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A Randomized, Double-Blind, Placebo-Controlled Trial to Determine the Effectiveness of Botanically Derived Inhibitors of 5AR in the Treatment of Androgenetic Alopecia

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Abstract

Background

Androgenetic alopecia (AGA) is characterized by the structural miniaturization of androgen-sensitive hair follicles in susceptible individuals and anatomically defined within a given pattern of the scalp. Biochemically, one contributing factor of this disorder is the endogenous conversion of testosterone (T) to dihydrotestosterone (DHT)

via the enzyme 5-alpha reductase (5AR). This metabolism is also key to the onset and progression of benign prostatic hyperplasia (BPH). Further, AGA has also been shown to be responsive to drugs and agents used to treat BPH. Of note, certain botanical compounds have previously demonstrated efficacy against BPH. Here, we report the first example of a placebo-controlled, double-blind study undertaken in order to examine the benefit of these botanical substances in the treatment of AGA.

Objectives

The goal of this study was to test botanically derived 5AR inhibitors, specifically the liposterolic extract of *Serenoa repens* (LSESr) and ß-sitosterol, in the treatment of AGA.

Subjects

Included in this study were males between the ages of 23 and 64 years of age, in good health, with mild to moderate AGA.

Results

The results of this pilot study showed a highly positive response to treatment. The blinded investigative staff assessment report showed that 60% (6/10) study subjects dosed with the active study formulation were rated as improved at the final visit.

Conclusions

This study establishes the effectiveness of naturally occurring 5AR inhibitors against AGA for the first time, and justifies the expansion to larger trials.

Introduction

Androgenetic alopecia (AGA) shares a number of endocrinolgic pathways with benign prostatic hyperplasia (BPH). Certain botanical compounds, and specifically those under investigation herein, have previously demonstrated the ability to inhibit key metabolic processes associated with BPH. Based on the parallel etiologies of these two disorders, it was the central hypothesis of this pilot research study to examine the putative benefit these botanicals may offer in the treatment of AGA.

Androgenetic alopecia (AGA) is characterized by a receding hairline and/or hair loss within a specific pattern on the scalp (Shapiro et al. 2000). This condition, which affects both men and women, is inherited as a polygenic disorder likely involving several genes and multiple pathways, although the precise mechanism(s) remain unknown. However, one factor, which has been demonstrated to contribute to the pathogenesis of

this condition, involves a genetically predetermined sensitivity to the effects of the androgenic hormone dihydrotestosterone, or DHT, in certain scalp hair follicles (Mowszowicz et al. 1993). DHT is believed to shorten the growth, or anagen, phase of the hair cycle, causing miniaturization of the follicles, and producing progressively finer hairs.

The production of DHT (reduced from T) is catalyzed by the enzyme 5-alpha reductase (5AR). In the prostate gland and in susceptible scalp hair follicles, androgen responsive cells express the genes encoding the steroid enzyme 5AR. 5AR is a membrane-bound enzyme that catalyzes the irreversible conversion of T to DHT (Itami et al. 1994). Two isozymes exist: the type 1 enzyme, encoded by the SRD5A1 gene, localized to chromosome 5p15, and the type 2 isozyme, encoded by the SRD5A2 gene localized to chromosome 2p23 (Morissette et al. 1996). Immunolocalization studies have shown that the type 1 enzyme is expressed primarily in newborn scalp, and in skin and liver, and the type 2 isozyme protein is expressed primarily in genital skin, liver and the prostate (Negri-Cesi et al. 1999). In the prostate gland, the conversion of T to DHT by 5AR has been strongly implicated in the pathogenesis of BPH. Of note, the endocrine dysfunction associated with BPH bears a striking similarity to that linked to AGA.

