Clinical
Drug Investigation

HairMax LaserComb® Laser Phototherapy in
Male Androgenetic Alopecia

HairMax LaserComb® Laser Phototherapy Device in the Treatment of Male Androgenetic Alopecia
A Randomized, Double-Blind, Sham Device-Controlled, Multicentre Trial

Matt Leavitt,[1] *Glenn Charles*,[2] *Eugene Heyman*[3] and *David Michaels*[4]

1 Private Dermatology Practice, Maitland, Florida, USA
2 Private Hair Transplantation and Restoration Practice, Boca Raton, Florida, USA
3 Biostatistician, Montgomery Village, Maryland, USA
4 Lexington International, LLC, Boca Raton, Florida, USA

Abstract

Background and objective: The use of low levels of visible or near infrared light for reducing pain, inflammation and oedema, promoting healing of wounds, deeper tissue and nerves, and preventing tissue damage has been known for almost 40 years since the invention of lasers. The HairMax LaserComb® is a hand-held Class 3R lower level laser therapy device that contains a single laser module that emulates 9 beams at a wavelength of 655 nm (±5%). The device uses a technique of parting the user's hair by combs that are attached to the device. This improves delivery of distributed laser light to the scalp. The combs are designed so that each of the teeth on the combs aligns with a laser beam. By aligning the teeth with the laser beams, the hair can be parted and the laser energy delivered to the scalp of the user without obstruction by the individual hairs on the scalp. The primary aim of the study was to assess the safety and effectiveness of the HairMax LaserComb® laser phototherapy device in the promotion of hair growth and in the cessation of hair loss in males diagnosed with androgenetic alopecia (AGA).

Methods: This double-blind, sham device-controlled, multicentre, 26-week trial randomized male patients with Norwood-Hamilton classes IIa–V AGA to treatment with the HairMax LaserComb® or the sham device (2:1). The sham device used in the study was identical to the active device except that the laser light was replaced by a non-active incandescent light source.

Results: Of the 110 patients who completed the study, subjects in the HairMax LaserComb® treatment group exhibited a significantly greater increase in mean terminal hair density than subjects in the sham device group ($p < 0.0001$). Consistent with this evidence for primary effectiveness, significant improvements in overall hair regrowth were demonstrated in terms of patients' subjective assessment ($p < 0.015$) at 26 weeks over baseline. The HairMax LaserComb® was well tolerated with no serious adverse events reported and no statistical difference in adverse effects between the study groups.

Conclusions: The results of this study suggest that the HairMax LaserComb® is an effective, well tolerated and safe laser phototherapy device for the treatment of AGA in males.

Background

Laser phototherapy is a popular therapeutic modality that relies on exposure of biological tissues to low power coherent monochromatic light;[1] this induces a variety of positive therapeutic benefits associated with a range of wavelengths from red through to infrared. Pioneer studies on laser biostimulation performed more than 40 years ago reported a prominent hair growth stimulatory effect in mice.[2] In recent years, considerable attention has been given to establishing a regeneration-promoting effect of laser phototherapy in wound healing and tendon, muscle,[3] fractured bone[4,5] and skin.[6] Most prominently, several recent studies have confirmed the stimulatory effect of laser phototherapy on cutaneous wound regeneration (i.e. wound healing).[6-10] Stimulation of proliferation was found to be at least one of the mechanisms underlying the pro-regenerative effect of laser phototherapy.[11-13] Because both reparative regeneration, which occurs during wound healing, and physiological regeneration, which occurs during the hair cycle, rely heavily on cell proliferation, it is plausible to suggest that the hair growth stimulatory effect of laser phototherapy is also mediated through either a direct or an indirect increase in proliferative activity within the hair follicle epithelial matrix.

The basis of the biostimulatory effect of laser phototherapy during wound healing is not fully understood. As noted above, at the cellular level, laser phototherapy has been shown to increase proliferation of fibroblasts,[11-13] including fibroblasts derived from streptozotocin-diabetic rats that otherwise exhibit impaired proliferative activity.[14] Several intracellular processes are believed to underlie this pro-proliferative effect, including short-term activation of the mitochondrial electron-transport chain, accumulation of intracellular adenosine triphosphate and alkalization of the cytoplasm.[11,15] Because laser phototherapy-promoted wound heal-

ing is also characterized by faster wound re-epithelialization and neovascularization,[14] direct enhancement of epidermal and endothelial proliferation in wound sites is plausible. In addition, the pro-proliferative action of laser phototherapy can be attributed to other indirect effects, one of which is a 'metabolic boost' of the regenerating tissues through increased cutaneous microcirculation that occurs upon laser irradiation.[16] Another effect is linked to stimulated secretion of endogenous growth factors, such as basic fibroblast growth factor and insulin-like growth factor-1, by fibroblasts exposed to laser phototherapy.[17] Both of these growth factors are potent natural stimulators of proliferation for a variety of cell types.[17]

