

Efficacy and safety of a dietary supplement containing a lipid co-extract from *Serenoa repens* and *Pygeum africanum* for the treatment of androgenetic alopecia (AGA) in women. Results of a randomized, double-blind, placebo-controlled clinical trial

Josep Maria Borrás
Reig Jofre Group, S.A.
Barcelona, Spain.

Núria Piqué
Pharmacy Faculty,
Universitat de Barcelona.
Barcelona, Spain.

Carlos Nieto
Reig Jofre Group, S.A.
Barcelona, Spain.

Jordi González
Reig Jofre Group, S.A.
Barcelona, Spain.

ABSTRACT

Background: Few clinical trials have assessed the usefulness of *Serenoa repens* and *Pygeum africanum* for the treatment of androgenetic alopecia (AGA).

Purpose: To assess the efficacy of a dietary supplement (RJ-SP4AGA) containing a lipid co-extract from *Serenoa repens* and *Pygeum africanum* in post-menopausal women with AGA.

Methods: A randomized, double-blind, placebo-controlled clinical trial was performed in post-menopausal women with AGA, who received RJ-SP4AGA capsules or placebo capsules (two capsules/day during 16 weeks). At baseline, after 8 and 16 weeks, a phototrichogram analysis (anagen and telogen hair), a pull test (hair resistance to traction) and tolerability assessments were performed.

Results: A total of 40 Caucasian women were included, with a mean age of 58 years. After 16 weeks of treatment with RJ-SP4AGA capsules, anagen hair significantly increased and telogen hair significantly decreased (as mean %), with significant differences in comparison with placebo ($p < 0.001$). Hair resistance to traction also increased after 8 and 16 weeks in both groups. The RJ-SP4AGA capsules were well tolerated during treatment.

Conclusions: The dietary supplement RJ-SP4AGA capsules is useful in reverting the signs of AGA in post-menopausal women.

Key words: androgenetic alopecia (AGA), *Serenoa repens*, *Pygeum africanum*, lipid extract, 5-alpha reductase inhibitors, post-menopausal women, efficacy, tolerability, anagen phase, resistance to traction.

INTRODUCTION

Androgenetic alopecia (AGA) is the most common form of scalp hair loss, affecting 60 – 70% of the population worldwide, up to 80% of men and 50% of women in the course of their life^{1,2}. AGA is caused by a progressive reduction in the diameter, length and pigmentation of the hair, which worsen with time due to two potent androgens, testosterone (T) and, more significantly, its metabolite 5 α -dihydrotestosterone (5 α -DHT), on androgen-sensitive follicles^{1,2}.

By action of the enzyme 5 α reductase, T is metabolized to DHT, which has 5 times more affinity for androgen receptors than T. It is for this reason that inhibition of 5 α reductase is actually the best known target for treating AGA³.

In AGA, there is progressive hair follicle miniaturization and conversion of terminal follicles into vellus-like follicles, which have a shortened hair cycle because their anagen phase is reduced and they produce hair shafts that are short and fine⁴.

In women, AGA produces female pattern hair loss (FPHL), with diffuse thinning over the crown region and mid-frontal scalp, with maintenance of the frontal hairline (Ludwig pattern AGA)^{1,2,5}, while in men it produces male pattern hair loss with bitemporal recession and vertex baldness⁵.

To facilitate the diagnosis and differential diagnosis with other diseases, scalp dermoscopy is used routinely in patients with AGA, allowing staging of severity and to monitor the progress of the disease in time and its response to treatment².

Nowadays, obtaining specific and effective drugs for AGA treatments represents an important challenge^{1,6,7}. Medical treatments of AGA include topical minoxidil, antiandrogen agents and 5-alpha reductase inhibitors^{2,3}, with cure rates of between 35% and 48%¹.

Among 5-alpha reductase inhibitors, while finasteride and dutasteride are contraindicated in women due to the risk of adverse events^{3,6}, there is broad clinical experience with plant extracts from *Serenoa repens* and *Pygeum africanum*, with a well-established use for benign prostatic hyper-

plasia in men and for nonspecific pelvic syndrome, cystocele, premenstrual tension and postpartum bladder atony in women^{3,8}. Plant extracts from *Serenoa repens* and *Pygeum africanum*, with 5-alpha reductase inhibiting activity, are thus becoming, in both men and women, a feasible and safe option for the treatment of AGA^{3,8}.