BPH affects almost all men to some degree as they age, and can cause a significant disruption of lifestyle due to urinary outflow obstruction and irritative symptoms. BPH is characterized clinically by large, discrete nodules formed in the periurethral region of the prostate. These nodules may narrow the urethra sufficiently to cause full or partial obstruction. An accumulation of estrogen in the aging prostate, along with increased conversion of testosterone to its more active metabolite, dihydrotestosterone (DHT), has been shown to contribute BPH, however, the specific etiology of BPH remains unknown. Nonetheless, studies have demonstrated that by blocking the conversion of T to DHT, with either pharmaceuticals or natural compounds, the circulating level of DHT is reduced by 80%, the size of the prostate gland is reduced by about 20% and the level of prostate-specific antigen (PSA) drops by about 50% (Mikolajczyk et al. 2000).

Interestingly, it has also been observed that eunuchs (males who have been castrated prior to the onset of puberty) do not develop BPH, nor do they develop AGA, and moreover, after castration BPH has been shown to regress (Wilson et al. 1999). Since normal testicular function appears to be necessary for the development of BPH, it is believed that the hyperplastic tissue metabolizes androgenic hormones differently than normal prostate tissue. Although by definition this tissue is benign, progressive growth of the tumor may cause significant obstruction of the urethra and interfere with the normal flow of urine (Wilt et al. 2000b). As with AGA, the incidence of BPH increases with advancing age. BPH is so common, that it is believed all men will develop benign prostatic hyperplasia if they live long enough. Some degree of BPH is present in 80% of all men over 40 years old and this figure increases to 95% of all men 80 years old (Guthrie and Siegel 1999).

In support of a relationship between AGA and BPH, several lines of evidence have converged to support the view that both circulating testosterone and the modifying enzyme, 5AR, have profound effects on androgen metabolism, and provide insight into the role of these hormones play in hair loss. Specifically, the absence of circulating testosterone and, therefore, its metabolite DHT, in males castrated prior to puberty has been shown to prevent AGA in later life. These findings demonstrate the importance of this metabolism in the pathogenesis of male pattern hair loss (Giltay and Gooren 2000).

Of equal relevance, it has been observed that, line in a group of male pseudohermaphrodites presenting inherited mutations in the 5AR gene, the preservation of the juvenile hair line invariably occurs (Imperato-McGinley et al 1990). These two examples demonstrate that whether the disturbance in androgen metabolism results from either the absence of substrate (T), the active metabolite DHT, or dysfunction of the enzyme 5AR, at least one phenotypic consequence is consistent and reproducible - terminal hair density as well as juvenile hairlines remain intact in such individuals.

In contrast, a third and critical observation has been noted in bodybuilders who self-administer anabolic steroids, in that excessive levels of circulating T and therefore DHT had the opposite effect of the first two examples – that of acceleration of hair loss in genetically susceptible individuals due to upregulation of the hormonal processes which result in AGA (Lise et al 1999).

Collectively, these lines of evidence point to a common theme among disorders resulting from dysregulation of the conversion of T to DHT, and have led to the central hypothesis of this research. Until now, the only treatments available for AGA have consisted essentially of the topically administered drug Rogaine™ (minoxidil 2% & 5%) and the orally delivered pharmaceutical Propecia™ (finasteride 1mg).

Rogaine (topically applied minoxidil 2%--5%) is the best known drug in the category of medical AGA treatment. Minoxidil delivered via oral ingestion was initially indicated in the treatment of refractory hypertension. It was noted to cause hypertrichosis (increased nonsexual hair growth), however, the mechanism by which it stimulates hair growth remains unknown. Clinical trials have shown that a 2% solution applied topically to the scalp can stimulate hair growth in some men and women (Rushton et al. 1989).