Hair is one of the fastest growing tissues of the human body. Hair follicles undergo repetitive physiological regenerative cycles,[18] and each such cycle consists of three principal phases: telogen (resting phase), anagen (active phase) and catagen (physiological involution phase). At the basis of this hair growth cycle are two major processes. The first represents tightly controlled activation of epithelial bulge stem cells and secondary hair germ cells that give rise to transient amplifying (TA) progeny cells during telogen-to-anagen transition.[19] The second process constitutes robust proliferation of these TA cells within the epithelial matrix of the hair follicle throughout the entire length of anagen. Proliferation trichocytes terminally differentiate to form the bulk of the hair filament – the final product of the hair cycle. The dermal papilla of the hair follicle is believed to play a key regulatory role in orchestrating the above described processes of progenitor cell activation, hair matrix cell proliferation and terminal differentiation of trichocytes.[20]

Androgenetic alopecia (AGA) is one of the most common forms of hair loss in males and females.[21] In genetically predisposed scalp hair follicles, dihydrotestosterone – a potent derivative of the male

sex hormone testosterone – initiates the cascade of downstream signalling changes beginning in the dermal papillae fibroblasts that ultimately disturb normal metabolic and cellular dynamics of the entire follicle.[22] As a result, a marked reduction in proliferative activity in the hair follicle epithelium leads to morphological miniaturization of terminal scalp hairs into vellus-like hairs.[23] Furthermore, a broken mechanism of bulge stem cell and secondary hair germ cell activation prevents new anagen re-entry, converting cycling hair follicles into quiescent telogen follicles. Thus, while the aetiological basis of AGA is clearly in abnormal androgen signalling, disruption of epithelial progenitor cell activation and TA cell proliferation forms an essential pathophysiological component of this condition.[23]

Since laser phototherapy has pro-proliferative effects in a variety of tissues and cell types, we hypothesized that it might have similar pro-proliferative activity in hair follicles and might normalize physiological regeneration of scalp hair follicles affected in AGA. The phenomenon of so-called 'terminalization' of vellus human hair follicles (i.e. when small vellus hairs transform into larger, terminal hairs) upon low fluence diode laser treatment has been independently reported by two researchers.[24,25]

To further evaluate the validity of our assumptions, we measured the hair growth-promoting efficacy of the HairMax LaserComb® laser phototherapy device in a randomized, double-blind, sham device-controlled, multicentre trial in male patients with AGA. The HairMax LaserComb® is a hand-held Class 3R lower level laser therapy device that contains a single laser module that emulates 9 beams at a wavelength of 655 nm (±5%). From past 'in-use' experience with the first devices it was found that there is a so-called 'optical window' for lower level light (LLL) in skin. LLL in skin appears to be effective in red and near-infared spectrum (600–950 nm) and the HairMax LaserComb® was found to be optimally effective at a wavelength of 655 nm (±5%).[26] The device uses a technique of parting the user's hair by combs that are attached to the device. This improves delivery of distributed laser light to the scalp. The combs are designed so that each of the teeth on the combs aligns with a laser beam. By aligning the teeth with the laser beams, the hair can be parted and the laser energy delivered to the scalp of the user without obstruction by the individual hairs on the scalp. Here we report on the outcome of this trial.

Methods

This clinical study was performed in accordance with Good Clinical Practice. The protocol was approved by the Investigational Review Board, Research Testing Laboratories Inc., Great Neck, NY, USA, and written informed consent was obtained from each patient in the study before study procedures were conducted.

Study Objectives

The primary aim of the study was to assess the safety and effectiveness of the HairMax LaserComb® laser phototherapy device in the promotion of hair growth and in the cessation of hair loss in males diagnosed with AGA. After the study began it was amended to include only males at the suggestion of the US FDA; female subjects will form the basis of a similar study.

Study Inclusion/Exclusion Criteria

For inclusion in the study, subjects must not have used or taken any of the following medications for 6 months prior to initiation of the study: minoxidil, finasteride (or any other 5α-reductase inhibitor medications), medications with anti-androgenic properties (e.g. cyproterone, spironolactone, ketoconazole, flutamide and bicalutamide), topical estrogens, progesterone, tamoxifen, anabolic steroids, medications that can potentially cause hypertrichosis (e.g. ciclosporin, diazoxide, phenytoin and psoralens), oral glucocorticoids (inhaled glucocorticoids were permitted), lithium, phenothiazines or other medications at the discretion of the investigator. Subjects were excluded if they had had hair transplantation, scalp reduction, current hair weave or tattooing of the alopecic area, which would have made for difficulties in performing objective hair

density assessments. Subjects were also excluded if they had any known underlying medical conditions that could adversely affect hair growth, such as HIV infection, connective tissue disease, inflammatory bowel disease, or other pathologies at the discretion of the investigator.

Patient Population

The study population included males between the ages of 30 and 60 years with a diagnosis of AGA who had been experiencing progressive hair loss within the last 12 months. Subjects were also required to have a Norwood-Hamilton male pattern hair loss classification of IIa to V and to have skin type I to IV on the Fitzpatrick Skin Type Scale.

