Clinical Safety and Efficacy of Dual Wavelength Low-Level Light Therapy in Androgenetic Alopecia: A Double-Blind Randomized Controlled Study

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BACKGROUND The light-emitting diode cap being investigated is FDA cleared for the treatment of androgenetic alopecia (AGA).

OBJECTIVE Evaluating 3 versions of a red and blue light LED cap: (1) 625- and 660-nm red light, (2) 425-nm blue light, and (3) both 425-nm blue light and 625- and 660-nm red light against sham.

PATIENTS AND METHODS Twenty-six-week, multicenter, randomized, controlled, double-blinded study. Adults aged 18 to 65 years with AGA were randomized to an active device or sham and underwent 10-minute treatments daily.

RESULTS One hundred sixty subjects were randomized. Ninety-one subjects were excluded for the per-protocol analysis. The per-protocol population included participants who completed 16 weeks of treatment, had no major protocol violations, and were at least 80% treatment compliant. Although the primary endpoint (mean change in non-vellus hair count from baseline to week 16) did not reach statistical significance in the individual study arms, in the pooled analysis (combining the 3 active study arms), there was a statistically significant ($p = .033$) difference versus sham. The pooled study cap group achieved 28.5 more hairs per cm^2 when compared with sham.

CONCLUSION The LED caps were well tolerated and increased hair density in patients with AGA.

Androgenetic alopecia (AGA) produces age-related, patterned balding in over 50% of women at the age of 80 years and older[1] and 50% of men by age 50 years.[2] The pathogenesis initially involves serial shortening of anagen duration with associated lengthening of the telogen subphase kenogen. Terminal follicles then miniaturize into vellus follicles. Eventually the arrector pili muscle separates from the bulge of the miniaturized follicle, disrupting the epithelial stem cell niche. Anagen shortening leads to telogen effluvium. Kenogen lengthening leads to empty hair follicles. Miniaturization leads to reduced fiber diameter. Baldness is the product of fewer large diameter hairs per cm.[3] Disruption of the epithelial stem cell niche makes the hair loss irreversible.[4] Many men and women perceive AGA as an unwelcome event, especially when the baldness is severe or perceived as premature.[5] Approved medical therapies for AGA include minoxidil 2% and 5% topical solution and finasteride 1 mg tablets.[5] Finasteride is contraindicated in women due to teratogenicity.[5]

Low-level laser therapy (LLLT) also known as photobiomodulation uses either coherent light sources (lasers) or noncoherent light sources; filtered lamps or light-emitting diodes (LED); or a combination of both.[6] The light source in LLLT is referred to as "low-level" because fluences are well below those used for ablation, cutting, and thermal coagulation.[6] At wavelengths of 650 to 900 nm, light waves are absorbed by the hair follicle bulb. This absorption is thought to stimulate several growth signaling pathways and promote proliferation of matrix and dermal papilla cells, thereby prolonging anagen duration.[7] Low-level laser therapy has also been used with variable success for skin rejuvenation, acne, vitiligo, hypertrophic scars and keloids, burns, and psoriasis.[8] Low-level laser therapy devices for hair loss are available as combs, helmets, hairbands, or cap-type devices.[8]

Low-level laser therapy devices represent a potential nonpharmacological option for AGA. Previous studies have demonstrated increased hair density in AGA after light treatment with minimal adverse effects.[8–10]

The aim of the study is to investigate the efficacy and safety of the REVIAN cap-type dual wavelength LED light device along with other investigational devices for treatment of AGA in men and women.

Materials and Methods

Patient Enrollment

The trial was registered with the Australian New Zealand Clinical Trials Registry (trial registration number ACTRN12617000775314). Each participant provided

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written informed consent. Subject screening, recruitment, and follow-up were conducted at 4 sites: Premier Specialists (Kogarah, NSW, Australia), Sinclair Dermatology (East Melbourne, VIC, Australia), The Skin Hospital (Darlinghurst, NSW, Australia), and Veracity Clinical Research (Woolloongabba, QLD, Australia). The full trial protocol is available upon request.

