Clinics in Surgery

Research Article
Published: 16 Aug, 2018

# Leg Ulcer Treatment using an Innovative Biodegradable Dressing not Requiring Replacements

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## Abstract

The aim of this study was to evaluate the efficacy of the DibuCell Active dressing, the fully biodegradable dressing based on dibutyrylchitin, in the treatment of venous ulcers. The dressing undergoes full degradation within the wound. It does not require to be replaced (what significantly reduces the traumatization of newly formed tissues) and the only thing that is needed is to add yet another layer of the dressing once the previous one has been degraded.

Evaluation of the effectiveness of the dressing was performed based on the analysis of results obtained during the prospective, multicentre, randomized, single-blinded clinical trial ULCERUS 1/2014. Statistical analysis was performed using data obtained from 137 patients. The control group was treated with the Biatain Ag dressing, while the study group with both the DibuCell Active and Biatain Ag dressings.

In the control group, 38.24% of ulcers were healed, while in the study group – 34.78%. Comparing only the subset of normotensive patients, the study showed statistically significant differences ($p<0.05$) in the rate of ulcer healing process between these two groups. The rate of the healing process of ulcers was higher in the group of patients treated with the DibuCell Active and Biatain Ag dressings compared to patients treated only with the Biatain Ag dressing.

Adding the investigated dressing to standard therapy results in beneficial acceleration of the healing process. Addition of the DibuCell Active dressing to standard therapy seems to improve the treatment efficacy, especially in the case of large and extensive ulcers.

**Keywords: Biodegradable dressings; Chitin dibutyrate; Chronic venous insufficiency; Venous ulcers**

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**Received Date**: *19 Jul 2018*
**Accepted Date:** *14 Aug 2018*
**Published Date:** *16 Aug 2018*

***Citation:***
*Bieniek E, Skołucka-Szary K, Lewiński A, Piaskowski S. Leg Ulcer Treatment using an Innovative Biodegradable Dressing not Requiring Replacements. Clin Surg. 2018; 3: 2071*



## Introduction

Venous ulcers are especially common in the population of elders [1-3]. The therapies applied in most cases are regarded expensive and of dubious effectiveness. Treatment of ulcers occurring as a consequence of chronic venous insufficiency requires highly specialized and multidisciplinary approach. Increasing knowledge in this area leads to increasingly effective treatment of this common disease that affects 0.3% adult population in the countries of Western Europe [4,5]. The best wound care strategy is based on the TIME framework. It includes the proper tissue preparation, control over the infections of wound, maintaining the proper wound moisture and stimulation of epidermal growth. Back in the sixties of the 20th century, the first generation of dressings had been designed. They were basically the polymer films made of polyethylene, polypropylene or polyester. They were, however, impermeable for moisture. As a result, this feature contributed to accumulation of body fluids upon the wound surface and thus hindered the healing process itself. Subsequently, the second generation of dressings, made of pure polyurethane or carboxymethylcellulose and polyisobutylene (hydrocolloid dressings), was introduced. Their main drawback, adherence to newly formed tissues, lead to tissue damage as the dressing was replaced. The third generation of dressing materials is based on hydrophilic polyurethane films and hydrogels [6]. Moistened hydrogel dressings have better mechanical properties, elasticity and very good biocompatibility [7,8]. Similarly to their predecessors, they also need to be replaced regularly, which brings about considerable, although minimized in relation to older types of dressing, traumatization of newly regenerated tissues. Elimination of this problem became possible following the progress in such scientific fields