Results of *in vitro* studies have demonstrated that *Serenoa repens* extracts, containing phytosterols as β -sitosterol and saponines, are able to inhibit type I and type II 5-alpha reductase^{3,8-10} and to decrease 5 α -DHT in humans⁸, and are also effective for the treatment of AGA³.

Although less studied⁸, extracts from the bark of *Pygeum africanum*, containing triterpens and phytosterols, mainly β -sitosterol, have also shown 5-alpha reductase inhibitory properties^{8,11}.

Currently, as finasteride has already done in the past, the lipid extracts of both *Serenoa repens* and *Pygeum africanum* are moving from the treatment of benign prostatic hyperplasia to the treatment of cutaneous disorders such as AGA.

In this context, Laboratorio Reig Jofre, S.A., has developed and marketed an oral dietary supplement (RJ-SP4AGA capsules) containing a lipid co-extract from both plants, *Serenoa repens* and *Pygeum africanum* for reverting AGA, particularly targeted at post-menopausal women.

In an *in vitro* study performed in fibroblasts from human scalp, we demonstrated that the lipid co-extract from both *Serenoa repens* and *Pygeum africanum* named “Complex Alphablok S” (the active ingredient of RJ-SP4AGA capsules) was able to inhibit 5-alpha reductase activity by up to 68% in comparison with control untreated cultures¹².

Based on these results and in the absence of clinical data evaluating this co-extract, we performed this randomized, double-blind, placebo-controlled study to assess the efficacy of RJ-SP4AGA capsules in reducing hair loss in comparison with placebo in post-menopausal women suffering from AGA (stage I – II of Ludwig’s scale).

METHODS

Study design and clinical protocol

A randomized, double-blind, placebo-controlled study was performed to assess the efficacy of RJ-SP4AGA capsules, containing the lipid co-extract “Complex Alphablok S” as its main active ingredient, in reducing hair loss in comparison with placebo in 40 post-menopausal women suffering from AGA (stage I – II of Ludwig’s scale)¹³ during a treatment period of 16 weeks.

The study design and clinical protocol were reviewed and approved by the clinical research ethics committee of the Institute of Skin and Product Evaluation, Milano, Italy (ISPE). The study was conducted at IPSE as well.

All subjects provided written informed consent before participating in the study. Full compliance by the participants with the study protocol was observed for the entire duration of the study.

Selection criteria

Forty Caucasian post-menopausal female women aged 50 to 65 years with general good health and suffering from AGA (stage I – II of Ludwig’s scale)¹³ were enrolled in this study. The women recruited had to be able to follow all the instruction of the study, attend all study visits and complete the informed consent process.

A general physical examination was conducted by physicians at the study period to confirm the women’s acceptable general health.

The main exclusion criteria included having a history of unusual skin reactions to skin care toiletry products or to cosmetics or sensitivity to any of the ingredients of the tested products; taking topical or systemic drugs that could affect the results of the tests (such as anti-inflammatory agents, corticosteroids, etc.), systemic diseases or skin disorders (such as eczema, psoriasis, severe acne, etc.) that could interfere in the evaluation of the product’s effects or increase the risks to the subjects’ health, use of adjuvant treatments for preventing hair loss (either topical and/or sys-

temic), and participation in another clinical investigation, current or within a period of 30 days prior to inclusion in this study.

The following reasons were established for discontinuation of the study: the subject’s free choice, reasons unrelated to the treatment (such as onset of a disease or surgical procedure) and reasons related to the study treatment (such as adverse reactions, etc.).

Randomization and treatment with RJ-SP4AGA capsules

The patients were randomly assigned to receive RJ-SP4AGA capsules (active group) or placebo. Both products were manufactured by Laboratorio Reig Jofre (Reig Jofre Group S.A., Barcelona, Spain) according to international Good Manufacturing Practices.

The products under study (RJ-SP4AGA capsules and placebo capsules) were assigned to subjects following a randomized treatment schedule. The assignment of subject number and subsequent placement on the randomization chart were made in order of appearance at the study center in the first visit of the study. The products were given to the subjects in anonymous containers, without any information related to the treatment. The treatment assigned to each patient was only decoded at the end of the study.

The study treatment involved taking two capsules per day (one in the morning and one in the evening) during the entire 16-week study period.

During the study period, subjects were instructed to wash their hair using their usual shampoo and to wash their hair 4 hours before each study visit, without using any styling products.

For the whole duration of the study, the use of products for preventing hair loss, either topical or systemic, other than the products under study, was forbidden.

