# Monochromatic phototherapy – effective treatment for grade II chronic pressure ulcers in elderly patients

A double-blind randomized placebo-controlled study in elderly patients, using pooled data

Running head: Phototherapy in pressure ulcers

1 Ove Dehlin, 1 Sölve Elmståhl, and 2 Finn Gottrup

1 Department of Community Medicine, Malmö University Hospital, Malmö, Sweden, 2 University Center for Wound Healing, Department of Plastic Surgery, Odense University Hospital, Odense, Denmark

Key words: Elderly patients, phototherapy, pressure ulcer, therapy, wound.

Correspondence:
Ove Dehlin, M.D., Department of Community Medicine, Lund University, Malmö University Hospital, 20502 Malmö, Sweden. Phone 040-333208; fax 040-336215; E-mail ove.dehlin@punkt.se

**ABSTRACT**

***Background and aims****: Monochromatic pulsating light may have effects on wound healing. In an earlier study of grade II ulcers, there was a tendency toward better healing in the phototherapy group (p=0.06). The present study on patients with grade II ulcers was performed to verify these findings. Data from this study were pooled with data from the earlier study.* ***Methods****: Ninety-four patients were offered participation in the new study and 76 patients were evaluated. They were pooled with 87 patients from the earlier study, bringing the total to 163. All patients were treated with monochromatic pulsating light or placebo over the ulcerated area, according to a specified program up to 12 weeks.* ***Results****: The mean normalized reduction in pressure ulcer size at week 12 was 0.79 for the phototherapy group and 0.50 for the placebo group (95 % CI 0.01–0.53; p=0.039). No serious sideeffects were noted.* ***Conclusions****: Monochromatic pulsating light accelerates healing in grade II pressure ulcers in elderly patients.*

## INTRODUCTION

Treatment with pulsed electromagnetic fields has been shown to improve microvascular perfusion of the skin after 40 minutes of treatment (1). In a literature overview from 1965 to 2003 on low-laser therapy for wound healing, focusing on both in vitro models and in vivo animal and human studies, some studies reported increased cell proliferation and collagen production; improvements in surgical wound healing were found in a rodent model; and, in humans, beneficial effects on superficial wound healing found in small case series have not been replicated in larger studies (2). In none of the reviewed studies was the exact mechanism of photothermal, photochemical or photomechanical action, reported. The precise mode of action of low-laser therapy on wound healing is still unknown (2). In a meta-analytic study of 34 peer-reviewed papers on the efficacy of low-power lasers in tissue repair, a positive effect was shown on collagen formation, rate of healing, tensile strength, and time needed for wound closure (3). In an experimental study on pressure ulcers in mice, a significant positive effect was shown on wound healing after treatment with low-laser therapy and this effect was independent of the temperature on the skin surface (4). In a systematic review of the effects of low-level laser therapy on wound healing in cell studies and animal model experiments by Lucas et al. (5), the 36 included studies contained 49 outcome parameters, of which 30 reported the positive effect of laser irradiation and 19 did not. The methodological quality of many studies was poor, and in-depth analysis of the studies with the highest methodological quality scores showed no significant pooled effect in favour of treatment (5).

A study of 20 spinal cord-injured patients with 22 pressure ulcers showed faster healing with a combination of ultrasound/ultraviolet-C and laser treatment, compared with nursing care alone (6). In a prospective, observer-blinded, multicenter randomized clinical study on the efficacy of low-level laser therapy in 86 patients with stage III decubitus ulcers, no evidence was found that justified the use of low-level laser therapy (7).

Biolight (registered trademark, Biolight International AB, Stockholm, Sweden, henceforth monochromatic phototherapy) is a pulsed monochromatic light, i.e., electromagnetic energy in the visible or near-visible spectrum. The equipment, which is non-invasive and non-thermal, is based on the biological effects of pulsed monochromatic light with wavelengths of between 637 and 956 nm and a pulse repetition frequency between 8 and 9900 Hertz.