as biotechnology and chemistry, due to the fact that innovative biodegradable dressing DibuCell Active has been developed. This dressing, unlike the older ones, is enzymatically degraded directly in the wound environment. It does not need to be replaced on regular basis and the only further treatment steps required are to add an additional layer of the dressing once the previous one has been degraded in the wound. This procedure is continued until the wound is completely healed. Lack of the need to replace the dressing considerably facilitates and simplifies the treatment. The healing of ulcerations occurring during the chronic venous insufficiency should also consider the need for systemic administration of antibiotics, analgesics and nutritional preparations, especially in specific situations. An attention is paid to patient's education and secondary prevention including modification of lifestyle. It is also necessary to mention the treatment of all accompanying comorbidities, which may render the treatment of ulcerations more difficult and increase the risk of its eventual recurrence. Cardiovascular diseases (including hypertension) deserve special attention mainly due to their widespread occurrence. Moreover, some medications used in therapeutic management of hypertension have beneficial effects on the healing process of ulcers. This is especially the case of calcium antagonists (such as unarisine and nifedipine). These drugs inhibit the calcium ion channels in vascular smooth muscle cells, abolishing strong and long-lasting contraction and stenosis of small blood vessels. They also inhibit blood platelets aggregation and reveal slight antihistamine effect. What is more, nifedipine is proved to have beneficial effects on the area of ulcer, leading to its faster reduction, what is explained by improved skin circulation [9,10].

## Material and Methods

The effectiveness of the DibuCell Active dressing was evaluated based on the analysis of results obtained during the prospective, multicentre, randomized, single-blinded clinical trial ULCERUS 1/2014. The dressing is undergoing enzymatic degradation within the wound. Therefore, there is no need to replace the dressing. It is to be left in the wound until it becomes completely degraded (by means of enzymes present physiologically within the wound), and all that is needed is just mere addition of its new additional layer. Such application scheme is repeated until the wound is completely healed. The dressing serves as a scaffold for migrating cells and newly created tissues. It stabilizes the newly created tissue in early stages of its development and then undergoes degradation. Biodegradability of the dressing, determining its uniqueness, results from the properties of material called chitin dibutyrate (DBC) – a material of which it is made of. This biopolymer has been developed in the Celther Polska. DBC is a diester derivative of chitin, a polymer which can be quite commonly found in the natural environment (fungi, exoskeleton of insect). Chitin is characterized by biocompatibility, biodegradability, lack of toxicity, adsorptive properties, and mechanical strength [11-13] and it positively affects the migration, adhesion, and proliferation of fibroblasts [14-17]. This in turn may positively affect the key stages of the healing process, i.e. granulation and epidermal growth. DBC is a biocompatible polysaccharide enzymatically degrading to simple sugars naturally occurring in human body [18]. The DibuCell Active dressing is of highly porous structure, consisting of a network of intermittent micro channels. Variety of their sizes and open porosity determines the characteristic structure of the dressing. This structure ensures an optimally humid environment within the wound. On the one hand, it allows the excretion excess to be removed from the wound and, on the other hand, protects the wound from excessive drying. It also ensures proper gas exchange and acts as a scaffold for migrating connective tissue cells. *In vitro* experiments have proved no propagation of bacteria growth on the investigated dressing. As required by the ISO 10993 standard, the hereby tested DibuCell Active dressing has positively passed the biocompatibility test, in vitro cytotoxicity test, *in vivo* irritation and sensitization tests, hemocompatibility studies and tests of genotoxicity as well as preclinical studies on diabetic mouse model with induced wounds. The study population consisted of adult subjects with flat and shallow venous ulcers of 5-50 $cm^2$, without any clinical signs of infection, located within the lower limb region (between ankle and knee). One hundred and sixty patients were enrolled in the study and randomized into two groups: the study group (treated with the DibuCell Active and Biatain Ag dressings) and the control group (treated only with the Biatain Ag dressing), both involving 80 patients. The main criteria for inclusion to the clinical trial ULCERUS 1/2014: the presence of flat and shallow ulcers, without the clinical features of infection, after prior surgical or enzymatic cleansing, localized within the lower limb (between the ankle and the knee), size 5-50$cm^2$; duration of ulceration not shorter than 6 weeks and not longer than 46 weeks, the ankle brachial index in the range of 0.8 - 1.1 or the toe pressure above 50 mmHg. The main exclusion criteria were the following: ulcers with active infection, contaminated and with a large amount of exudate; dry wounds, necrobiosis lipoidica diabeticorum, current or previous cancer disease in the last 5 years (with the exception of pre-invasive cervical cancer or properly treated skin cancers other than melanoma). Of all 160 subjects enrolled in the study, those patients for which at least one episode of significant non-compliance with the study protocol was noted were excluded from the final statistical analysis. Ultimately, the final analysis was performed upon 68 (49.6%) patients from the control group treated with only the Biatain Ag dressing and 69 (50.4%) patients from the study group treated with both the DibuCell Active and Biatain Ag dressings, making together 137 subjects from both groups (Table 1). In both groups, all patients were treated according to the TIME strategy and the current state of the art. The wound dressings were applied on flat and shallow ulcers following their surgical and/or enzymatic debridement. In the study group, the Biatain Ag dressing was applied during each visit in the active phase of the study as a second layer covering the primary layer of the DibuCell Active dressing. The DibuCell Active dressing undergoes spontaneous degradation within the wound (the time of degradation depends, among others, on the amount of exudate). Where the structure of dressing became obliterated, another layer of the DibuCell Active dressing was applied with a maximum margin of 0.5 cm overlapping the previous dressing layer and/or the edges of the wound. Such application scheme was repeated until the wound became completely healed or until the end of the study. The Biatain Ag dressing was replaced regularly, at time intervals recommended by manufacturer's instructions. In the study group, it was used as the secondary dressing (not directly in contact with the wound). In the control group, the Biatain Ag dressing was used as both the primary and secondary dressing. This study design gave the opportunity to ensure the same standards of medical care in both groups of patients. The secondary dressing used in the study group was the same as the primary and secondary dressings used in the control group. It allowed showing differences between these two groups. All other components of the treatment were identical in both groups. Once the dressings were applied to the limb with ulcer a multilayer compression system (JOBST Comprifore® 4 layer) was applied. During the stage of patients' qualification to the study, which was based on physical