Study visits took place at baseline (visit 1) and after 8 (visit 2) and 16 weeks (visit 3). The assessment of hair quality during the study visits was performed in a temperature and humidity

controlled room ($24 \pm 2^\circ\text{C}$; $50 \pm 10\%$ relative humidity) at IPSE (Institute of Skin and Product Evaluation, Milano, Italy).

At the three study visits, hair evaluations were performed including phototrichogram analysis and resistance of the hair to traction (pull test), as well as an overall assessment of tolerability.

Phototrichogram analysis

The phototrichogram analysis was performed using the TrichoScan system, based on the principle of epiluminescence microscopy, including the Fotofinder Dermoscope and the software Trichoscan Professional version 2.0, to obtain the percentage of anagen (phase of active growth) and telogen (rest phase) hair related to the area analyzed by the software (0.651 cm^2).

For this purpose, dermoscopy images were taken, stored and compared with Fotofinder Dermoscope. The same standard floodlight illumination and distance holder were used to take all the images. The software was able to measure the lengths and surfaces of the images, such as lines, plane curves, circular surfaces, rectangles and polygons.

The phototrichogram was obtained after taking photographs of the previously defined alopecic area of the scalp, following a hair clipping at each study visit. A frontal glass slide was mounted on the recording device to reduce the curvature of the scalp and allow better image definition. Contrast-enhanced phototrichograms were used to help distinguish hair on a skin background of the same color. Application of dyes on hair was recommended for this purpose. After taking a clipping in a 1 cm^2 area and dyeing, a digital image with 20-fold magnification (analyzed area of 0.651 cm^2) was taken by means of an epiluminescence microscopy system.

The digital images were analyzed by the software Trichoscan Professional version 2.0, giving the percentage of hair in anagen and telogen phases in the area analyzed.

Pull test

A clinical evaluation of the hair's resistance to traction was performed according to a 4-point semi-quantitative scale, carried out by applying a constant traction on a strand of hair taken from 3 different areas of the scalp: temporal area (located 3 cm above the back auricle-line), frontal area (located on the median line, 4 cm from the frontal hairline) and occipital area (located on the median longitudinal line, 4 cm from the back hairline).

The hair's resistance to traction was evaluated based on the total number of hairs removed from all three areas, according to the following semi-quantitative 4-point scale: 0 = > 6 hairs, 1 = 6 – 4 hairs, 2 = 3 – 1 hairs, 3 = 0 hair.

Tolerability assessment

The tolerability of the products under study was also assessed during the whole study period through an assessment of the incidence of adverse reactions reported by the women according to a 4-point scale: 0 = poor tolerability; 1 = mild tolerability; 2 = moderate tolerability and 3 = very good tolerability.

Objectives

The primary objective of the study was to assess the efficacy of a 16-week oral treatment with RJ-SP4AGA capsules containing the lipid co-extract "Complex Alphablok S" in comparison with placebo, to reduce hair loss in post-menopausal women with AGA.

As a secondary objective, the tolerability profile of the dietary supplement RJ-SP4AGA capsules was assessed.

Statistical analysis

Descriptive analyses (within-patient n, mean, median, standard deviation, minimum and maximum) were performed for quantitative variables, and frequency counts by category were calculated for qualitative variables.

Following the results of normality tests (Kolmogorov-Smirnov test), data obtained at the three visits (baseline, at 8 and 16 weeks) were compared by means of Friedman's Anova and Kendall's coefficient of concordance for non-parametric dependent data. The tolerability scores obtained at 8 and 16 weeks were compared using the Wilcoxon test for non-parametric dependent data.

Comparisons of data obtained at a given visit between both treatments were performed using the Mann-Whitney U test for non-parametric and independent data. Statistical significance was set at a p -value of $p < 0.05$.

RESULTS

A total of 40 Caucasian healthy women were selected; all of them were randomized, they all completed the study, and they were included for efficacy and tolerability analyses.

Baseline demographic, analytical and clinical characteristics were homogeneous among subjects, with a mean age of 58.0 years in the active group and 58.1 in the placebo group.