A few years ago a placebo-controlled, randomized, open study was performed using pulsating monochromatic light in 74 patients with grade II and III chronic pressure ulcers (8). Most of the patients had grade II ulcers, and only 14 % had grade III ulcers. Most of the patients had suffered a hip fracture and were post-operative. The results showed a statistically significant reduction in ulcer size and earlier healing of ulcers in the phototherapy group compared with the placebo group (8).

To verify these findings, a double-blind, randomized, placebo-controlled study was performed in patients with grade II and III pressure ulcers. The hypothesis was that treatment of chronic pressure ulcers in geriatric patients using pulsed monochromatic phototherapy should result in a shorter length of time until total healing and a greater reduction in pressure ulcer area, in comparison with placebo light. The results, presented in “Aging” in 2003 (9) showed no significant effect in total material. Almost half the patients had grade III ulcers. However, in a sub-analysis of grade II ulcers, there was a tendency toward better healing in the phototherapy group ($p=0.06$). A significantly larger reduction in pressure ulcer size was found in patients in the treatment group with a BMI below 20.

Based on the tendency toward better healing in patients with grade II ulcers in the treatment group – and with regard to the divergent results of earlier studies as shown above - it was considered of interest to study that group of patients separately. For this reason the present double-blind, randomized, placebo-controlled study included patients with grade II ulcers only, and these patients´ data were pooled with data from patients with grade II ulcers in the previous study (9).

## METHODS

*Subjects*

The study was performed in inpatients and outpatients at eight geriatric centres in Denmark and Sweden. Inclusion criteria were grade II (Shea score) pressure ulcer, location on trunk or foot, ulcer age 2 weeks to 6 months, initial ulcer area 1 $cm^2$ to 20 $cm^2$, and patient age at least 65.

Exclusion criteria were: unstable diabetes mellitus (HbA1C >10 %), serious or terminal malignancy or terminal illness, treatment with radiotherapy or cytotoxins, suspected or proven osteomyelitis, antibiotic treatment of ulcer within 2 weeks, corticosteroid use (> 10 mg/day of prednisolone), significant abnormal blood tests in the month before inclusion, pacemaker, photosensitivity or sensitivity to electromagnetic radiation, life expectancy < 3 months, and participation in any other clinical study during the last month.

A sample size estimate was based upon the previous studies (8, 9) and on the variable "expected ulcer survival time". A coefficient of variation for this variable of 0.4 to 0.6 was assumed, and 160 patients should have been included in order to reach 90% power to obtain a p-value of less than 5%. 87 patients were available from the earlier study (9), 43 placebo and 44 monochromatic phototherapy patients, and thus an additional 73 patients were needed.

A total of 94 patients were offered participation in the new study, and agreed. Of these, 11 died, 2 withdrew their consent, one patient developed gangrene in one foot, in one patient the ulcer size was too small, and for 3 patients there was no nurse available to perform the treatment, leaving 76 patients to be included in the material.

The characteristics of the 163 patients (87 patients from the earlier study, and 76 from the new one) are shown in Table 1.

*Procedures*

The methods were exactly similar to the earlier study. At the first visit, the physician performed a general physical examination, collected medical history, and blood tests were taken and repeated at week 13 after completion of the study. Functional assessment, medication, date of ulcer onset, classification and location of the ulcer, and measurement of ulcer area were also recorded at visit 1. Photo documentation of ulcers was obtained at the first and last visits. Concomitant medication, ulcer area measurement, ulcer healing date, adverse events, and a check of compliance and randomization were also carried out at weekly

visits. Randomization was performed in blocks of appropriate and variable sizes, according to a computer-generated list.