**Table 1:** Characteristics of subjects enrolled in the study (included in the statistical analysis).

| | The study group (treated with the DibuCell Active and Biatain Ag dressings) | The control group (treated with the Biatain Ag dressing) |
|---|---|---|
| Number of patients | 69 (50.4%) | 68 (49.6%) |
| 29-50 years | 9 (13.04%) | 8 (11.77%) |
| 51-61 years | 16 (23.19%) | 7 (10.29%) |
| 62-72 years | 21 (30.44%) | 22 (32.36%) |
| 73 years or older | 23 (33.33%) | 31 (45.58%) |
| Women | 38 (55.1%) | 41 (60.3%) |
| Men | 31 (44.9%) | 27 (39.7%) |
| Subjects declaring antihypertensive treatment | 27 (39.1%) | 36 (52.9%) |
| Subjects taking antihypertensives | 29 (21.2%) | 30 (21.9%) |
| Subjects with elevated blood pressure identified during the recruiting visit (treated and untreated). | 42 (30.7%) | 34 (24.8%) |
| Subjects with high blood pressure values found during the recruiting visit but without any antihypertensive treatment | 27 (19.7%) | 23 (16.8%) |
| Subjects with high blood pressure values found during the recruiting visit with antihypertensive treatment | 17 (12.4%) | 10 (7.3%) |
| Subjects with previous myocardial infarction | 2 (2.9%) | 5 (7.4%) |
| Subjects diagnosed with diabetes mellitus | 5 (7.2%) | 11 (16.2%) |