Regarding efficacy assessments, the results obtained were favorable for RJ-SP4AGA capsules. In the phototrichogram analyses, a statistically significant increase in the percentage of anagen hair was observed after 16 weeks ($49.5 \pm 15.5\%$ at baseline vs $55.6 \pm 15.0\%$ at 16 weeks, $p < 0.001$), while no statistically significant differences were observed with placebo ($50.7 \pm 19.8\%$ at baseline vs $52.7 \pm 18.6\%$ at 16 weeks, $p > 0.05$) (Table 1) (Figure 1 A). In the comparison of percentage of anagen hair between the two groups, the values obtained at 16 weeks were significantly higher in the active group than in the placebo group ($55.6 \pm 15.0\%$ for RJ-SP4AGA capsules vs $51.3 \pm 18.8\%$, $p < 0.001$, Mann-Whitney U test) (Table 1) (Figure 1 A). Anagen hair had increased to 112.32% at 16 weeks, taking 100% as the baseline value at T0 (Table 1) (Figure 1 B).

On the other hand, we reported a statistically significant decrease in the mean percentage of telogen hair from baseline to 16 weeks of con-

tinued use of RJ-SP4AGA capsules ($50.6 \pm 15.5\%$ at baseline vs $44.4 \pm 15.0\%$ at 16 weeks, $p < 0.001$), while no statistically significant differences were observed with placebo throughout the study ($49.3 \pm 19.8\%$ at baseline vs $48.8 \pm 18.8\%$ at 16 weeks) (Table 1) (Figure 2). After 16 weeks of treatment, the mean percentage of telogen hair was significantly lower in the active group than in placebo (44.4 ± 15.0 vs 48.8 ± 18.8 , $p < 0.001$) (Table 1) (Figure 2 A). Telogen hair had decreased to 87.7% at 16 weeks, taking 100% as the baseline value at T0 (Table 1) (Figure 2 B).

In the evaluation of the hair's resistance to traction (pull test), we detected a statistically significant increase in the hair's resistance to traction after 8 and 16 weeks of treatment with both groups (1.6 ± 0.7 at baseline to 2.4 ± 0.5 at 16 weeks for the active group; 1.5 ± 0.7 at baseline to 1.9 ± 0.7 at 16 weeks for placebo), without significant differences between RJ-SP4AGA capsules and placebo (Table 1) (Figure 3 A). However, RJ-SP4AGA capsules increased the hair resistance to traction to 150% after 16 weeks of continued use, taking 100% as the baseline value at T0 (Table 1) (Figure 3 B).

In the overall assessment of tolerability, both the RJ-SP4AGA capsules and the placebo were safe and well tolerated during the whole study period, with similar mean scores between both groups, indicating optimum/good tolerability (2.9 ± 0.4 for RJ-SP4AGA capsules and 3.0 ± 0 for placebo, at 16 weeks).

Only in the active group, two patients reported very mild digestive discomfort (one of them during the whole study period) and another only during the last weeks of the study). Another subject in the active group noticed some mild stomach heaviness during the whole treatment period. No adverse events were reported in the placebo group.

DISCUSSION

AGA is a highly prevalent condition that can profoundly impair the quality of life of both men and women¹⁴. In addition, in women, female

Table 1. Percentages of anagen hair during treatment (n = 40)

Treatment	T0 Mean ± SD	T8 Mean ± SD	T16 Mean ± SD	Difference T8-T0	Difference T16-T0	T0 vs T8 p-value	T0 vs T16 p-value	T8 vs T0 p-value (active vs placebo)	T16 vs T0 p-value (active vs placebo)
Percentage of anagen hair (%)									
RJ-SP4AGA	49.5 ± 15.5	51.6 ± 16.4	55.6 ± 15.0	+2.1	+6.1	>0.05	<0.001	>0.05	<0.05
Placebo	50.7 ± 19.8	52.7 ± 18.6	51.3 ± 18.8	+2.0	+0.6	>0.05	>0.05		
Percentage of telogen hair (%)									
RJ-SP4AGA	50.6 ± 15.5	48.5 ± 16.4	44.4 ± 15.0	+2.1	+6.2	>0.05	<0.001	>0.05	<0.05
Placebo	49.3 ± 19.8	47.4 ± 18.6	48.8 ± 18.8	+1.9	+0.5	>0.05	>0.05		
Pull test (4-point scale)									
RJ-SP4AGA	1.6 ± 0.7	2.1 ± 0.6	2.4 ± 0.5	+0.5	+0.8	<0.01	<0.001	>0.05	<0.05
Placebo	1.5 ± 0.7	1.8 ± 0.6	1.9 ± 0.7	+0.3	+0.4	<0.05	<0.05		

pattern hair loss has a strikingly overwhelming psychological effect, which leads to a need for successful treatments⁶.

In contrast to the high prevalence of AGA, approved therapeutic options are limited, with a paucity of pharmacologic treatments and numerous non-prescription products whose efficacy has not always been tested¹⁵.