*Phototherapy.* Phototherapy (placebo or monochromatic phototherapy) was administered according to a fixed scheme: 5 days during week 1; 2 days during weeks 2, 4, 6, 8 and 10; and 3 days during weeks 3, 5, 7, 9 and 11. No phototherapy was administered on Saturdays or Sundays. Treatment duration was 9 minutes for the first 5 sessions (week 1) and 6 minutes for all remaining sessions. In total, this involved a possible maximum of 30 treatment sessions for 11 weeks. Therapy was administered by specially trained nurses, who were employed or salaried especially for the study. It was stressed that the patients taking part in the study should not receive another or "better" treatment than patients not participating in it. The equipment is non-invasive, non-thermal, and based on the effects of pulsed monochromatic light in the visible or near-visible spectrum. A probe contained 30 diodes emitting infrared light at 956 nm and also 80 diodes emitting red light at 637 nm. At a test before the clinical study started, the peak for infrared monochromatic light at 956 nm was 960 nm +/- 4 nm, and the values for red monochromatic light at 637 nm was 636 nm +/- 8 nm, respectively (Saven Test & Mät AB, Sweden, holder of "Certificate of Compliance and Conformance"). A software-controlled desktop device controlled light emission. The light – placebo or monochromatic phototherapy – was applied locally to the ulcer area. The probe, the size of the palm of the hand, was held approximately 3 cm above the ulcer and was advanced around its surface to ensure illumination of the whole area. Infrared and red pulsed monochromatic light were used in sequence. Infrared light, with an irradiance of 55 $W/m^2$, was given first and then red light, with an irradiance of 21 $W/m^2$. Using a duty cycle of 80%, both infrared and red light were pulsed at the following frequencies: infrared – 287 Hz, 31.2 Hz, 9900 Hz, 8 Hz, 15.6 Hz and 780 Hz; red – 8 Hz, 31.2 Hz, 9900 Hz, 5 Hz and 8.6 Hz. The placebo light simply consisted of a white light diode painted red. The equipment for both monochromatic phototherapy and placebo was identical in appearance and both emitted red light. No heating was observed in either treatment.

*Local wound treatment*. All patients received the same conventional treatment: protection of the ulcer area, a regular turning schedule, emollient or moisturizing cream around the ulcer, a pressure-reducing mattress, and a pressure-reducing cushion for wheelchair-bound patients. Hydrocellular/hydrocolloid bandages (Comfeel, Coloplast, Thigaderm) were applied to clean ulcers. Chemical or enzymatic debridement was not allowed. Wound treatment was performed by the patient´s regular nurse, at the clinic, at the doctor´s office, or at home visits, but the phototherapy (active or placebo) was given by the specially employed nurse.

*Ulcer area measurement*. Ulcer area was measured twice during week 1 and once weekly for the remaining 11 weeks, or until the ulcer had healed. The area was measured with a plastic film (Op-site Flexigrid, Smith & Nephew), marked with a grid with 0.25 $cm^2$ divisions, placed on the ulcer by the specially employed nurse. The ulcer area for patients in all centers was determined by an independent individual, through the use of a planimeter. This person did not know the patients or what type of treatment had been given. These measurements were done each week of the study. Photos were also taken of all ulcers at day 1, at 6 weeks and after 12 weeks, if the wound had not healed earlier.
Time until total healing was assessed every week for 12 weeks or until healing.

*Statistical analysis*
Analyses were performed on pooled data from the patients with grade II pressure ulcers in the earlier study (9) and in the present one. This was done in order to achieve a more precise estimate of differences in treatment effects between monochromatic phototherapy and placebo, compared when analysing the studies separately. The efficacy data were based on the per protocol set. Patients were included in the full analysis set provided they had performed at least three consecutive treatments according to the treatment plan. Patients who withdrew from treatment were included in the efficacy and safety evaluations up to the time of withdrawal.
The primary efficacy variable normalized reduction in pressure ulcer size was calculated as the percentage change in ulcer size from baseline to week 12. Thus, normalized value =

$$\frac{\text{size at baseline} - \text{end-point}}{\text{size at baseline}}$$

The last-value-carried-forward technique was used, e.g., for those patients with totally healed ulcers before week 12, the normalized reduction at week 12 was 100 %. For patients withdrawing prior to week 12, the normalized reduction at week 12 was the corresponding value at the time of withdrawal. ANOVA was used, which allowed for variations due to treatment and center and also included the baseline measurement, to increase precision. Secondary efficacy variables were percentage of totally healed ulcers, i.e., 100 % reduction of ulcer size relative to baseline; time to totally healed ulcers, i.e., number of weeks from baseline measurement to the first week when pressure ulcer size was zero; normalized weekly reduction in pressure ulcer size over time, i.e., percentage change in ulcer size from baseline to each week, using the last-value-carried-forward technique; and the rate of normalized