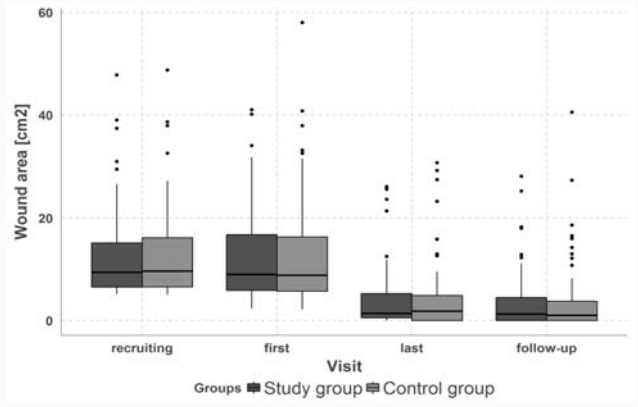


**Figure 1:** Changes of wound area during the study in the control and the study group.

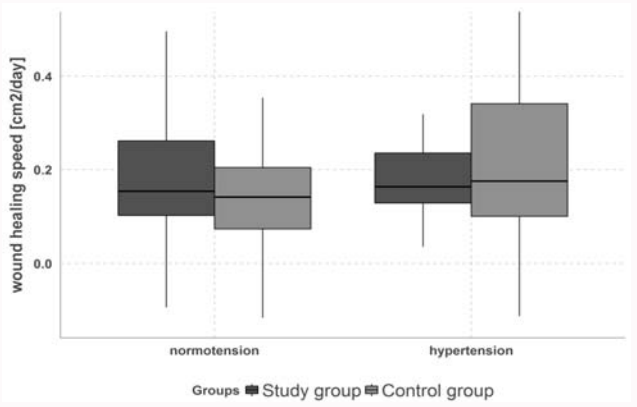


**Figure 2:** Change of wound healing speed according to level of blood pressure in study and control group.

examinations and interview, the ankle-brachial pressure index value and the USG Doppler examinations of lower limbs were used to exclude any possible contraindications of the above described scheme of treatment. At the each visit, a 0.9% NaCl solution and Octenisept (Schülke) were used in all subjects to clean the wound. All patients were subjects to interview and physical examinations. The patient's follow-up period in the study was approx. 11 weeks, during which each patient took part in 12 visits (plus any additional visits if necessary). The healing rate and the rate of reduction of ulcer surface area were analysed. In addition, the fraction of completely healed wounds in both groups was also assessed. Statistical significance was inferred for $\alpha=0.05$ in the case of all statistical tests used in the study. The normal distribution of random variables was tested using the Shapiro-Wilk test. The analysis of outliers was made using the Cook's distance method. Analysis of primary endpoints: healing rate and reduction of surface area in time: depending on the variable distribution and its type, a Student's t-test or U Mann-Whitney or ANOVA or Kruskal Wallis tests were performed; percentage of healed ulcers: a percentage calculation was performed along with a confidence interval in individual groups along with the chi-square test.

The clinical trial ULCERUS 1/2014 was accepted by the Bioethics Committee (Approval No. RNN/189/14/KE). The study protocol *was conformed to the ethical guidelines of the 1975 Declaration of Helsinki.* All patients participating in the clinical trial, prior to the start of the clinical trial, have accepted informed consent, including the agreement of clinical trial results publication.

## Results

No statistically significant differences in the rate of healing of ulcers, the rate of reduction of their surface area (Figure 1, Table 1), and the fraction of healed ulcers were found between the patients treated with both the DibuCell Active and Biatain Ag dressings and the patients treated with the Biatain Ag dressing only ($p>0.05$). In the control group, the median rate of healing was 0.157 $cm^2$/day while in the control group it was 0.156 $cm^2$/day. Median change of the wound area between the first and the last visit of the active stage of the study in the control and the study group was 75.5% and 77.9%, respectively. In the control group, 38.24% (95%CI lower bound 26.7%, upper bound 50.8%) of ulcers were healed, while in the study group this fraction reached 34.78% (95% CI lower bound 23.7%, upper bound 47.2%), significance level was 0.67 (Table 3). Statistically significant differences ($p<0.05$) in the rate of ulcer healing process were, however, found comparing only the subset of normotensive subjects.

