that patients who have previously worn absorbent fibre dressings may have different views and expectations compared with patients who have not worn such a dressing before.

Exufiber<sup>®</sup> has previously been shown to be effective and well tolerated in managing patients with highly exuding diabetic foot ulcers.<sup>11</sup> In a group of 21 patients, followed-up for 12 weeks, the use of Exufiber<sup>®</sup> was shown to lead to a gradual but significant decline in all wound size parameters (wound area and wound volume) from baseline to the final visit. The authors noted that a small reduction in the mean percentage of granulation tissue within the wound paralleled a gradual increase in the mean percentage of epithelialisation. Encouragingly, the number of patients with healthy/intact periwound skin rose from 6 at baseline (29%) to 14 at the final visit (67%).<sup>11</sup> In the current study, Exufiber<sup>®</sup> and Aquacel<sup>®</sup> Extra<sup>™</sup> were both well tolerated by patients and no new safety concerns emerged. Three patients experienced an ADE which was thought to be related to the dressing but none of the 13 SAEs recorded, nor the two deaths, were considered related to study participation or to the wound dressing. The fact that most patients said they would be willing to use the dressings again highlighted the acceptability of both Exufiber<sup>®</sup> and Aquacel<sup>®</sup> Extra<sup>™</sup>.

In a recently published laboratory study, Lustig et al. (2020)<sup>12</sup> described the ability of a primary dressing to effectively transport fluids away from the wound bed and towards a secondary dressing (against gravity if that is required due to the positioning of the patient and configuration of the wound) as the sorptivity of the dressing. The authors developed a robotic phantom of an exuding sacral pressure ulcer, simulating an active wound environment in an anatomically and pathophysiologically realistic form; they used this model to reflect the impact of real-world factors on dressing performance. Dressings were exposed to exudate-like fluids released from a simulated wound. The model was used to compare the performance of Exufiber<sup>®</sup> and Exufiber<sup>®</sup> Ag+ with another market-leading gelling fibre dressing (in combination with a secondary dressing, Mepilex Border Sacrum). Exufiber<sup>®</sup> demonstrated consistent effective sorptivity for different simulated patient body postures; the comparative gelling fibre dressing acted more as a “plug”, which in real-world conditions, may lead to an accumulation or pooling of exudate under or around the dressing. The authors also used this phantom model to demonstrate the durability (defined as the capacity of the dressing to maintain its [structural] integrity over time and during removal) of the test dressings. Exufiber<sup>®</sup> demonstrated

superior mechanical endurance, approximately 5-times more than that of the comparator dressing.<sup>12</sup>

In terms of validity of data, the current study benefited from its prospective, randomised, parallel-group multicentre design, in a large study population (n = 248), in which the two treatment groups were well balanced at baseline, both in terms of demography and predictive wound-related factors (e.g., ulcer duration, ABPI, wound size, use of compression, wound location and recurrence). However, not every data point was captured at each visit; some visits were missed by patients, and some data points were missed by site staff. There may have been inconsistencies of use between the blinded assessor using the digital planimetry software and the clinician's use of cameras to capture the size and changes of the wound throughout the study due to improper angle, lighting and focus when capturing photos of the wounds. These limitations were mitigated as much as possible by appropriate training of staff, checklists, and continuous follow-up of uploaded images.

## 6 | CONCLUSIONS

Chronic wounds, such as leg ulcers, often produce excessive levels of exudate. If not managed appropriately, this can lead to maceration of the surrounding skin and in some cases precipitate wound infection, ultimately extending healing times. For many patients, appropriate exudate management is an essential part of managing the symptoms of their wound and can also help to provide an optimal healing environment. Gelling fibre dressings are an important part of managing wounds with excessive exudate and also help to support autolytic debridement by forming a soft, conformable gel on the wound bed.