Study Design

The study was designed as a randomized, double-blind, sham device-controlled, multicentre trial conducted at four sites in the US. Subjects who met all entry criteria received either the HairMax LaserComb®, which emitted laser light, or a sham device, which was identical to the active device in appearance but emitted incandescent light instead.

Screened subjects who fulfilled study entry criteria attended a baseline visit. At this visit, medical personnel assessed the subject's scalp for any signs of irritation or dermatological conditions that would disqualify the subject from participation. All subjects had systolic and diastolic blood pressure (mmHg) and heart rate (beats/min) vital signs recorded. Scalp macroimages utilizing dot mapping and computer-aided hair counts (see Evaluation of Clinical Efficacy section) were taken to document hair loss progression since the screening visit. Each target site for investigation was chosen by the clinical investigator based on the appearance of miniaturized hairs, which are the hallmark of AGA. Target scalp areas were identified and tattooed, then clipped to determine baseline hair density. Subjects were then provided with their randomized HairMax LaserComb® or sham device (see Statistical Analysis section for randomization scheme). In previous 'in-use' studies utilizing various application regimens to find the effective minimum dose of the HairMax LaserComb®, it was found that application of the device three times a week was sufficient to induce hair growth.[26] Therefore, subjects were asked in the current study to use the device assigned three times per week for 15 minutes on non-concurrent days for a total of 26 weeks/6 months. Subjects were given diaries to document use of the device.

Subjects returned to the clinic at 8 and 16 weeks to undergo assessment for adverse events and concomitant medications, collection of vital signs, scalp evaluation for local dermatitis and other pathological conditions, and completion of an 11-item questionnaire. Clinical assessment of treated scalp sites was carried out objectively at 26 weeks/6 months utilizing macroimaging techniques, hair clippings, computer-aided hair counts (see Evaluation of Clinical Efficacy section) and global assessment of new hair growth (i.e. without referring to any macroimages) by subjects and the investigator. Subjects who terminated prematurely had their hair density measured at their termination visit.

The evaluator of the baseline and endpoint analyses of the macroimages used blinded patient files and was not involved in patient selection or distribution of either device. The cut-off time for use of the device was 6 months. At the completion of the study, all subjects in each arm of the study were offered a HairMax LaserComb® for their personal use.

No post-study follow-up was conducted.

Evaluation of Clinical Efficacy

Hair Clipping

A circle of approximately 2.96 cm diameter, positioned in the vertex portion of the scalp, was identified as the site for hair clipping. This site contained some miniaturized hairs and was the target area for the hair density evaluation. A template was provided to the investigator for identifying the area for hair clipping. Once the hair had been clipped, trained study personnel used a professional tattooing machine to apply a permanent ink dot, approximately the size of a full stop/period (.), in the centre of the circle. The tattoo was used as a guide for placing the template on the scalp surface at

subsequent visits for the hair clipping and macroimages for hair density evaluation.

Macroimaging and Hair Density Evaluation Procedures

Macroimage Acquisition

The subject sat in a chair and was correctly placed in the stereotactic apparatus. The digital images were standardized for lighting, camera angle and position of the subject's head in each digital image to achieve a similar camera angle and relative image size. For macrodigital images a template as described in the previous section was placed on the lenses for precise and consistent alignment on the tattoo. A 10 mm scale divided into 0.1 mm increments was etched into the template for calibration purposes during the hair density evaluations. The images were recorded on compact flash cards. During the subject's visit, the images were previewed to see if they were acceptable; unacceptable images were retaken. After the subject's visit had been completed, the images were printed and signed by the investigator and uploaded to a designated site for image archiving.

Image Analysis and Management

A state-of-the art software system was utilized for image management. Macroimages were imported into a blinded subject file labelled by subject number. The images displayed included a means of marking each individual hair. Each hair was 'clicked' and a running count was displayed at the bottom of the software window. Only terminal hairs were counted. Archives of the counted hairs were maintained in the subject file. Images could be displayed side by side.

The database software functionality also allowed subjects to be identified by number while the advanced multiple criteria searches facilitated quick retrieval of information. In addition, the subject's chart view allowed all of a subject's images to be viewed on one screen with scalable thumbnails. Blinded subject records containing hair density measurements were forwarded to data management for inclusion in the study data base.

Study Endpoints

The primary efficacy endpoint was change in non-vellus terminal hair density (hairs/cm^2) in the target region between baseline and endpoint (26 weeks/6 months or the earlier termination visit), as assessed by scalp macroimaging using dot mapping and computer-aided hair counts (see Evaluation of Clinical Efficacy section). The techniques used were comparable to those used in the protocols for minoxidil.

Secondary effectiveness endpoints were subjective global assessment of hair regrowth by subjects and the investigator at week 26. Patients were asked to complete the 11-question proprietary Subject Questionnaire without assistance, aimed at evaluating perception of overall hair regrowth characteristics. These questions encompassed overall results, rate of hair loss, assessment of dandruff, scalp health, hair health, hair thickness, hair shine, hair growth rate, manageability and hair colour changes. Investigators were asked to evaluate the subject's hair growth looking at the baseline and week 26/6 months (or early termination) visit global images (without reference to macroimages) and graded the hair growth on a 4-point scale.