Study Inclusion/Exclusion Criteria

Inclusion criteria were as follows: age between 18 and 65 years, Fitzpatrick skin type I–IV, and active androgenetic hair loss (Norwood–Hamilton classification of IIa–V for male subjects and Ludwig–Savin classification of I-1 to I-4, II-1, II-1, II-2, or frontal for female subjects). Washout period for finasteride or any other oral hair growth supplements was 12 months and 6 months for any topical hair growth medications. Other excluded medications were photosensitizers or any medication deemed to inhibit hair growth. Participants were excluded if they had a previous hair transplant, cell treatment, microneedling, tattooing, or any other treatment to the scalp. Participants were excluded if they had radiation or chemotherapy within the last 12 months and/or if they had an active autoimmune disease. Participants were excluded if they had a dermatological condition affecting the scalp (e.g., eczema, psoriasis, infection), or a scar, burn, or malignancy in the target area. Participants with hair shorter than 1 inch were also excluded. Female participants of childbearing potential were required to be on some form of birth control and record a negative pregnancy test at baseline.

Active Caps and Sham Device

The product being investigated is a cordless "smart cap" that delivers light therapy for a daily 10-minute treatment operated by a Bluetooth connected mobile app. Three versions of the cap using different treatment wavelengths were evaluated in this study: (1) 625- and 660-nm red light (cap 101), (2) 425-nm blue light (cap 102), and (3) a version that emitted both 425-nm blue light and 625- and 660-nm red light (cap 103) as well as a sham device (cap 100) that emitted no light once placed on the scalp.

The sham cap (cap 100) was identical to the active caps in appearance and used the same haptic tones for a 10-minute treatment executed with the mobile app but did not emit light once placed on the scalp.

All cap models contain a capacitive sensor that shuts off the light when the device is removed, thereby preventing differentiation between active or sham. The LED pattern and density were the same for cap 101, cap 102, and sham caps. Cap 103 cap had a greater number of LEDs (168 rather than 119 LEDs). Nominal irradiance was 1.67 mW/cm^2 for the 101 and 102 caps, 3.34 mW/cm^2 for the 103 cap, and 0 mW/cm^2 for the sham cap.

Scalp Photography and Hair Counts

Hair count was quantified based on macrophotographic images of a 1-cm^2 target in the thinning area of the scalp that was marked through tattoo at baseline and remarked at each postbaseline clinic visit. Images were captured using a handheld CANON VEOS T6i SLR camera. Hair counts were then obtained from macrophotographic images by an independent reviewer (Trilogic/B&B International Enterprises, Boston, MA).

Study Design

Participants underwent 10-minute treatments daily during the 26-week study period, for a total of 182 treatments.

Outcomes

The primary endpoint was mean change in hair count from baseline to week 16. Secondary endpoints included mean change from baseline hair count to week 8 and 26; the rate of change in hair growth at 8, 16, and 26 weeks, calculated as a ratio of change from baseline to the baseline total hair count; Independent Physician's Global Assessment at 8, 16, and 26 weeks; site Physician's Global Assessment at 8, 16, and 26 weeks; Subjective Scalp Hair Growth Score (SSHG) at 16 and 26 weeks; and Hair Specific Skindex-29 Quality of Life Score Questionnaire at 8, 16, and 26 weeks. All reported adverse events (AEs) were recorded.

Statistical Analyses

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Sample Size Calculation

Based on a review of previous hair growth studies, mean change in total hair count from baseline to 16 weeks when undergoing treatment with LLLT is typically in the range of 15 to 22 hairs/cm^2 with a SD of around 20 hairs/cm^2. For the sample size calculation, the SD was 20 hairs/cm^2 and the treatment difference was assumed to be 15 hairs/cm^2. The trial had a planned enrollment of 50 subjects per study arm in a 1:1:1:1 allocation to achieve at least 90% power while allowing a 10% dropout rate.

Analysis of Primary and Secondary Endpoints

The intent-to-treat (ITT) analysis population included all participants that were randomized. The per-protocol (PP) population included the subset of participants who had 16-week follow-up data and no major protocol deviations. Major protocol deviations were defined as treatment compliance less than 80% over the 26-week study period, being outside the study age window, deleterious concomitant medications, and scalp tattoo outside the specified location.

Descriptive statistics were calculated for continuous variables (sample size, mean, SD, minimum and maximum) and categorical variables (number and percentage in each category). For the primary endpoint (change in hair count from baseline to 16 weeks), each active cap group was compared with the sham group using an analysis of covariance (ANCOVA) using 1 degree of freedom and adjustment for multiple comparisons using Dunnett

correction. No comparisons between the active caps were performed. Statistical analysis of the primary endpoint was performed for both the ITT and PP populations. Covariate selection tests using variability criterion $p < .1$ were performed for site, age, sex, baseline weight, and baseline height; however, none of these variables met the covariate selection criterion and so they were not included in the ANCOVA analysis. Secondary outcomes were analyzed with statistical methods appropriate for the type of endpoints tested. Continuous variables were analyzed using parametric methods such as ANCOVA, while categorical variables were analyzed by nonparametric methods such as the Cochran–Mantel–Haenszel test. p-values of ≤ 0.05 were considered statistically significant.