reduction in pressure ulcer size; i.e., percentage change in ulcer size from baseline to total healing, withdrawal, or end of study, whichever occurred first, divided by the number of weeks from baseline to the last measurement. These were analysed using the chi-square test and ANOVA and – for survival of ulcers – the Kaplan-Meier technique and the log-rank test. Comparisons between patients´ variables in Table 1 were made with the t-test with the Welch correction.

All tests were two-sided and a p-value of less than 0.05 was considered as statistically significant. All analyses were performed with SAS version 6.12 for Windows.

## Ethics

The study was performed according to the declaration of Helsinki and all patients gave their written informed consent.

The Ethics Committee of the University of Lund approved the study.

**RESULTS**

Of the 163 patients who were available for evaluation, 79 were treated with monochromatic phototherapy and 84 with placebo light. The two groups did not differ significantly in a number of variables, although there was a tendency toward lower diastolic blood pressure in the monochromatic phototherapy group (Table 1).
The mean normalized reduction in pressure ulcer size at week 12 - the primary efficacy variable - was 0.79 for the monochromatic group and 0.50 for the placebo group (95 % CI 0.01–0.53; p=0.039), see Table 2. The normalized weekly reduction in pressure ulcer size over time was 15.1 % for monochromatic treated patients and 10.9 % for placebo-treated patients.

*Secondary efficacy variables:* There were no statistically significant differences between the treatments in the variables percentage of totally healed ulcers (monochromatic phototherapy 54.4 %; placebo light 59.5 %, p= 0.52) and time to totally healed ulcers (number of days), p= 0.58. Also, the rate of normalized reduction in pressure ulcer size did not differ significantly between treatment groups (p=0.12). For patients with a BMI less than or equal to 20, there was no significant difference between monochromatic phototherapy and placebo-treated patients in normalized reduction in pressure ulcer size.
*Adverse events:* In total, 67.5 % of patients reported at least one adverse event: 66 % in the monochromatic phototherapy group and 69 % in the placebo group. Most adverse events were considered unrelated to the treatment given; 83.5 % in the phototherapy group and 85 % in the placebo group. In 9 cases in the phototherapy group adverse events (mostly tingling in and around the wound or pain in the wound during treatment) were considered as possibly related to treatment; in the placebo group, 9 patients had skin symptoms that were considered as possibly related to treatment. The location of the adverse symptoms in the various organ systems are shown in Table 3.

**DISCUSSION**

This study shows that monochromatic pulsating light, compared with placebo light, accelerated healing in grade II pressure ulcers in elderly patients. There were, however, no significant differences between the treatments in the percentage of totally healed ulcers (100 % reduction relative to baseline) and time to totally healed ulcers (number of weeks from baseline to the first week when pressure ulcer size was zero). The faster healing of the grade II ulcers fits results from the open study, in which the majority of patients had grade II ulcers (8), and also with those from the sub-analysis of grade II ulcer patients in our earlier study (9). Also, in that study, stratified analysis of all material for body mass index (BMI) showed that those with an index of <20 had a greater reduction in pressure ulcer size in the monochromatic phototherapy group compared with the placebo group ( $p<0.01$). No differences were noted among patients with a BMI > 20.1. Due to these findings in the earlier study, a sub-analysis was performed in the present study between patients with a BMI > 20 or $\leq$ 20, but no significant differences between the treatments were found.
For power reasons, the size of the previous study (9) did not allow subdivision of grade II and III ulcers with regard to BMI. Therefore, the question if the different results in grade II and III ulcers were due to differences in BMI cannot be answered. The study was not designed for sub-analyses with regard to treatment site (facility), location or type of treated lesion. Likewise, patients with or without diabetes were not analyzed separately, since this would have necessitated a study with a higher number of patients.