**Table 2:** Change of the wound area between the recruiting visit and the follow-up visit in the study and control groups.

| **Study group** | | | | | |
|---|---|---|---|---|---|
| **Wound area [cm²]** | **N** | **Min** | **Max** | **Median** | **Interquartile range** |
| Recruiting visit | 69 | 5.13 | 47.75 | 9.38 | 9 |
| The first visit | 69 | 2.38 | 41 | 9 | 11.06 |
| The last visit | 69 | 0 | 26 | 1.38 | 5 |
| The follow-up visit | 69 | 0 | 28 | 1.25 | 4.63 |
| **Control group** | | | | | |
| **Wound area [cm²]** | **N** | **Min** | **Max** | **Median** | **Interquartile range** |
| Recruiting visit | 68 | 5 | 48.75 | 9.63 | 9.78 |
| The first visit | 68 | 2.125 | 58 | 8.81 | 11.28 |
| The last visit | 68 | 0 | 30.63 | 1.81 | 4.88 |
| The follow-up visit | 68 | 0 | 40.5 | 1 | 3.75 |

Among normotensive subjects from the control group, the median rate of ulcer healing was 0.14 cm²/day, while in the study group (with the DibuCell Active dressing included); the healing rate was 0.21 cm²/day (Figure 2).

## Discussion

The treatment of lower leg ulcers, as well as other chronic wounds, is a difficult and expensive process. This is implied by both the underlying changes as well as by the general state of patents. Primary causes that have led to the development of ulcer cannot often be removed. Therefore, they exert their adverse effects even once the lesion has been healed, leading often to relapses. One of the ulcer development risk factors unable to be modified is patient's age. The incidence of venous pathologies increases with the duration of life. The problem of varicose veins of the lower limbs concerns 40% of men and 50% of women at the age of 70 years or older. A similar relationship is observed in the case of trophic changes of the skin and ulcers [9]. Elderly people often suffer from the individual multi morbidity phenomenon. It consists in the increased incidence of various diseases. Diseases, the incidence of which increases with age other than those mentioned above, include diabetes, atherosclerosis, arterial hypertension, cancer, and psychiatric disorders [19]. All these accompanying diseases should be considered during the treatment process. The ULCERUS 1/2014 clinical trial, in which the efficacy and safety of the DibuCell Active dressing was investigated, was conducted in the elderly population (according to WHO criterion, the early old-age starts at the age of 60 years), which comprised 70% of all subjects enrolled in the study. In the analysis, it was thus necessary to take the effect of the above mentioned accompanying diseases on the healing process into account.

Even though no significant differences in the rate of the ulcer healing process were observed when all subjects treated with both the DibuCell Active and Biatain Ag dressings (i.e. from the study group) were compared to all subjects from the control group treated only with the Biatain Ag dressing (Figure 1, Table 3), significant differences were, however, revealed when only the subset of normotensive patients from both these groups were compared. The study showed statistically significant differences ($p<0.05$) in the rate of ulcer healing process comparing the normotensive subjects from the study group to those of the control group (Figure 2). Patients were divided into two abovementioned subsets (i.e. normotensive patients *vs.* hypertensive patients) based on the blood pressure measurement performed during the first recruiting visit. The goal of such measurement was to assess the prevalence of hypertension in the population enrolled in the clinical trial. Hypertension has a huge effect on the treatment process and general condition of patients and due to rare occurrence of any symptoms of this disease, some patients may not be aware of its presence at all. The analysis was based on the value of arterial pressure measured during the first recruiting visit, since the arterial pressure values obtained during the subsequent visits as well as their potential changes (optimization) may have resulted from started or intensified treatment of arterial hypertension following its identification during the first visit. Thus, subjects declaring arterial hypertension comprised 27% of the study group and 35% of the control one. However, elevated values of arterial pressure during the first recruiting visit were observed among 42% of subjects from the study group and 34% of the control one. Subjects with high arterial pressure values without any treatment comprised 27% of the study group and 23% of the control one, and those treated for hypertension comprised 17% and 10%, respectively (Table 1). The study showed statistically significant differences ($p<0.05$) in the rate of ulcer healing between the normotensive subjects (blood pressure measured during the first recruiting visit) from the control group and respective subset of normotensive subjects (blood pressure measured at the same time) from the study one (Figure 2). This leads to the conclusion that the DibuCell Active dressing is more effective in the group of normotensive patients (blood pressure <140/90 mmHg). At the same time, the lack of any advantage of the DibuCell Active/Biatain Ag combined treatment over the treatment with the Biatain Ag dressing only among patients with hypertension results most likely from the disproportion in the distribution of patients in individual groups. As far as the blood pressure analysis data is concerned, it should be noted that in the control group more patients were treated for hypertension. In the study group, during the incidental blood pressure measurement, higher blood pressure values were found. Thus, there were more patients with suboptimal treatment in this group. In addition, subjects from the study group were more frequently unaware of the disease than subjects from the control group, owing to which they were not treated (Table 1). Consequently, subjects from the study group may have presented worse overall condition. Potentially, they may have suffered from