Finasteride 1 mg (Propecia™, Merck) was approved by the US FDA December, 1997 for the treatment of male pattern hair loss (androgenetic alopecia, AGA) in men only. Safety and efficacy were demonstrated in men between 18 and 41 years of age with mild to moderate hair loss of the vertex and anterior mid-scalp area. Efficacy in bi-temporal recession has not been established (Kaplan and Olsson, 1996). Propecia™ is not approved for use in women or children. Finasteride is a preferential, competitive inhibitor of the intracellular, type II, 5 alpha-reductase isoenzyme which converts testosterone into dihydrotestosterone (DHT), the more potent androgen. In humans, the type II 5 alpha-reductase isoenzyme is primarily found in the root sheath of the hair follicle, prostate, seminal vesicles, epididymis, fetal genital skin and in fibroblasts from normal adult genital skin, as well as liver, and is responsible for two-thirds of circulating DHT (Sawaya and Price 1997). In target organs, finasteride treatment is thought to result in selective androgen deprivation affecting DHT without lowering circulating levels of testosterone, thus preserving the desired androgen mediated effects on muscle strength, bone density and sexual function. As noted above, the balding scalp in AGA contains miniaturized hair follicles and increased amounts of DHT compared with non balding scalp, and finasteride treatment produces inhibition of the isozyme, resulting in a rapid reduction in scalp and serum DHT concentrations.

Since AGA shares similar hormonal pathways with BPH, it was previously recognized that the pharmaceutical agents useful against BPH may offer some potential benefit in the treatment of AGA. The modification of Proscar™ (finasteride 5mg—initially indicated for BPH), to Propecia™ (finasteride 1mg—new indication AGA) serves as a paradigm for this rationale (Kaufmann 1999). Like finasteride, several botanically derived substances have also demonstrated the ability to inhibit key hormonal processes associated with BPH. Importantly, these botanicals have not been linked with the spectrum of negative side effects, adverse reactions, or teratogenicity, associated with the pharmaceutically derived alternatives (Klepser and Klepser, 1999).

Recently, several clinical trials have been reported demonstrating the efficacy of botanical compounds in the treatment of a number of androgen dependent conditions, and, specifically, BPH. For example, among 1,098 BPH patients tested in one recent study, the general safety profile of the lipsterolic extract of *Serenoa repens* (LSESr 320 mg/day), or saw palmetto berry extract, compared favorably with that of finasteride, and sexual side effects were less common with the extract than with the drug. In particular the use of this extract has not been associated with erectile dysfunction, ejaculatory disturbance, or altered libido (Wilt et al. 2000a). Remarkably, in another biochemical study, it was found that LSESr was a 3-fold more effective inhibitor than finasteride (5 mg/day) at concentrations adjusted to the recommended doses for BPH treatment. It should be noted that finasteride as indicated for AGA is dosed significantly lower (1 mg/day), suggesting, a 15-fold more potent level of inhibition at the recommended daily dose of LSESr (320 mg/day) (Delos et al. 1994).

LSESr is the first line of BPH treatment in Europe and elsewhere, and is believed to act by inhibiting 5AR. Several *in vitro* experiments in cultured human foreskin fibroblasts have found LSESr to be a strong and specific inhibitor of the enzyme 5AR (Swoboda and Kopp, 1999). *In vitro* studies have also shown that LSESr inhibits both isozymes, whereas finasteride selectively inhibits only type 2 5AR (Iehle et al 1995). Moreover, finasteride demonstrates a solely competitive inhibition, while LSESr has additionally been found to display noncompetitive as well as uncompetitive inhibition of the type 1 as well as type 2 5AR isozyme (Gerber 2000).

As with LSESr, the primary indication for treatment with the plant phytosterol ß-sitosterol has been in the treatment of BPH. In addition to a potential role in 5AR inhibition, as a minor component of LSESr, ß-sitosterol in particular has been shown to lower the bioavailability of cholesterol in the local environment in animal models, thereby suggesting it may inhibit downstream steriod hormone biosynthesis, most specifically testosterone (Wang and Ng, 1999). One potential mechanism of action of ß-sitosterol in the prostate and the hair follicle, therefore, may involve a local reduction of T (substrate) in the microenvironment of 5AR active tissues.

In one large clinical study, a total of 519 men undertook a 26 week double-blind controlled study testing ß-sitosterol against placebo in assessing urinary flow as the operative criterion. Compared with placebo, ß-sitosterol significantly improved urinary symptom scores and flow measures (Bracher 1997). Based on the success of ß-sitosterol in the treatment of BPH, as well as other factors, it was incorporated as an active component of the AGA trial study formulation. IN RECOGNITION OF THE EFFICACY THESE BOTANICALLY DERIVED 5AR INHIBITORS DEMONSTRATED IN THE TREATMENT OF BPH, IT WAS THE CENTRAL HYPOTHESIS OF THIS STUDY TO TEST THEM FOR THE FIRST TIME AGAINST AGA.