The safety endpoints for the study were adverse events of any nature and vital signs.

Statistical Analysis

Based on prior data for the HairMax LaserComb®[26] and the drug minoxidil (NDA 20-834, Pharmacia and Upjohn Consumer Healthcare, November 14, 1999) the standard deviation of change from baseline in terminal hair density was assumed to be 30 hairs/cm^2. Based on this estimate, 93 subjects randomized 2:1 (62 in the HairMax LaserComb® group and 31 in the sham device group) would provide 85% power to detect a difference of 20 hairs/cm^2. To allow for a 20% dropout rate, 123 subjects needed to be enrolled. Statistical comparisons were made between treatment groups for all baseline demographic variables. Continuous variables were compared using two-sample t-tests: dichotomous variables were compared using Pearson's chi-squared test (χ^2) and ordinal variables by

density assessments. Subjects were also excluded if they had any known underlying medical conditions that could adversely affect hair growth, such as HIV infection, connective tissue disease, inflammatory bowel disease, or other pathologies at the discretion of the investigator.

Patient Population

The study population included males between the ages of 30 and 60 years with a diagnosis of AGA who had been experiencing progressive hair loss within the last 12 months. Subjects were also required to have a Norwood-Hamilton male pattern hair loss classification of IIa to V and to have skin type I to IV on the Fitzpatrick Skin Type Scale.

Study Design

The study was designed as a randomized, double-blind, sham device-controlled, multicentre trial conducted at four sites in the US. Subjects who met all entry criteria received either the HairMax LaserComb®, which emitted laser light, or a sham device, which was identical to the active device in appearance but emitted incandescent light instead.

Screened subjects who fulfilled study entry criteria attended a baseline visit. At this visit, medical personnel assessed the subject's scalp for any signs of irritation or dermatological conditions that would disqualify the subject from participation. All subjects had systolic and diastolic blood pressure (mmHg) and heart rate (beats/min) vital signs recorded. Scalp macroimages utilizing dot mapping and computer-aided hair counts (see Evaluation of Clinical Efficacy section) were taken to document hair loss progression since the screening visit. Each target site for investigation was chosen by the clinical investigator based on the appearance of miniaturized hairs, which are the hallmark of AGA. Target scalp areas were identified and tattooed, then clipped to determine baseline hair density. Subjects were then provided with their randomized HairMax LaserComb® or sham device (see Statistical Analysis section for randomization scheme). In previous 'in-use' studies utilizing various application regimens to find the effective minimum dose of the

HairMax LaserComb®, it was found that application of the device three times a week was sufficient to induce hair growth.[26] Therefore, subjects were asked in the current study to use the device assigned three times per week for 15 minutes on non-concurrent days for a total of 26 weeks/6 months. Subjects were given diaries to document use of the device.

Subjects returned to the clinic at 8 and 16 weeks to undergo assessment for adverse events and concomitant medications, collection of vital signs, scalp evaluation for local dermatitis and other pathological conditions, and completion of an 11-item questionnaire. Clinical assessment of treated scalp sites was carried out objectively at 26 weeks/6 months utilizing macroimaging techniques, hair clippings, computer-aided hair counts (see Evaluation of Clinical Efficacy section) and global assessment of new hair growth (i.e. without referring to any macroimages) by subjects and the investigator. Subjects who terminated prematurely had their hair density measured at their termination visit.

The evaluator of the baseline and endpoint analyses of the macroimages used blinded patient files and was not involved in patient selection or distribution of either device. The cut-off time for use of the device was 6 months. At the completion of the study, all subjects in each arm of the study were offered a HairMax LaserComb® for their personal use.

No post-study follow-up was conducted.

Evaluation of Clinical Efficacy

Hair Clipping

A circle of approximately 2.96 cm diameter, positioned in the vertex portion of the scalp, was identified as the site for hair clipping. This site contained some miniaturized hairs and was the target area for the hair density evaluation. A template was provided to the investigator for identifying the area for hair clipping. Once the hair had been clipped, trained study personnel used a professional tattooing machine to apply a permanent ink dot, approximately the size of a full stop/period (.), in the centre of the circle. The tattoo was used as a guide for placing the template on the scalp surface at

subsequent visits for the hair clipping and macroimages for hair density evaluation.

Macroimaging and Hair Density Evaluation Procedures

Macroimage Acquisition

The subject sat in a chair and was correctly placed in the stereotactic apparatus. The digital images were standardized for lighting, camera angle and position of the subject's head in each digital image to achieve a similar camera angle and relative image size. For macrodigital images a template as described in the previous section was placed on the lenses for precise and consistent alignment on the tattoo. A 10 mm scale divided into 0.1 mm increments was etched into the template for calibration purposes during the hair density evaluations. The images were recorded on compact flash cards. During the subject's visit, the images were previewed to see if they were acceptable; unacceptable images were retaken. After the subject's visit had been completed, the images were printed and signed by the investigator and uploaded to a designated site for image archiving.