Despite the broad use of both plants, *Serenoa repens* and *Pygeum africanum*, few clinical trials have been conducted on the efficacy or safety of their extracts for the treatment of AGA, particularly in women.

Our study has assessed for the first time the efficacy and tolerability of a lipid co-extract of *Serenoa repens* and *Pygeum africanum* ("Complex Alphablok S") in a randomized, double-blind, placebo-controlled clinical trial in post-menopausal women. The favorable results are in line with the *in vitro* results obtained in fibroblasts from human scalp, indicating a significant 5-alpha reductase inhibiting activity of the lipid co-extract. Overall, these results support the use of this extract, as 5-alpha reductase inhibitor, for the treatment of AGA, par-

ticularly in women, in whom other 5-alpha reductase inhibitors, such as finasteride or dutasteride, are contraindicated^{3,6}.

Although other studies had previously demonstrated the efficacy and safety of the lipid extract of *Serenoa repens* or β -sitosterol alone for the prevention of hair loss^{3,9}, we have shown for the first time the efficacy and tolerability of a lipid co-extract of both plants, *Serenoa repens* and *Pygeum africanum*, for the treatment of AGA.

In our study, using the well-established methodology to test the efficacy of products in alopecia, such as phototrichogram analysis and pull test^{2,4}, we demonstrated that, after a 16-week treatment, the lipid co-extract was able to increase the anagen hair and decrease the percentage of hair in telogen phase, increasing hair resistance to traction.

The increase observed in the mean percentage of anagen hair in the group treated with RJ-SP4AGA capsules supports its efficacy at a dosage of 2 capsules per day, and is in line with the observed 5-alpha reductase inhibiting activity to decrease the level of 5 α -DHT, which is known