This study showed that Exufiber<sup>®</sup> is at least as effective as Aquacel<sup>®</sup> Extra<sup>™</sup> in relation to wound area reduction in the management of moderately and highly exuding chronic wounds in patients with leg ulcers, thus achieving the objective of confirming non-inferiority. The results for the primary endpoint are robust and of high validity, and applicable for both short (6 weeks) and long-term (24 weeks). Both groups showed improvement in all aspects of wound healing. In addition, clinicians' evaluations (dressing features and technical performance) were more favourable for Exufiber<sup>®</sup> than for Aquacel<sup>®</sup> Extra<sup>™</sup>.

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## DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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## REFERENCES

- World Union of Wound Healing Societies. Consensus document. *Wound Exudate: Effective Assessment and Management*. London, UK: Wounds International. 2019. <https://www.wuwhs.org/wp-content/uploads/2020/09/exudate.pdf>
- Alvarez O, Granick M. A new multilayer wound dressing that transports toxic matrix metalloproteases from chronic wound fluid away from the wound (Abstract CS-002). Presented at the Symposium on Advanced Wound Care (SAWC) Fall meeting; 12-14 November, 2019; Las Vegas, Nevada, USA.
- Benbow M. The expense of exudate management. *Br J Nurs*. 2015;24(15):S8.
- Vowden P, Bond E, Stryja J. Changing the way we look at viscous exudate. *Wounds Int*. 2015;6(3):35-41.
- Rippon M, Waring M, Bielfeldt S. An evaluation of properties related to wear time of four dressings during a five-day period. *Wounds UK*. 2015;11(1):45-54.
- Rippon M, Davies P, White R. Taking the trauma out of wound care: the importance of undisturbed healing. *J Wound Care*. 2012;21(8):359-360, 362, 364-368.
- Chadwick P, McCardle J. Exudate management using a gelling fibre dressing. *Diabet Foot J*. 2015;18(1):43-48.
- Strohal R, Dissemond J, Jordan O'Brien J, et al. EWMA document: debridement. An updated overview and clarification of the principle role of debridement. *J Wound Care*. 2013;22(1):5,S1-S49.
- Reyzelman AM, Vartivarian M. Evidence of intensive autolytic debridement with a self-adaptive wound dressing. *Wounds Compend Clin Res Pract*. 2015;27(8):229-235.
- Tickle J. Effective management of exudate with AQUACEL extra. *Br J Community Nurs*. 2012;17(Suppl:S38):s40-s36.
- Chadwick P, McCardle J. Open, non-comparative, multi-Centre post clinical study of the performance and safety of a gelling fibre wound dressing on diabetic foot ulcers. *J Wound Care*. 2016;25(4):290-300.
- Lustig A, Alves P, Call E, Santamaria N, Gefen A. The sorptivity and durability of gelling fibre dressings tested in a simulated sacral pressure ulcer system. *Int Wound J*. 2021;18:194.
- Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. The accuracy of venous leg ulcer prognostic models in a wound care system. *Int J Tissue Repair Regen*. 2004;12(2):163-168.
- Wendelken ME, Berg WT, Lichtenstein P, Markowitz L, Comfort C, Alvarez OM. Wounds measured from digital photographs using photodigital planimetry software: validation and rater reliability. *Wounds Compend Clin Res Pract*. 2011;23(9):267-275.
- Gilman T. Parameter for measurement of wound closure. *Wounds Compend Clin Res Pract*. 1990;3:95-101.
- Meaume S, Dissemond J, Addala A, et al. Evaluation of two fibrous wound dressings for the management of leg ulcers: results of a European randomised controlled trial (EARTH RCT). *J Wound Care*. 2014;23(3):105-106,108-111, 114-116.
- Moore Z, Strapp H. Managing the problem of excess exudate. *Br J Nurs (Mark Allen Publishing)*. 2015;24(15):S12, S14-S17.
- Davies P, Stephenson J, Manners C. Understanding undisturbed wound healing in clinical practice - a global survey of healthcare professionals. *Wounds UK*. 2019;15(4):56-65.

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