## A CLINICAL TRIAL SYNOPSIS

# Low radiant exposures delivered by high-frequency and/or long-pulsed diode laser energy output in hair reduction: an intrapatient comparative, randomized double-blind trial

## Introduction

Laser hair removal is based on the principles of selective photothermolysis with an appropriate combination of the laser wavelength, pulse duration, and radiant exposure.[1] The major chromophore is melanin within the hair shaft. Pulse duration (or pulse width) must be equal to or shorter than the thermal relaxation time (TRT) of the target to confine thermal damage. Terminal hairs are roughly 300 μm in diameter, and thus the calculated TRT of a terminal hair follicle is roughly 100 ms. The TRT of the epidermis is about 3–10 ms. Yet unlike many other laser applications, the hair follicle is distinct in that there is a spatial separation of the chromophore (melanin) within the hair shaft and the biological "target" stem cells in the bulge and bulb areas of the follicle. The expanded theory of selective photothermolysis takes this spatial separation into account and proposes a **thermal damage time**, which is thought to be longer than the TRT.[2] Shorter pulse widths are also capable of removing hair, but are probably not as effective in producing permanent hair removal. Longer pulse widths are more selective for melanin within the hair follicle and can minimize epidermal damage as the pulse widths are greater than the TRT of the melanosomes and melanocytes within the epidermis. Despite these facts, it is fascinating that for decades laser hair removal has been (though successfully) performed with much shorter wavelengths.[3,4]

There are two mechanisms for permanent hair reduction: miniaturization of coarse hair follicles to vellus-like hair follicles, and destruction of the hair follicle with granulomatous degeneration, leaving a fibrotic remnant.[1] Treatment should be performed with the highest fluence the skin can tolerate. Studies have shown that the percentage hair loss is fluence-dependent, with higher percentages of hair loss at higher fluences.[5] Hair color and skin color determine the best radiant exposure to use. In case of diode lasers, darker skin types IV to VI can be treated between 10 and 20 J/cm$^2$. Fair skin types I to III can take the highest fluences, from 25 to 40 J/cm$^2$. For most diode (~800 nm) and Nd:YAG (1064 nm) lasers used in persons with

phototype I-IV, recommended radiant exposures and pulse widths are 30-40 J/cm$^2$ and 30 ms, respectively.

Avalable trials confirmed clinical efficacy of diode and alexandrite (755 nm) lasers and somewhat lower hair reduction rates in Nd:YAG lasers.[6-13] Generally, pulse durations ranged between 3 and 30 ms, well below time suggested by extended theory of photothermolysis and confirmed by one preliminary clinical study (100 ms).[14]

A variety of a diode laser has been developed that uses lower radiant exposures (up to 12 J/cm$^2$), larger spot size (22x35 mm) and a vacuum-assisted hand-piece: it showed efficacy comparable to standard diode lasers but with less intraoperative pain.[15,16] In addition, a special combination of short pulses (20 ms), high repetition rate (10 Hz) and low radiant exposures (5-8 J/cm$^2$) was devised to achieve good efficacy with lower incidence of side effects. A single randomized trial compared this approach (7-9 J/cm$^2$, 10 Hz, 6-10 passes, delivering up to 90 J/cm$^2$ of laser energy per spot treated) to Nd:YAG laser (20-30 J/cm$^2$, 10-20 ms, low repetition rate). The latter was superior as for hair reduction rates.[17] Uncontrolled clinical trials confirmed lower intraoperative pain and higher efficacy of the the combination of parameters applied in a swift constant motion (so called »super hair removal«).[18-20]

**Hypothesis**

The use of a low radiant exposure (6 J/cm$^2$), standard pulse width (30 ms) and high repetition frequency (10 Hz) or the use of a medium radiant exposure (18 J/cm$^2$), longer pulse width (100 ms) and medium repetition frequency (4 Hz) diode laser is equally efficacious but safer than standard diode laser hair reduction protocol (25-35 J/cm$^2$, 12.5-30 ms, 1 Hz).

**Trial design**

Randomized, double-blind, intrapatient left-to-right trial. It has been designed as a non-inferiority trial with a non-inferiority margin (d) being either difference in 13 hairs (absolute number of three areas) or 65% reduction in hair counts.

**Study subjects**

Thirty (30) subjects will be consecutively recruited for this trial (Figure). Inclusion criteria will be: age >18 years, Fitzpatrick skin type I–III and brown to black axillary

and bilkini hairs. Exclusion criteria will be: a history of axillary laser hair removal or electrolysis, a history of hypertrophic scars or keloids, photosensitivity, pregnancy or lactation, a history of pigmentary disorders, intake of any medication with photosensitizing properties and subjects incapable of following the treatment protocol. All trial participants will be given written and oral information on the nature of the trial. Signed informed consent will be obtained from all study subjects before treatment. The trial will be approved by the local ethics committee (VIST) and carried out in accordance with the Declaration of Helsinki. The trial will be conducted at the Dermatology Center Parmova, Ljubljana, Slovenia, starting in 2015.

**Randomization and treatment protocols**

The two axillary and bikini regions of each subject will be randomized to the two sets of competing procedures, two low radiant exposure modalities and a standard protocol. The randomization list will be generated with a web-based tool (http://www.random.org/lists/). One axilla and one bikini area will be treated with the LightSheer ET system (Lumenis Inc., Santa Clara, CA, USA) using a wavelength of 800 nm. Treatments will be conducted by a contact probe with a window of 12x12 mm, radiant exposures of 25–35 J/cm$^2$ and a pulse duration of 12.5–30 ms. A lower radiant exposure will be used for the first treatment (25 J/cm$^2$), which will be gradually increased in the following treatments if tolerated by the study subject. The epidermis will be cooled during the laser procedure by placing a sapphire window-based 5ºC cooling hand-piece tip (ChillTip) onto the skin surface. The treatment technique involves moving the hand-piece slowly in a constant gliding movement to cover the complete treatment area. A thin layer of water-based ultrasound gel was applied onto the skin to facilitate the gliding of the laser nozzle.