It is unclear if monochromatic phototherapy has an analgesic effect. In one study comprising 20 randomly selected patients, no pain-relieving effect was found after scaling and rootplaning (10). In that study, however, patients on analgesics and anti-inflammatory drugs were not included. In another study, a reduction of neuropathic pain, mostly due to diabetes, was found after treatment (11). In a meta-analytic study of nine peer-reviewed papers on the efficacy of low-power lasers in the reduction of pain, a positive effect was found (3). A possible analgesic effect, if present, is unlikely to have influenced pressure ulcer healing time (3), and that would also be valid for the present study.
How do the results from the present study compare with other patient studies? Using non-thermal pulsed electromagnetic energy treatment, also in a randomized double-blind study, Salzberg et al. found faster healing in grade II pressure ulcers in spinal cord-injured patients, but not in grade III ulcers when the sample size was limited (12). No significant effects were

found in a study of 35 spinal cord-injured patients with 64 pressure ulcers after treatment with multi-wavelength light therapy, although limited evidence suggested that the therapy improved healing in stage III and IV pressure ulcers (13). In a systematic review of the effects of low-level laser therapy on wound healing by Lucas et al. (5), as well as in a prospective randomized clinical trial in 86 patients with stage III ulcers, no evidence of efficacy was found (7).

Thus, the results of the present study seem to be in accordance with some, but not all, earlier studies using a similar technique.

Why did treatment with monochromatic light in this study enhance healing in patients with grade II pressure ulcers, but not in patients with grade III ulcers? One explanation is that patients with grade III ulcers represent a more disabled group than patients with grade II ulcers, resulting in greater difficulties in healing.

Most adverse effects were considered not to be related to treatment. Tingling in and around the wound and pain in the wound during treatment were considered to be treatment-related. In an animal study focusing on the possible adverse effects of pulsating monochromatic light, with similar equipment and similar infrared and red light exposure as in the present study, except for exposure 5 times a week during a 2-week period, no effects on morbidity were found (14).

The etiology of pressure ulcers includes extrinsic factors such as pressure, shear stress, friction, and impaired lymphatic function due to local hypoxic effects or mechanical stress, and intrinsic factors such as immobility, acute illness, infection, terminal illness, malnutrition, anemia, peripheral vascular disease, drug therapy, and incontinence (15). The patients in this study showed some of these risk factors: e.g., more than 50 % were bedridden or wheelchair-bound, 70-81% had cardiovascular diseases and had low mean BMI. They were therefore probably representative of the pressure ulcer-prone elderly population.

This study combined the raw data from the earlier study (8) with new patients, to increase statistical power, both studies aiming at the same research question. This was done to lower the possibility of type II errors. The pooling of data, statistical methods and end-points were pre-defined and the inclusion criteria, exclusion criteria, methods and evaluations were all the same in both studies, with one exception: only patients with grade II ulcers were studied and pooled in this analysis, due to the findings in the first study of no effects in patients with grade III ulcers (9).

What are the treatment requirements and what training is needed? The treatment requires equipment, consisting of a probe the size of the palm of the hand, and a software-controlled desktop device to control light emission. Nurses have to be trained to use the equipment according to a fixed scheme, with a possible total number of 30 treatment sessions for 11 weeks. The method is not time-consuming, as treatment duration is 9 minutes for the first 5 sessions (week 1) and 6 minutes for all remaining sessions. The extra costs of monochromatic phototherapy treatment may be calculated as follows. The equipment is leased and 1000 wound dressings per year are performed, for instance in a nursing home or in home care. Leasing cost and extra nurse time amounts to approximately 3.5 euros/treatment session.

Hitherto, low-energy irradiation has not been regarded as sufficiently established to allow its recommendation to treat pressure ulcers (15). However, the present study shows that monochromatic pulsating light, compared with placebo light, accelerates healing in grade II pressure ulcers in elderly patients.