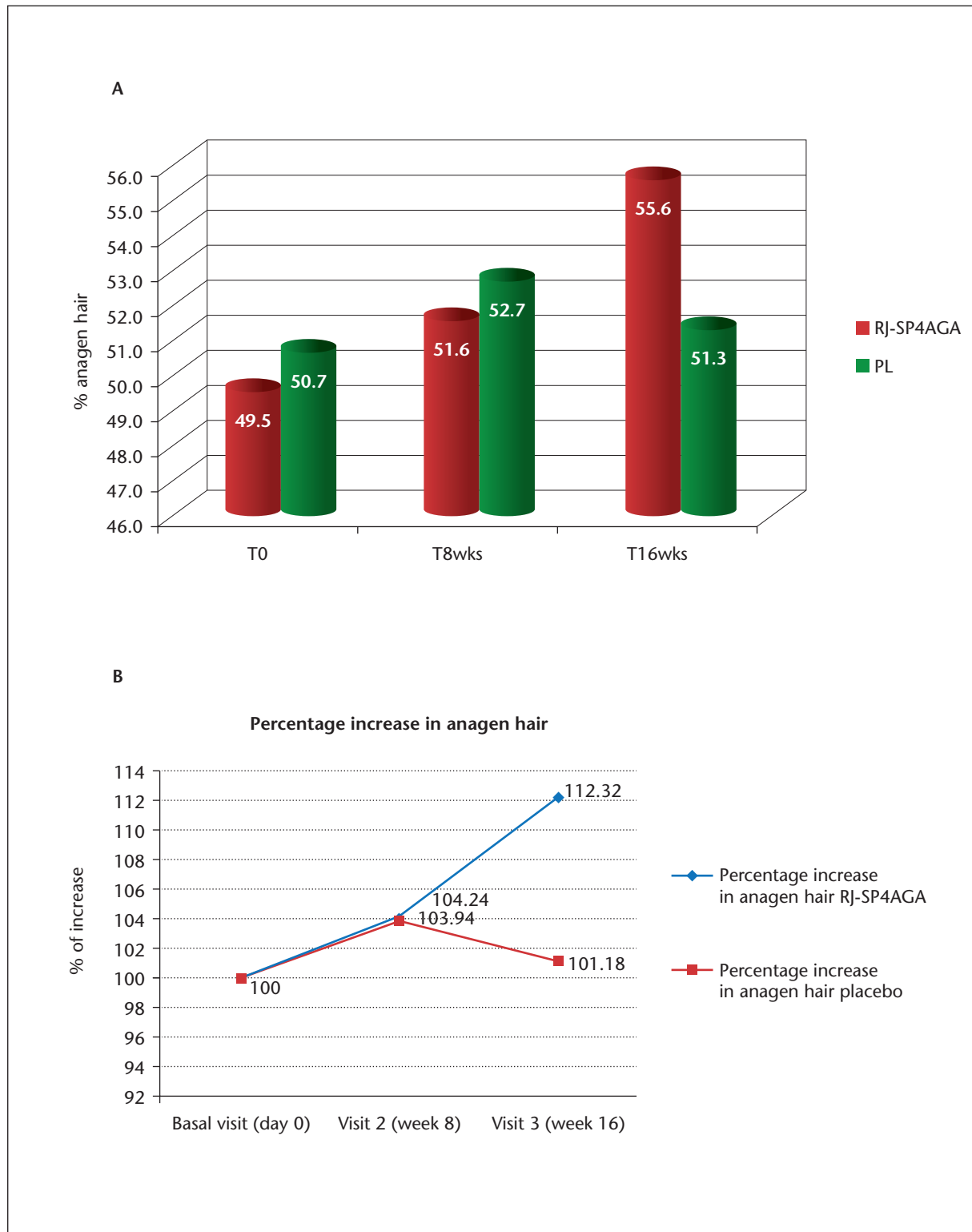


Figure 1. Evaluation of anagen hair. A) Mean percentage of anagen hair. B) Mean percentage of anagen hair, considering 100% at baseline.