Image Analysis and Management

A state-of-the art software system was utilized for image management. Macroimages were imported into a blinded subject file labelled by subject number. The images displayed included a means of marking each individual hair. Each hair was 'clicked' and a running count was displayed at the bottom of the software window. Only terminal hairs were counted. Archives of the counted hairs were maintained in the subject file. Images could be displayed side by side.

The database software functionality also allowed subjects to be identified by number while the advanced multiple criteria searches facilitated quick retrieval of information. In addition, the subject's chart view allowed all of a subject's images to be viewed on one screen with scalable thumbnails. Blinded subject records containing hair density measurements were forwarded to data management for inclusion in the study data base.

Study Endpoints

The primary efficacy endpoint was change in non-vellus terminal hair density (hairs/cm^2) in the target region between baseline and endpoint (26 weeks/6 months or the earlier termination visit), as assessed by scalp macroimaging using dot mapping and computer-aided hair counts (see Evaluation of Clinical Efficacy section). The techniques used were comparable to those used in the protocols for minoxidil.

Secondary effectiveness endpoints were subjective global assessment of hair regrowth by subjects and the investigator at week 26. Patients were asked to complete the 11-question proprietary Subject Questionnaire without assistance, aimed at evaluating perception of overall hair regrowth characteristics. These questions encompassed overall results, rate of hair loss, assessment of dandruff, scalp health, hair health, hair thickness, hair shine, hair growth rate, manageability and hair colour changes. Investigators were asked to evaluate the subject's hair growth looking at the baseline and week 26/6 months (or early termination) visit global images (without reference to macroimages) and graded the hair growth on a 4-point scale.

The safety endpoints for the study were adverse events of any nature and vital signs.

Statistical Analysis

Based on prior data for the HairMax LaserComb®[26] and the drug minoxidil (NDA 20-834, Pharmacia and Upjohn Consumer Healthcare, November 14, 1999) the standard deviation of change from baseline in terminal hair density was assumed to be 30 hairs/cm^2. Based on this estimate, 93 subjects randomized 2:1 (62 in the HairMax LaserComb® group and 31 in the sham device group) would provide 85% power to detect a difference of 20 hairs/cm^2. To allow for a 20% dropout rate, 123 subjects needed to be enrolled. Statistical comparisons were made between treatment groups for all baseline demographic variables. Continuous variables were compared using two-sample t-tests: dichotomous variables were compared using Pearson's chi-squared test (χ^2) and ordinal variables by

the Cochran-Mantel-Haenszel procedure after assignation of uniform scores (1, 2, 3, etc.) to the four ordered categories of response.

The primary analysis of effectiveness was performed on all randomized subjects who had a postbaseline hair density measurement. The last value was carried forward for subjects who terminated prematurely. All randomized subjects who used the study device at least once were included in analyses of safety. The primary analysis of effectiveness was an analysis of covariance (ANCOVA), which included the effects of treatment group, study centre, age (as a continuous variable), and Fitzpatrick Skin Type Scale classification (as a categorical variable with four levels).

Adverse events were summarized as the number and percentage of subjects reporting each event. Statistical comparisons were made between treatment groups using Fisher's exact test.

All statistical analyses were two-sided at a 5% level of significance.

Results

Study Population

A total of 123 subjects were enrolled at four study sites. Table I shows the mean age, race and Fitzpatrick Skin Type Scale classification of sub-

Table I. Baseline demographics of the study population (males, n = 123)

Characteristic	Value
Age (y)	
Mean ± SD	47.9 ± 8.7
Range	30–60
Race [n (%)]	
White, non-Hispanic	111 (90.2)
Hispanic	9 (7.3)
Black	0 (0)
Other	3 (2.4)
Fitzpatrick Skin Type Scale classification [n (%)]	
I	4 (3.3)
II	17 (13.8)
III	65 (52.9)
IV	37 (30.1)

jects entered into the study. Seven subjects were discontinued from the study by the sponsor because of deviations from baseline entry criteria. This was because the site location chosen for the target area for hair density evaluation was found to be outside the zone of miniaturized hairs. The study design required that chosen sights for evaluation had to have miniaturized hairs. One subject was discontinued because of noncompliance with study visits. One subject was lost to follow-up. Four subjects withdrew consent for other reasons. Of these four subjects, two subjects in the sham device group had early termination visits (at 71 and 112 days) at which hair density measurements were completed. Ten subjects in the HairMax LaserComb® group who terminated prematurely were not included in the primary analysis of effectiveness, and one of the three subjects in the sham device group who terminated prematurely was not included.

Primary Efficacy

As noted previously, hair counts were performed utilizing macroimages imported into blinded patient files by an evaluator who was not connected with the clinical trial. The two subjects with the greatest decreases in hair density (subject 04-039 in the sham device group with -145 hairs/cm^2 and subject 01-039 with -56 hairs/cm^2) appeared to be outliers in the statistical analysis. The residual standard deviation was used as an estimate of the accuracy of the dependent variable being measured, hair density. The ANCOVA was 18.6 hairs/cm^2 and these subjects had residuals of -128.0 (subject 04-039) and -75.8 (subject 01-039). To assess the impact of these subjects on analysis, they were removed and the results are shown in table II. Removal of these subjects reduced the residual standard deviation from 18.6 to 11.2 hairs/cm^2; however, the impact of the removal of these two outlier subjects on the final results was negligible.