Appendix: *Participating physicians and centers:*
*Sweden: Vivianne Schubert; Annika Takman; Sonia Muzikants; Göran Hilding, Stockholm; Sölve Elmståhl; Margareta Nilsson, Malmö, Margareta Hellman, Uppsala;*
*Denmark: Finn Rönholt Hansen, Glostrup; Finn Gottrup, Copenhagen.*

**ACKNOWLEDGMENTS**

This study was supported by Biolight International AB. Statistical analyses were performed by Clinical Data Care AB, Sweden.

**REFERENCES**

1. Mayrovitz HN, Larsen PB. Effects of pulsed electromagnetic fields on skin microvascular perfusion. Wounds 1992; 4: 197-202.

2. Posten W, Wrone DA, Dover KS, Arndt KA, Silapunt S, Alam M. Low-level laser therapy for wound healing: mechanism and efficacy. Dermatol Surg 2005; 31: 334-40.

3. Enwemeka CS, Parker JC, Dowdy DS, Harkness EE, Sanford LE, Woodruff LD. The efficacy of low-power lasers in tissue repair and pain control: a meta-analytic study. Photomed Laser Surg 2004; 22: 323-9.

4. Lanzafame RJ, Stadler I, Coleman J, et al. Temperature-controlled 830-nm low-level laser therapy of experimental pressure ulcers. Photomed Laser Surg. 2004; 22: 483-8.

5. Lucas C, Criens-Poublon LJ, Cockrell CT, de Haan RJ. Wound healing in cell studies and animal model experiments by Low Level Laser Therapy; were clinical studies justified? a systematic review. Lasers Med Sci 2002; 17: 110-34.

6. Nussbaum EL, Biemann J, Mustard B. Comparison of ultrasound/ultraviolet-C and laser treatment of pressure ulcers in patients with spinal cord injury. Phys Ther 1994; 74: 812-25.

7. Lucas C, van Gemert MJ, de Haan RJ. Efficacy of low-level laser therapy in the management of stage III decubitus ulcers: a prospective, observer-blinded multicentre randomised clinical trial. Lasers Med Sci 2003; 18: 72-7.

8. Schubert V. Effects of phototherapy on pressure ulcer healing in elderly patients after a falling trauma. Photodermatol Photoimmunol Photomed 2001; 17: 32-8.

9. Dehlin O, Elmståhl S, Gottrup F. Monochromatic phototherapy in elderly patients: a new way of treating chronic pressure ulcers? Aging Clin Exp Res 2003; 15: 259-63.

10. Takas D, Tellefsen G, Johannsen G. Pain relief after scaling and rootplaning by monochromatic phototherapy (Biolight). Swed Dent J 2006; 30: 69-75.

11. Harkless LB, DeLellis S, Carnegie DH, Burke TJ. Improved foot sensitivity and pain reduction in patients with peripheral neuropathy after treatment with monochromatic infrared photo energy – MIRE. J Diabetes Complications 2006; 20: 81-7.

12. Salzberg CA, Cooper-Vastola SA, Perez F, Viehbeck MG, Byrne DW. The effects of non-thermal pulsed electromagnetic energy on wound healing of pressure ulcers in spinal cord-injured patients. A randomized double-blind study. Ostomy Wound Manage 1995; 41: 42-8.

13. Taly AB, Sivaraman Nair KP, Murali T, John A. Efficacy of multiwavelength light therapy in the treatment of pressure ulcers in subjects with disorders of the spinal cord: a randomized double-blind controlled trial. Arch Phys Med Rehabil 2004; 85: 1657-61.

14. Jensen-Waern M, Ekman S. Effects of a two-week treatment with pulsed monochromatic light in healthy pigs: a clinical and morphological study. Photodermatol Photoimmunol Photomed 2000; 16: 178-82.