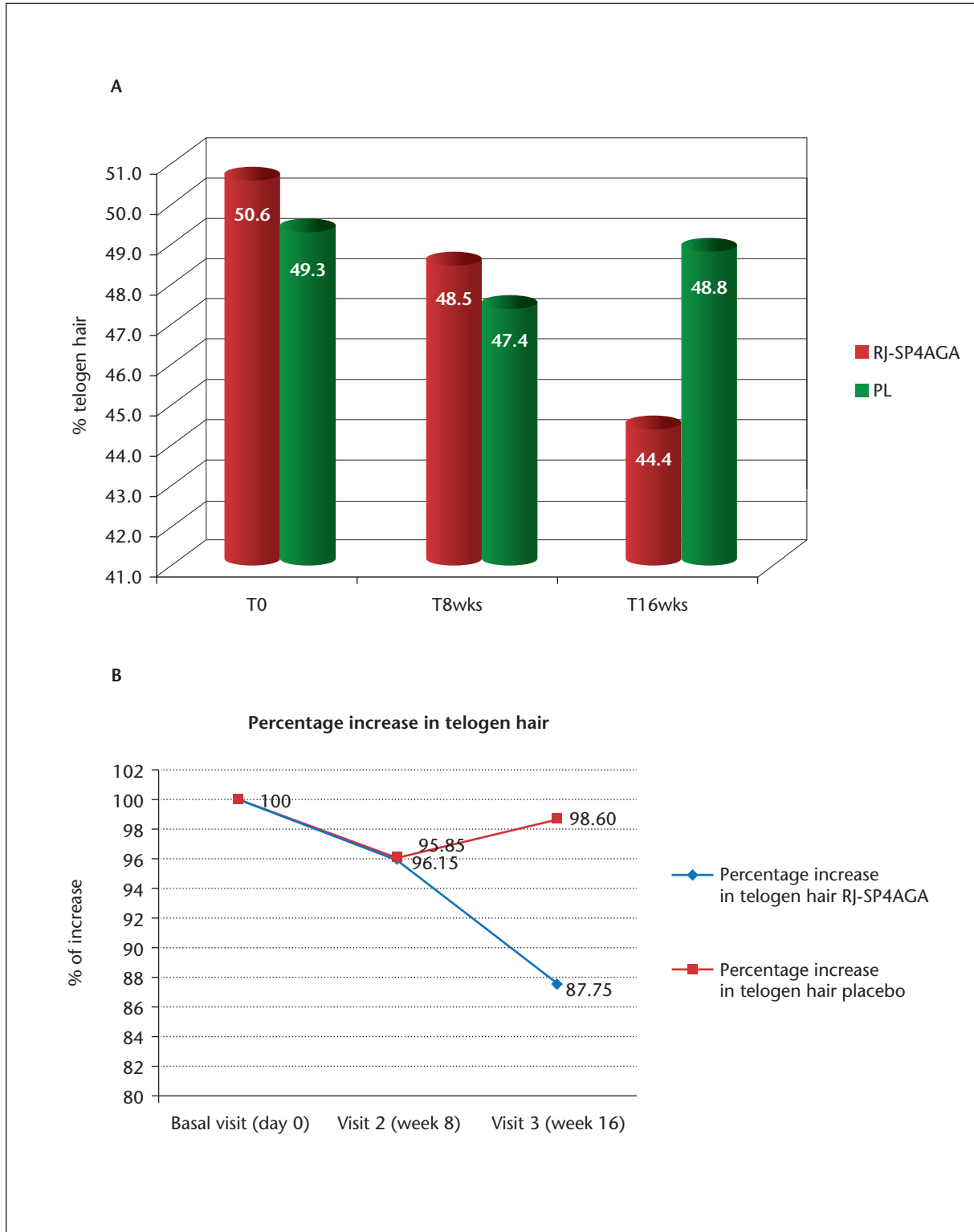


Figure 2. Evaluation of telogen hair. A) Mean percentage of telogen hair. B) Mean percentage of telogen hair, considering 100% at baseline.

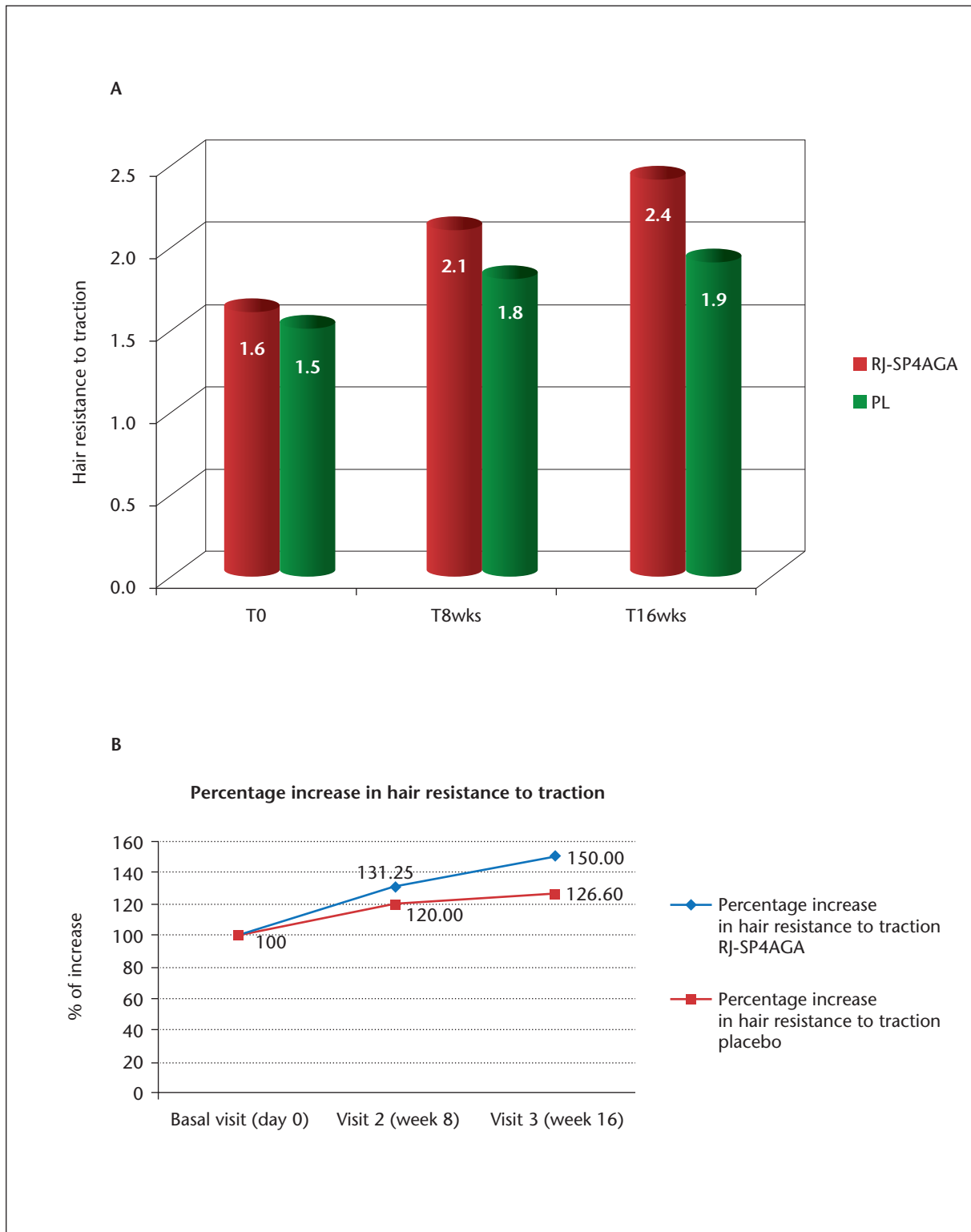


Figure 3. Pull test scores. A) Pull test scores at the three study visits. B) Mean percentage of hair resistance to traction, considering 100% at baseline.

to shorten the growth or anagen phase of the hair cycle, causing the miniaturization of the follicles, and producing progressively finer hairs³. Also in accordance with the increased hair growth, we observed a statistically significant reduction in telogen hair.