Missing Data

Participants who withdrew from the study or were lost to follow-up after enrollment were still included in the ITT analysis, using a last observation carried forward approach. The participant's outcomes at the last available visit were carried forward to all subsequent missing assessment times.

Safety Analysis

All AEs were tabulated and summarized as counts and percentages.

Results

Study Population

One hundred sixty participants were randomized across the 4 sites: 39 to Cap 101, 41 to Cap 102, 38 to Cap 103, and 42 to the sham study arm. The mean age was 43.2 (range 19–69 years). Seventy-five percent of participants were male. Participants were 74% Caucasian, 12% Asian, and 15% other. Demographic characteristics were similar across the study arms (Table 1). Overall, 52.8% of male participants randomized to an active cap had stage IV or above Norwood–Hamilton hair loss compared with 40% in the sham group (Table 2). Thirty-seven percent of women receiving active treatment had Ludwig–Savin stage II-1 or II-2 hair loss compared with 50% of women in the sham group. There were no women with stage III, advanced or frontal hair loss (Table 2).

The PP analysis population consisted of only 69 participants (Table 2). The remaining 91 were excluded due to major protocol deviations. The most common reason for exclusion was low treatment compliance (<80% at week 26), which accounted for 62 participants (this number also includes discontinuations): 47/118 (40%) across the active device study arms and 15/42 (36%) in the sham group. The second most common major protocol deviation was "Tattoo outside of the anterior leading edge of the vertex thinning area of the scalp," which accounted for 39 exclusions. A total of 16 subjects (10%) discontinued participation; reasons for discontinuation included withdrawal of consent, loss to follow-up, physician decisions, and 1 due to an AE (Table 2); the AE that resulted in study discontinuation was headache and occurred in the sham cap group.

Primary Endpoint

In the ITT analysis population, there was no statistically significant change in total hair count in any study arm at week 16 (Table 3). In the PP analysis population, all 3 active study arms had positive mean change in total hair count at week 16 (10.6 hairs/cm^2 for cap 101, 22.7 hairs/cm^2 for cap 102, and 5.8 hairs/cm^2 for cap 103), while the sham cohort had negative mean change (-15.7 hairs/cm^2). There was a statistically significant difference in change in total hair count between the pooled active cohorts and sham. In the pooled active group, the mean change was an increase of 12.8 hairs/cm^2 from baseline. This equates to a difference of 28.5 hairs/cm^2 between sham and pooled active caps at week 16, $p = .033$. The differences were not significant when comparing sham to the individual active arms given the smaller than anticipated sample size in the PP population ($p > .05$) (see **Supplemental Digital Content 1, Table S1**, http://links.lww.com/DSS/B559).

Secondary Endpoints

At 8 weeks, although the mean change in hair count from baseline was greater for pooled active caps versus sham in both the ITT population (6 hairs/cm^2 active vs 0.5 hairs/cm^2 sham) and the PP population (1.2 hairs/cm^2 active vs -2.2 hairs/cm^2 sham), neither result was statistically significant. Similarly, at week 26, although the mean change in hair count was greater for pooled actives versus sham in both the ITT population (7.0 hairs/cm^2 active vs -3.5 ± 13 hairs/cm^2 sham) and the PP population (4.1 hairs/cm^2 active vs -4.5 hairs/cm^2 sham), neither result was statistically significant (see **Supplemental Digital Content**

TABLE 1. Participant Demographics

	All Active Caps ($n = 118$)	Cap 101 ($n = 39$)	Cap 102 ($n = 41$)	Cap 103 ($n = 38$)	Sham Cap 100 ($n = 42$)
Age (yr)					
N	118	39	41	38	42
Mean (SD)	43.0 (10.91)	41.0 (12.31)	45.4 (9.71)	42.6 (10.41)	43.9 (12.06)
Min–max	19.0– 64.0	19.0– 64.0	24.0– 62.0	19.0– 58.0	20.0– 69.0
Gender					
Males (%)	90 (76.3)	30 (76.9)	30 (73.2)	30 (78.9)	30 (71.4)
Females (%)	28 (23.7)	9 (23.1)	11 (26.8)	8 (21.1)	12 (28.6)