When the two outliers were excluded from the analysis, subjects treated with the HairMax LaserComb® had a mean increase in terminal hair density of $+19.8$ hairs/cm^2, while subjects in the sham device group had a mean decrease of -7.6

Table II. Mean baseline and change from baseline to 26 weeks in terminal hair density[a] (hairs/cm^2) – two outliers excluded

Time	HairMax LaserComb® (n = 71)	Sham device (n = 39)
Baseline		
mean ± SD	122.9 ± 51.4	120.7 ± 48.6
range	21.6, 252.1	25.5, 225.4
Change from baseline		
mean ± SD	17.3 ± 11.9	–8.9 ± 11.7
range	–6.4, 52.2	–54.7, 7.6
Adjusted mean[b]	19.8	–7.6
Difference (95% CI)	27.4 (22.9, 31.9)	
p-Value	<0.0001	

a Last value carried forward for subjects who terminated prematurely.

b Adjusted for study centre, subject's age and skin type.

hairs/cm^2 at the completion of the study (table II). This difference was significant (p < 0.0001). An example of terminal hair regrowth in the non-vellus hair density macroimages of one patient in the HairMax LaserComb® group is shown in figure 1.

Table III shows individual subject changes from baseline in terminal hair density, divided into six categories. Only two subjects in the HairMax LaserComb® group (2.8%) had a decrease in hair density ≥5 hairs/cm^2, whereas 26 subjects in the sham device group (65.0%) had a similar decrease. Furthermore, 62 subjects in the HairMax LaserComb® group (86.1%) had an increase in hair density >5 hairs/cm^2, while only two subjects in the sham device (5.0%) group had such an increase.

Significant improvements in overall hair regrowth were demonstrated in terms of patients' subjective assessment (p < 0.01) at 26 weeks over baseline.

Secondary Efficacy Analyses

Secondary effectiveness endpoints included subjects' assessment of overall hair growth (table IV), the investigator's global assessment of overall hair growth (table IV), and responses to ten additional questions in the Subject Questionnaire. In each of the following analyses, subjects who terminated prematurely had their last value carried forward to each subsequent visit.
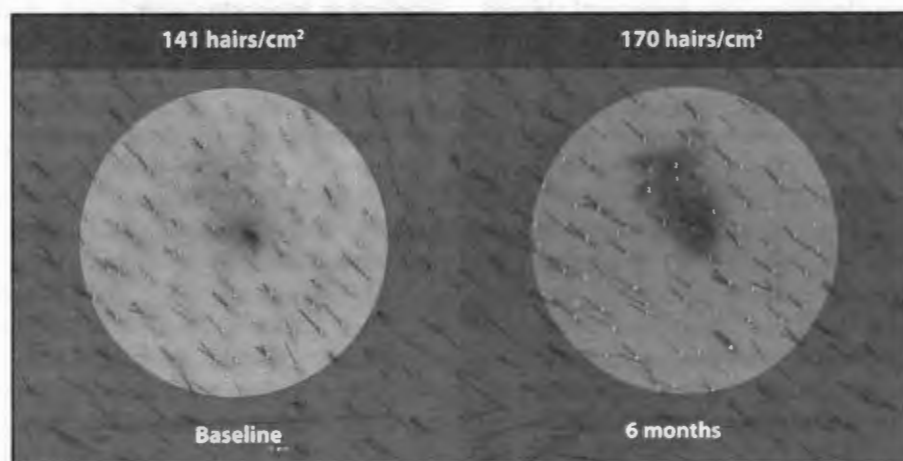

Fig. 1. Non-vellus hair density macroimages at baseline and 6 months in one patient in the HairMax LaserComb® group (6-month image shows evidence of ink spread).

Table III. Categorical changes from baseline to 26 weeks in terminal hair density[a]

Change in hair density/cm²	HairMax LaserComb® (n=72) [n (%)]	Sham device (n=40) [n (%)]
≤–20	1 (1.4)	7 (17.5)
≥–20 to –5	1 (1.4)	19 (47.5)
≥–5 to 0	3 (4.2)	9 (22.5)
>0 to 5	5 (6.9)	3 (7.5)
>5 to 20	34 (47.2)	2 (5.0)
>20	28 (38.9)	0 (0)

a   Last value carried forward for subjects who terminated prematurely.

As seen in table IV showing subjects' assessment of overall hair growth, the p-value for the comparison between treatment groups achieved statistical significance (p=0.01) at the last visit. Thus, subjects in the HairMax LaserComb® group perceived significantly greater improvement in hair regrowth than those in the sham device group at the end of the study.