Finally and also relevantly, the administration of RJ-SP4AGA capsules was well tolerated during the whole study period, with only mild digestive adverse events being reported. Its good tolerability profile is in line with the well-established use of both *Serenoa repens* and *Pygeum africanum* in clinical practice and with their regulatory classification as a dietary supplement granted to them by the health authorities.

Although additional larger studies could be carried out with the product, assessing other variables such as quality of life, the results of this study support the use of RJ-SP4AGA capsules containing the lipid co-extract “Complex Alphablok S” as an efficacious and very well tolerated therapeutic strategy to revert hair loss in patients with AGA.

Funding sources

Reig Jofre Group, S.A., Barcelona, Spain

Conflicts of interest

Josep Maria Borrás is Medical Director of Reig Jofre. Núria Piqué received fees from Reig Jofre to write the article. Carlos Nieto is Biological Development R&D Manager of Reig Jofre. Jordi González is Manager of the Topical and Oral Development Department of Reig Jofre.

REFERENCES

- Jain R, De-Eknamkul W. Potential targets in the discovery of new hair growth promoters for androgenic alopecia. *Expert Opin Ther Targets*. 2014;18(7):787-806.
- Piraccini BM, Alessandrini A. Androgenetic alopecia. *G Ital Dermatol Venereol*. 2014;149(1):15-24.
- Prager N, Bickett K, French N, Marcovici G. A randomized, double-blind, placebo-controlled trial to determine the effectiveness of botanically derived inhibitors of 5-alpha-reductase in the treatment of androgenetic alopecia. *J Altern Complement Med*. 2002;8(2):143-52.
- Herskovitz I, Tosti A. Female pattern hair loss. *Int J Endocrinol Metab*. 2013;11(4):e9860.
- Sinclair R, Patel M, Dawson TL Jr, Yazdabadi A, Yip L, Perez A, et al. Hair loss in women: medical and cosmetic approaches to increase scalp hair fullness. *Br J Dermatol*. 2011;165 Suppl 3:12-8.
- Levy LL, Emer JJ. Female pattern alopecia: current perspectives. *Int J Womens Health*. 2013;5:541-56.
- Georgala S, Katoulis AC, Georgala C, Moussatou V, Bozi E, Stavrianeas NG. Topical estrogen therapy for androgenetic alopecia in menopausal females. *Dermatology*. 2004;208(2):178-9.
- Guerra Tapia A. Inhibidores de la 5(alfa) reductasa en la alopecia androgénica presente y futuro. *Opciones terapéuticas*. *Act Dermatolog*. 2007;46(8/9):539-47.
- Marks LS, Hess DL, Dorey FJ, Luz Macairan M, Cruz Santos PB, Tyler VE. Tissue effects of saw palmetto and finasteride: use of biopsy cores for in situ quantification of prostatic androgens. *Urology*. 2001;57(5):999-1005.
- Wilt TJ, Ishani A, Stark G, MacDonald R, Lau J, Mulrow C. Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. *JAMA*. 1998;280(18):1604-9.
- Schleich S, Papaioannou M, Baniahmad A, Matusch R. Extracts from *Pygeum africanum* and other ethnobotanical species with antiandrogenic activity. *Planta Med*. 2006;72(9):807-13.
- Reig Jofre, S.A. Company report 0146. 5-alpha reductase expression in cultured human fibroblasts: effects of plant extracts. Research and development. Reig Jofre, S.A. January 2012.
- Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. *Br J Dermatol*. 1977;97(3):247-54.
- Rouso DE, Kim SW. A review of medical and surgical treatment options for androgenetic alopecia. *JAMA Facial Plast Surg*. 2014;16(6):444-50.
- Varothai S, Bergfeld WF. Androgenetic alopecia: an evidence-based treatment update. *Am J Clin Dermatol*. 2014;15(3):217-30.