TABLE 2. Severity of Hair Loss at Baseline by Treatment Allocation

	All Active Caps (*n* = 118)	Cap 101 (*n* = 39)	Cap 102 (*n* = 41)	Cap 103 (*n* = 38)	Sham Cap 100 (*n* = 42)
Males (graded according to the Hamilton–Norwood hair loss scale) (%)	91	31	30	30	30
IIa	6 (6.6)	3 (9.7)	0 (0.0)	3 (10)	2 (6.7)
III	11 (12.1)	4 (12.9)	2 (6.7)	5 (16.7)	3 (10)
IIIa	4 (4.4)	0 (0.0)	3 (10)	1 (3.33)	1 (3.33)
III vertex	22 (24.2)	7 (22.5)	9 (30)	6 (20)	12 (40)
IV	31 (34.1)	10 (32.3)	10 (33.3)	11 (36.7)	5 (16.7)
V	17 (18.7)	7 (22.5)	6 (20)	4 (13.3)	7 (23.3)
Females (graded according to the Ludwig–Savin hair loss scale) (%)	27	8	11	8	12
I-1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)
I-2	4 (14.9)	1 (12.5)	2 (18.2)	1 (12.5)	1 (8.3)
I-3	5 (18.5)	1 (12.5)	2 (18.2)	2 (25)	1 (8.3)
I-4	8 (29.6)	3 (37.5)	2 (18.2)	3 (37.5)	2 (16.7)
II-1	3 (11.1)	1 (12.5)	1 (9.1)	1 (12.5)	3 (25)
II-2	7 (25.9)	2 (25)	4 (36.4)	1 (12.5)	3 (25)

1, Table S3, http://links.lww.com/DSS/B559). In the PP analysis population, there was a statistically significant increase in rate of change in total hair count from baseline to week 16 in the pooled active cohort versus sham (+0.05 active vs −0.03 sham; $p = .042$) but not in any of the individual active treatment arms or in the ITT population (see **Supplemental Digital Content 1, Table S2,** http://links.lww.com/DSS/B559).

For the following secondary endpoints, full tabulated results are available as supplementary materials. There were no statistically significant differences in Independent Physician's Global Assessment scores compared with sham for either superior or vertex scalp at weeks 8, 16, or 26 in any of the 3 active study arms, except for cap 101 versus sham at week 16 in the PP analysis population ($p = .029$ without adjustment for multiple comparisons). In the ITT population, there were no statistically significant changes in Physician's Global Assessment (PGA) scores compared with sham. In the PP population, there was a statistically significant change in PGA scores in the cap 103 treatment arm at week 16 ($p = .047$), but there was not a statistically significant change in PGA for any other treatment arm at any other time point. There was a significant reduction in the mean SSHG score in all active caps versus sham caps in the ITT population ($N = 143$, $p = .036$), but not in the smaller PP population ($N = 69$, $p = .059$) at 16 weeks. There were no statistically significant differences in the total Hair Specific Skindex-29 Quality of Life Score Questionnaire score between active and sham caps at weeks 8, 16, or 26 in the ITT or PP analysis populations.

Safety

Overall AE frequencies were similar between study arms. The AE rate for all active caps (35.6%) was equal to sham (35.7%) (see **Supplemental Digital Content 1, Table S1,** http://links.lww.com/DSS/B559). A total of 46/57 AEs (81%) were classified as "unrelated to device," the 11 remaining AEs were classified as "possibly device-related" (9/11), "probably device-related" (1/11), or "definitely device-related" (1/11, in a participant using a sham device). The most common AE was upper respiratory tract infection (9.3% in active caps, 4.8% in sham), followed by headache (4.2% active, 7.1% sham), pruritus (2.5% active, 4.8% sham), dandruff (0.8% active, 0% sham), pruritic rash (0.8% active, 0% sham), and a skin burning sensation (0% active, 2.4% sham).