The other axilla will be treated with the 808 nm Diode Laser D8 (Shanghai Vanoo Laser Technology, Shanghai, PR China) using a contact probe with a window of 10x14 mm, radiant exposure of 6 J/cm$^2$, pulse width of 30 ms and repetition frequency of 10 Hz (for bikini), and radiant exposure of 18 J/cm$^2$, pulse width of 100 ms and repetition frequency of 4 Hz (for axilla). Ten passes of irradiation will be applied on an bikini area of about 100 cm$^2$ using a constant motion technique at an average of 10 cm per second. For the similar area of the axilla, 4 passes of irradiation will be applied using a constant motion technique at roughly 5 cm per second. The nozzle of this device’s hand-piece incorporates a sapphire chill window technology

through which a coolant is in constant circulation maintaining temperature of 5ºC. As for the other side, a thin coat of ultrasound gel was applied onto the skin surface to make gliding of the laser nozzle easier.

**Treatment protocol**

After the screening visit, study participants will receive the first treatment within 3 weeks (visit 1). Study subjects will be instructed to come to each laser treatment with hairs roughly 2-3 mm long. Each treatment site will be randomized to LightSheer and D8 treatments at the screening visit. Treated areas will be marked with a white marker and photographed. The photographs will be obtained before each of the treatments and at the 3- and 6-month follow-up visits following the last treatment. The photographic conditions including the camera model (Canon EOS 600D, auto mode, no flash), the lighting associated with the camera, and the subjects' positioning remained the same throughout each photographic session.Then three representative regions of interest (ROI) of each axilla and bikini 2 cm in diameter will be chosen, marked on the skin and photodocumented with a dermoscope (Fotofinder, Bad Birnbach, Germany). Topographical hallmarks will be used to locate the exact positions of the studied areas. The documentation will be saved as macro and dermatoscopic images and entered the hair count analysis. A trained therapist will conduct all treatments. Study participants will receive six treatments at 4-week intervals (visits 1–6) with both diode lasers. Follow-up visits will took place 3 and 6 months after the last treatment session (visits 7 and 8).

**Assessment and response evaluation**

After each laser treatment, study subjects were evaluated for immediate side-effects, such as burning, oedema and blistering. A visual analogue scale (VAS) ranging from 0 to 10 was used for the self-assessment of pain (0 = no pain, 10 = maximum pain). The same questionnaire was handed out during every treatment visit. The mean score for all six visits was obtained.

For the quantitative evaluation of hair growth, the 3 ROIs of each axillary region will be photodocumented at each visit with a dermoscope. At the treatment visits (visits 1–6), photodocumentation will be done prior to laser therapy. A physician-based response evaluation will be carried out on the basis of the dermoscopic images by an independent, blinded investigator, a consultant dermatologist, who will manually

count the number of hairs in the three ROIs. Before performing the hair counts, clear definitions are determined for the counting technique: (a) if two or more hairs emerge from one follicle each will be counted separately; (b) if hairs appear only partly within the image, they will be counted; (c) regrowing hairs that penetrate the stratum corneum with an identifiable follicle and appear as a black spot will be also counted; (d) only dark terminal hairs will be counted. The mean number of hairs counted in the three ROIs will be calculated. The hair reduction rate used in this clinical trial is calculated as: hair removal rate = (hair counts before treatment – hair counts after treatment) / hair counts before treatment. Hair reduction (as a percentage) was calculated by comparing the baseline visit (visit 1) with the last visit (visit 6) as well as the baseline visit with the follow-up visits (visits 7 and 8) using the mean number of hairs of the three ROIs per area.

At the end of each treatment session, the study participants were asked at which side the treatment was more uncomfortable. At the follow-up visits, participants were also evaluated regarding their overall satisfaction with hair reduction in each treatment area (patient-rated efficacy). Patient satisfaction rating was subjectively measured at 3-, and 6-month follow-up visits on a visual analog scale (VAS) ranging from 0 to 100 (0 = no improvement at all, 100 = total disappearance of hairs). Side effects were evaluated and documented at each treatment session and at all follow-up visits. Treatment time was documented for each treatment.

**Outcome measures**

The primary outcome parameter was reduction of hair growth evaluated 3 and 6 months following the last treatment.

Secondary outcome parameters were treatment-related pain, adverse effects and treatment duration, as well as patient-rated efficacy evaluated 3 and 6 months following the last treatment.

**Statistical methods**

Primary outcome analysis is based on the reduction of hair growth at the follow-up visits in the intention-to-treat (ITT) population. ITT was defined as all patients who had received all 6 study treatments. Missing values at visit 8 were implemented using the conservative last-observation-carried-forward (LOCF) approach. Additionally, a

per-protocol (PP) analysis was performed as a sensitivity analysis. The goal of the trial is to show non-inferiority of the new treatment protocols.
All recorded data were tabulated and analyzed by using SPSS statistical analysis software version 12. All data were analysed with the paired two-sample Student's t-test because the baseline data were normally distributed. All data are given as mean ± SD. A P-value below 0.05 was considered significant. To assess consistency in hair counts, a Mann–Whitney U-test was performed. The patient satisfaction were compared between two lasers by using Wilcoxon Signed-Rank test. The differences of treatment time and pain score were also compared by using two-tailed paired t-test.

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