**Table 3:** The rate of the healing process, change of the ulcer area.

| **The rate of the process of ulcer healing (cm²/day)** | N | Min | Max | Median | Interquartile range | Median rank | Sum of ranks | Significance level |
|---|---|---|---|---|---|---|---|---|
| Control group | 68 | -0.591 | 2.875 | 0.157 | 0.226 | 67.81 | 4611 | 0.364 |
| Study group | 69 | -0.095 | 1.625 | 0.156 | 0.138 | 70.17 | 4842 | |
| **Change of the wound area between the first and the last visit** | | | | | | | | |
| Control group | 68 | -126.90% | 100.00% | 75.50% | 58.20% | 61.75 | 3767 | 0.35 |
| Study group | 69 | -44.80% | 100.00% | 77.90% | 43.80% | 63.22 | 3983 | |

more aggravated atherosclerosis and vascular remodeling resulting from the adverse effects of hypertension. This may have led to worse functionality of internal organs and worse blood supply to the skin resulting in impaired healing process. Patients with hypertension without any hypertensive treatment also lacked the potentially beneficial effect exerted by antihypertensive drugs on the process of ulcer healing. The literature suggests a beneficial effect of calcium channel blockers on the course of the ulcer healing process, especially in the case of nifedipine [10,20,21]. This drug inhibits progression of atherosclerosis and possesses antioxidant properties [22]. This may improve the skin oxidation and blood supply and accelerate the ulcer healing process, as a consequence. Moreover, some of the medications used in the treatment of hypertension are known to have endothelial and vasoprotective effects, as well. These include the Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin Receptor Antagonists AT1 (sartans). These drugs, irrespective of their hypotensive effects, trigger a broad spectrum of endothelial changes [23]. This may lead to improved blood supply and nourishment of the skin and acceleration of the ulcer healing process.

In view of the disproportions in the distribution of hypertension, the disease awareness, blood pressure values and the effect of medications between the study and control group, it seems apparent that all of them may have influenced the results of the ULCERUS 1/2014 trial, especially among patients with elevated blood pressure. Lack of any effect of addition of the DibuCell Active dressing to standard therapy in the subset of hypertensive patients from the study group seems to be related to poorer general condition of these patients. Patients comprising this subset, when compared to respective counterparts from the control group, presented higher values of blood pressure, were less likely to be aware of the disease, more often they were untreated, or their treatment was suboptimal. As a consequence, the condition of their circulatory system and especially the condition of their blood vessels was poorer, possibly contributing to poorer blood supply of the skin, hindering furthermore the process of healing. At the same time, it should be noted that both the median as well as the distribution of all results of hypertensive patients in the study group are better comparing to respective values of normotensive patients from the control group (Figure 2). Considering these data, the DibuCell Active dressing seems to have beneficial effects on the course of the healing process also in the subset of patients with abnormal blood pressure values.

An objection may be raised against the above described analysis, that it has been performed based on only one blood pressure measurement (during the first recruiting visit). The diagnosis of hypertension under such circumstances is subject to error resulting from the fact that the group of hypertensive patients may also have included patients suffering from the so-called white coat hypertension. It should be emphasized that in the light of current opinions, the decision to implement an antihypertensive treatment should depend not only on the value of blood pressure, but also on the presence and nature of target organ damages, other risk factors as well as other accompanying comorbidities. Considering the information that the values of blood pressure obtained during the subsequent visits of the clinical trial may have been subject to change due to introduced or optimized antihypertensive treatment, it seems that the selection of time point for blood pressure values measurement and analysis was optimal. This study shows that while treating leg ulcers, efforts should be made to achieve optimal blood pressure values. The inclusion or optimization of pharmacotherapy may not only translate into improved general condition of a given patient, but also to improved time course of the lesion healing process, as well.