TABLE 3. Intention-To-Treat Analysis of Mean Change in Hair Count From Baseline to Week 8, 16, and 26

	Total Hair Count (Hairs/cm^2) Reported as Mean ± SD, *p* versus Sham		
	Change from Baseline to Week 8	Change from Baseline to Week 16	Change from Baseline to Week 26
All active caps	6.0 ± 41.7, $p = .502$	9.7 ± 54.8, $p = .401$	7.0 ± 56.8, $p = .296$
Cap 101	2.2 ± 52.6, $p = .991$	5.0 ± 51.5, $p = .967$	−2.9 ± 46.5, $p = .998$
Cap 102	6.5 ± 41.6, $p = .936$	10.0 ± 59.6, $p = .903$	13.0 ± 55.6, $p = .517$
Cap 103	9.4 ± 27.5, $p = .681$	14.3 ± 53.8, $p = .546$	10.7 ± 67.0, $p = .478$
Sham cap	0.5 ± 49.1	1.6 ± 42.2	−3.5 ± 46.8

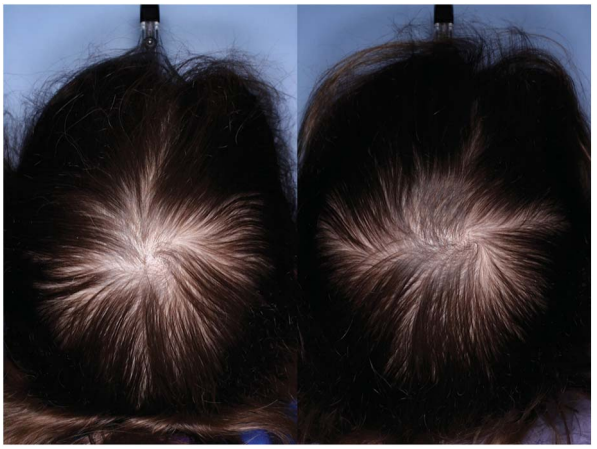

Figure 1. Improvement in vertex scalp hair density in a female AGA patient from baseline to 26 weeks, after daily 10-minute use of cap 101. AGA, androgenetic alopecia.

Discussion

Currently only one-third of male AGA patients are satisfied with the treatments they have tried.[11] Low-level laser therapy devices are emerging as a promising therapeutic modality.

Compared with the helmet-type and handheld comb LLLT devices, most individuals prefer a cap-type device.[12] A hands-free device was also preferred regardless of the cost.[12] Low-level laser therapy devices appear to be safe and well tolerated. A large study with 127 patients being treated with an LLLT device found no serious adverse effects. The most commonly reported LLLT-associated AEs were skin dryness (5.1%) and pruritus (2.5%).[2]

The first study to investigate LLLT for the treatment of AGA was published by Satino and Markou in 2003. They found an increase in hair counts with 6 months of use of a comb-type LLLT device called the HairMax LaserComb. However, they did not have a comparator group and therefore could not assess statistical significance.[9] Since then, several studies of similar devices have been reported and have found statistically significant improvements in hair density.

Though not statistically significant, the 102 cap that emitted only blue light outperformed the study caps emitting red light and a combination of red and blue light. To the best of the authors' knowledge, there is only 1 other published prospective study investigating blue light for AGA.[13] Blue light could surpass red light in effectiveness for AGA, and further studies comparing blue and red light are necessary.

All 3 active study arms had increased hair growth from baseline to week 16 compared with sham. Figures 1 and 2 demonstrate improved hair density in a male and female participant using cap 101. Although the primary efficacy endpoint (mean change in hair count from baseline to week 16) did not reach statistical significance in the individual study arms, in the pooled analysis (combining the 3 active study arms), there was a statistically significant ($p = .033$) difference versus sham. The lack of statistical significance for the primary endpoint in the individual active study arms is likely related to the reduction in statistical power resulting from the exclusion of 91/160 study participants due to major protocol deviations, most commonly poor treatment compliance. Hair growth declined between 16 and 26 weeks in this study, likely due to suboptimal treatment adherence. Up to week 16, only participants with at least 80% treatment compliance were included in the PP analysis. However, by week 26, all participants from the earlier analysis were included regardless of their compliance levels.

There are limitations to this trial, such as the short-term follow-up and the high noncompliance rate. Further studies to evaluate long-term outcomes, different treatment protocols, and combination therapies used in conjunction with the cap would also be beneficial.

Figure 2. Generalized improvement in scalp hair density in a male AGA patient from baseline to 16 weeks, after daily 10-minute use of cap 101. AGA, androgenetic alopecia.

Conclusion

Use of the LED cap system for 10 minutes daily was well tolerated and increased hair density in patients with AGA at 16 weeks.

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