The results of the investigator's global assessments of hair growth are also shown in table IV. No substantial differences were seen between treatment groups within each assessment category (p=0.45). The discordant results between the investigator's subjective global assessment shown in this table and the objective hair density measurements shown in table II were assessed by comparing the median changes from baseline in terminal hair density within each treatment group and category of response. Medians are used rather than means to lessen the impact of large decreases. This assessment showed that there was no correlation between median

changes from baseline in actual terminal hair density shown in table II and investigator subjective global assessment shown in table IV among subjects in the HairMax LaserComb® group. These results question the validity of the investigator's subjective global assessment because of their lack of any agreement with actual terminal hair growth shown in table II. It also brings into question the validity of global photography of hair due to the numerous inherent variables that effect the appearance of hair at each evaluation point.

Of the ten additional questions remaining in the end-of-study Subject Questionnaire after subjects' assessment of overall hair regrowth (table IV), answers to seven were analysed statistically (three questions – reduced dandruff, return to natural colour, and scalp irritation – were excluded because of high proportions of 'not applicable' answers). For the remaining seven questions, the responses to five (slower hair loss, better scalp health, thicker feeling hair, more shine to hair and overall hair improve-

Table IV. Subjects' and investigator's assessment of overall hair regrowth at week 26

Assessment	HairMax LaserComb® [n (%)]	Sham device [n (%)]	p-Value[a]
Subjects' assessment at week 26	n=76	n=39	
No growth	28 (36.8)	21 (53.9)	0.01
Minimal growth	30 (39.5)	16 (41.0)	
Moderate growth	17 (22.4)	2 (5.1)	
Dense growth	1 (1.3)	0 (0)	
Investigator's assessment at week 26	n=72	n=38	
No growth	46 (63.9)	22 (57.9)	0.45
Minimal growth	18 (25.0)	10 (26.3)	
Moderate growth	7 (9.7)	5 (13.2)	
Dense growth	1 (1.4)	1 (2.6)	

a   HairMax LaserComb® vs sham device.

ment) were statistically significantly different ($p < 0.05$) between the groups, i.e. the assessments were significantly better in subjects in the HairMax LaserComb® group compared with those in the sham device group. Although between-group differences in responses to the last two questions (faster growing hair, more manageable hair) did not achieve statistical significance ($p < 0.05$), a more favourable overall assessment was observed for subjects in the HairMax LaserComb® group compared with those in the sham device group.

Safety and Tolerability

The HairMax LaserComb® device was found to be well tolerated. No serious adverse effects were reported. The only adverse events considered to be possibly device related were four cases of mild paraesthesia and four cases of mild urticaria. These showed no statistical difference between study groups. Changes in vital signs from baseline were very small in both treatment groups and similar between both groups.

Discussion

While many unknowns remain, an important component of the treatment of AGA is to provide non-biased demonstration of laser phototherapy effectiveness in hair growth stimulation in humans. Here we report on the first known double-blind, controlled trial of laser phototherapy for the treatment of AGA, that is, sex hormone-dependent male pattern hair loss. Overall, the results of the trial demonstrate significantly greater increase in mean terminal hair density (primary effectiveness) in subjects treated with the HairMax LaserComb® device over the sham device ($p < 0.0001$). Consistent with this evidence for primary effectiveness, significant improvements in overall hair regrowth were demonstrated in terms of patients' subjective assessment ($p < 0.01$) at 26 weeks over baseline. Subjects in the HairMax LaserComb® group perceived significantly greater improvement ($p < 0.05$) regarding overall hair improvement, slowing of hair loss, thicker feeling hair, better scalp health and hair shine.

This study was a pivotal part of the Premarket Notification 510(k) submission in February 2006 and subsequent clearance for marketing by the FDA in January 2007. To date, no other laser therapy device has been cleared by the FDA for marketing and all other similar products on the market are sold as cosmetic devices. This clearance means that the HairMax LaserComb® has been the subject of a rigorous review and clearance process, which differentiates it from other marketed devices that have no clinical proof of efficacy. Thus, it is impossible to compare the HairMax LaserComb® with other devices marketed without clinical studies or FDA clearance.

Conclusions

The current study has accomplished an important goal. This is the first study demonstrating efficacy in hair growth with a laser phototherapy device, the HairMax LaserComb®. This randomized, double-blind, sham device-controlled, multicentre efficacy trial indicates that the HairMax LaserComb® laser phototherapy device with its patented hair-parting teeth mechanism is an effective, well tolerated treatment for hair loss of androgenetic aetiology. Indeed, the HairMax LaserComb® is currently the only laser therapy device that has been clinically studied and proven to grow hair in males with certain classes of AGA.

In the future, the efficacy of HairMax LaserComb® should also be evaluated in subjects with hair loss of non-androgenetic aetiology. It will also be very important to establish the cellular and molecular mechanisms behind the hair growth-promoting effect of laser phototherapy. Future research should help us to differentiate if laser phototherapy predominantly: (i) stimulates anagen re-entry by telogen hair follicles; (ii) increases rates of proliferation in active anagen hair follicles; (iii) prevents premature catagen development; or (iv) extends the duration of the anagen phase. Cellular events, such as activation of dormant hair follicle stem cells, or increase in proliferation of hair matrix trichocytes, should be investigated. In addition, subcellular and molecular signalling events, such as direct short-

term activation of the mitochondrial electron-transport chain, or long-term up-regulation of growth factors, should be evaluated.