In assessing the rate of the healing process, attention should also be paid to the initial area of the ulcer. During the qualification stage of the study, the median ulcer area in the control group was 9.63 $cm^2$ (min=5 $cm^2$, max=48.75 $cm^2$), during the first visit, following the proper cleaning of wounds, the median surface area was 8.81 $cm^2$ (min=2.125 $cm^2$, max=58 $cm^2$). In the study group, the median ulcer area during the recruiting visit was 9.38 $cm^2$ (min=5.13 $cm^2$, max=47.75 $cm^2$), during the first visit, following the proper cleaning of wounds, the median surface area was 9.0 $cm^2$ (min=2.38 $cm^2$, max=41.0 $cm^2$). At the qualification visit in the study group wounds were larger than in the control group. But, at the first visit of the active phase, the sizes of wounds in the control group were significantly decreased compared to the study group. This indicates their higher therapeutic potential resulting from a local better condition of the wound or better general condition of these patients.

Moreover, the wounds in the study group, treated with the DibuCell Active and Biatain Ag dressings, were, in fact, larger and with lower therapeutic potential therefore more difficult to be treated. At the end of the study, the median ulcer area in the control group was 1.81 $cm^2$ (min=0 $cm^2$, max=30.63 $cm^2$) while in the study group it was 1.38 $cm^2$ (min=0 $cm^2$, max=26.0 $cm^2$) (Table 2). Taking the above presented results into account as well as the fact that similar therapeutic effects were achieved in both groups, it seems that adding the DibuCell Active dressing into standard therapy (especially in the case of large ulcers) may improve the treatment effectiveness.

## Conclusion

The scientific progress determining the knowledge and understanding of the pathophysiology of venous ulcers and their healing process, together with the development of biomaterials and biotechnology, provides new therapeutic possibilities. Work that has been done in these fields, resulted in development of the biodegradable dressing made of chitin dibutyrate (DBC) called the DibuCell Active dressing. This dressing undergoes full degradation within the wound environment. There is no need to change the dressing and the only necessary thing is to add its additional layer once the previous one (placed in the wound) has been fully degraded. This minimizes the traumatization of newly created tissues and facilitates and simplifies the treatment process. The ULCERUS 1/2014 clinical trial showed that addition of the DibuCell Active dressing to standard therapy increases the therapeutic efficacy of the treatment of ulcers occurring during the chronic venous insufficiency among normotensive patients when compared to those from the control group and exerts beneficial effects on the rate of the wound healing process in the case of hypertensive patients. Results of this study emphasize the need for control and possible stabilization of blood pressure in the group of patients treated for chronic wounds. Moreover, the addition of the DibuCell Active dressing to standard therapy, especially in the case of large ulcers, may improve the effectiveness of the treatment.

## Article Summary

- DibuCell Active undergoes enzymatic degradation within wound environment; therefore it does not require to be replaced.
- The aim of the study was to evaluate the efficacy of the DibuCell Active dressing, the fully biodegradable dressing based on dibutyrylchitin, in the treatment of venous ulcers.

- Addition of the DibuCell Active dressing to standard therapy seems to improve the treatment efficacy and eliminates the traumatization of newly formed tissues.

## Acknowledgment

Funding: The study was sponsored by Polish Agency for Enterprise Development, Grant No. POIG.01.04.00-10-020/10.

## Disclosure

Conflict of interests: Ewa Bieniek- employed as medical consultant in Celther Polska;

Sylwester Piaskowski- employed as project coordinator and President in Celther Polska;

Karolina Skołucka-Szary- employed as project coordinator in Celther Polska.

## Author contributions (%)

Ewa Bieniek (40%) - the conception and the design of the study, acquisition of the data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Karolina Skołucka-Szary (25%) - the conception and the design of the study, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

Andrzej Lewiński (10%) - analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

Sylwester Piaskowski (25%) - the conception and the design of the study, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

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