15. Bello YM, Phillips TJ. Recent advances in wound healing. JAMA 2000; 283: 716-718.

*Table 1 - Characteristics of 163 patients.*

| **Variable** | **Phototherapy group (N=79)** | **Placebo group (N=84)** |
|---|---|---|
| Women (%) | 65 | 60 |
| Age (mean, SD, range) | 84; 7.5; 68-101 | 84; 7.7; 65-105 |
| BMI (mean, range) | 20; 12-31 | 21; 12-41 |
| Cardiovascular disease (%) | 81 | 70 |
| Neurological disease (%) | 65 | 63 |
| Musculo-skeletal disease (%) | 71 | 70 |
| Current smoker (%) | 5 | 6 |
| Systolic blood pressure (mean, SD + range) | 125; 22; 80-180 | 130; 20; 100-200 |
| Diastolic blood pressure (mean, SD + range) | 70; 10; 40-90 | 73; 12; 50-100 |
| % bedridden or wheelchair-bound | 54 | 53 |
| % walking with support | 39 | 37 |
| Ulcer age (days, mean, SD + range) | 55; 37; 14-167 | 59; 41; 15-183 |
| Foot ulcer location (% on heel and malleolus) | 41 | 46 |
| Trunk ulcer location (% on trochanter, sacrum, ischial tuberosity) | 59 | 54 |
| Mean baseline ulcer size | 4.1 (S.D. 3.2, median 3.0) | 4.7 (S.D. 4.0, median 3.3) |

*No significant differences between groups, but a tendency toward lower diastolic blood pressure in phototherapy group (p=0.08).*

*Table 2 - Summary of weekly reduction in pressure ulcer size (area) normalized to baseline according to therapy.*

| | **Monochromatic phototherapy** | | | **Placebo light** | | |
|---|---|---|---|---|---|---|
| Week | Mean | S.D. | Median | Mean | S.D. | Median |
| 1 | 0.206 | 0.320 | 0.203 | 0.224 | 0.341 | 0.142 |
| 2 | 0.395 | 0.384 | 0.394 | 0.335 | 0.450 | 0.401 |
| 3 | 0.529 | 0.444 | 0.596 | 0.401 | 0.572 | 0.482 |
| 4 | 0.586 | 0.435 | 0.662 | 0.416 | 0.863 | 0.688 |
| 5 | 0.642 | 0.423 | 0.752 | 0.393 | 0.993 | 0.738 |
| 6 | 0.672 | 0.465 | 0.863 | 0.422 | 1.007 | 0.788 |
| 7 | 0.659 | 0.495 | 0.889 | 0.447 | 1.039 | 0.893 |
| 8 | 0.701 | 0.465 | 0.946 | 0.472 | 1.041 | 0.932 |
| 9 | 0.734 | 0.421 | 0.975 | 0.485 | 1.060 | 0.989 |
| 10 | 0.761 | 0.406 | 0.984 | 0.501 | 1.061 | 1.000 |
| 11 | 0.768 | 0.417 | 1.000 | 0.484 | 1.109 | 1.000 |
| 12 | 0.785 | 0.418 | 1.000 | 0.502 | 1.082 | 1.000 |

*Mean normalized reduction in ulcer size at week 12 was 0.79 for monochromatic phototherapy group and 0.50 for placebo light group (p=0.039).*

*Table 3 – Percentage of adverse events in various organ systems.*

| **Adverse events (%), location** | **Monochromatic phototherapy (N=79)** | **Placebo (N=84 )** |
|---|---|---|
| Whole body | 27 | 20 |
| Skin | 16 | 17 |
| Gastro-intestinal | 11 | 12 |
| Respiratory | 9 | 10 |
| Cardio-vascular | 8 | 4 |
| Infection | 6 | 12 |
| Genito-urinary | 6 | 5 |
| Metabolic-nutrition | 3 | 2 |
| CNS | 1 | 4 |
| Blood | 3 | 2 |
| Musculo-skeletal | 2 | 1 |
| Psychiatric | 1 | 2 |
| Other (eyes, falls, tumors) | 7 | 9 |

*In total 67.5 % of patients reported 342 adverse events at weekly visits during study period, until 12 weeks. "Whole body" includes symptoms such as fever (without obvious infection), syncope, oedema, chest pain, aggravation of underlying disease.*