Acknowledgements

References

1. Hawkins D, Houreld N, Abrahamse H. Low level laser therapy (LLLT) as an effective therapeutic modality for delayed wound healing. Ann N Y Acad Sci 2005; 1056: 486-93

2. Mester E, Szende B, Gartnerne TJ. Influence of laser beams on the growth of hair in mice. Kiserl Orvostud 1967; 19: 628-31

3. Bibikova A, Oron U. Promotion of muscle regeneration in the toad (Bufo viridis) gastrocnemius muscle by low-energy laser irradiation. Anat Rec 1993; 235: 374-80

4. Pinheiro AL, Gerbi ME. Photoengineering of bone repair processes. Photomed Laser Surg 2006; 24: 169-78

5. Liu X, Lyon R, Meier HT, et al. Effect of lower-level laser therapy on rabbit tibial fracture. Photomed Laser Surg 2007; 25: 487-94

6. Yu W, Naim JO, Lanzafam RJ. Effects of photostimulation on wound healing in diabetic mice. Lasers Surg Med 1997; 20: 56-63

7. Reddy GK, Stehno-Bittel L, Enwemeka CS. Laser photostimulation accelerates wound healing in diabetic rats. Wound Repair Regen 2001; 9: 248-55

8. Reddy GK. Comparison of the photostimulatory effects of visible He-Ne and infrared Ga-As lasers on healing of impaired diabetic rat wounds. Lasers Surg Med 2003; 33: 344-51

9. Byrnes KR, Barna L, Chenault VM, et al. Photobiomodulation improves cutaneous wound healing in an animal model of type II diabetes. Photomed Laser Surg 2004; 22: 281-90

10. de Carvalho PT, Mazzer N, dos Reis FA, et al. Analysis of the influence of low-power He-Ne laser on the healing of skin wounds in diabetic and non-diabetic rats. Acta Cir Bras 2006; 21: 177-83

11. Loevschall H, Arenholt-Bindslev D. Effect of low level diode laser irradiation of human oral mucosa fibroblasts in vitro. Lasers Surg Med 1994; 14: 347-54

12. Vink EM, Cagnic BJ, Cornelissen MJ, et al. Increased fibroblast proliferation induced by light emitting diode and low-power laser irradiation. Lasers Med Sci 2003; 18: 95-9

13. Pal G, Dutta A, Mitra K, et al. Effect of low intensity laser interaction with human skin fibroblast cells using fiber-optic nano-probes. J Photochem Photobiol 2007; 86: 252-61

14. Mirzaei M, Bayat M, Mosafa N, et al. Effect of low-level laser therapy on skin fibroblasts of streptozotocin-diabetic rats. Photomed Laser Surg 2007; 25: 519-25

15. Pereira AN, Eduardo Cde P, Matson E, et al. Effect of low-power laser irradiation on cell growth and procollagen synthesis of cultured fibroblasts. Lasers Surg Med 2002; 31: 263-7

16. Schindl A, Schindl M, Schön H, et al. Low-intensity laser irradiation improves skin circulation in patients with diabetic microangiopathy. Diabetes Care 1998; 21: 580-4

17. Saygun I, Karacay S, Serdar M, et al. Effects of laser irradiation on the release of basic fibroblast growth factor (bFGF), insulin like growth factor-1 (IGF-1), and receptor of IGF1(IGFBP3) from gingival fibroblasts. Lasers Med Sci 2007; 23: 211-5

18. Paus R, Foitzik K. In search of the "hair cycle clock": a guided tour. Differentiation 2004; 72: 489-511

19. Tiede S, Kloepper JE, Bodò E, et al. Hair follicle stem cells: walking the maze. Eur J Cell Biol 2007; 86: 355-76

20. Plikus MV, Sundberg JP, Chuong CM. Mouse skin ectodermal organs. In: James Fox, Stephen Barthold, Muriel Davisson, et al., editors. The mouse in biomedical research. New York (NY): Academic Press, 2006: 691-694

21. Otberg N, Finner AM, Shapiro J. Androgenetic alopecia. Endocrinol Metab Clin North Am 2007; 36: 379-98

22. Trüeb RM. Molecular mechanisms of androgenetic alopecia. Exp Gerontol 2002; 37: 981-90

23. Itami S, Inui S. Role of androgen in mesenchymal epithelial interactions in human hair follicle. J Investig Dermatol Symp Proc 2005; 10: 209-11

24. Bernstein EF. Hair growth induced by diode laser treatment. Dermatol Surg 2005; 31: 584-6

25. Bouzari N, Firooz AR. Lasers may induce terminal hair growth [comment]. Dermatol Surg 2006; 32: 460

26. Data on file, Lexington International, LLC

Correspondence: Dr *Matt Leavitt*, 2600 Lake Lucien Drive, Ste 180, Matiland, FL 32751, USA.
E-mail: mlleavitt@aol.com