Subjects and Methods

Patient Population

INCLUDED IN THIS STUDY WERE males between the ages of 23 and 64 years of age, in good health, with mild to moderate AGA. Exclusion criteria CONSISTED OF 1) those who had been on prescription or over-the-counter treatment for AGA or a prostate condition within the past 30 days prior to initiation of the trial; 2) symptomatic cardiac problems, uncontrolled hypertension, symptomatic hypotension, autoimmune disorders; 3) those who had participated in a clinical trial within 30 days prior to enrollment 4) those with any known allergy to any ingredients in the test products; and 5) those with any other medical condition that could interfere with successful conclusion of the study. Subjects enrolled in this study met guidelines established under the Hamilton/Norwood scale of hair loss. Study subjects presented with moderate to significant male pattern hair loss in the vertex area (grade II vertex through grade VI vertex). Baseline characteristics of study subjects were reasonably well matched and fell within the desired study protocol inclusion parameters. The protocol was approved by the Western Institutional Review Board, Olympia, SA, and all investigation was performed following written informed consent in accordance with these guidelines. All investigative staff members participating in this study were trained to evaluate and report the parameters described in the study protocol.

Study Protocol

After informed consent, approximately twenty-six (26) male subjects aged 23 to 64 with AGA were initially evaluated and randomly assigned, in a double-blind manner, to one of the following groups: either active oral softgel supplement, 1 softgel twice daily or matching oral placebo, 1 softgel twice daily.

The composition of the softgels, a GMP-compliant product manufactured by Softgel Technologies Inc. Los Angeles CA, encased in an inert carob colored soluble shell, was as follows: The active softgel components consisted of ß-sitosterol 50mg, and saw palmetto extract (standardized to 85-95% liposterolic content) 200mg. Systemic absorption of the active softgel components' bioavailability WAS enhanced by the use of

lecithin 50mg, inositol 100mg, phosphatidyl choline 25mg, niacin 15mg, biotin 100mcg. The historical experience of other investigators testing these botanicals against BPH was an important factor in determination of the recommended drug-dosage levels for this study.

Historically, a number of animal studies support the safety, efficacy, and dosage for these botanical agents, however, no animal research was undertaken as a part of this proof-of-concept trial (Schilcher 1999). The placebo soft gels, encased in an inert carob colored soluble shell, were composed as follows: soybean oil 540mg.

Test product and placebo were prepared by Softgel Technologies Inc. (Los Angeles, CA) to be identical in appearance. Product was randomly assigned code numbers. Codes were not available to involved personnel until after completion of the trial and final data review. Study participation encompassed a duration of approximately 4.6 months, with a maximum duration of approximately 5.4 months. There were three scheduled clinic visits. Baseline/randomization (approximately week 0), enrollment (approximately week 0), conclusion (approximately week 21). The enrollment visit (Visit 1) was also the randomization visit. During this visit subjects were randomized, study medication was dispensed, and baseline investigative staff evaluations were made. The block size for this study was 30 with a treatment vs. control ratio of 1:1. All subjects were instructed to use Neutrogena T/Gel or similar shampoo to standardize any variable which might otherwise occur by the use of differing shampoo formulations.

Written informed consent was obtained from all study subjects prior to entry, with a copy given to each subject. A brief medical history was obtained including vital signs (weight, blood pressure, heart rate. Overall hair assessment was made using a standardized 7 point scale (Table I).

Subjects were asked to rate their current level of satisfaction with their hair. Subjects were then assigned to treatment in sequential order and given instructions regarding study agent. Study supplies were then dispensed and subjects were sent home to begin the study.

Study completion

As with the enrollment visit, a brief medical history was obtained including vital signs (weight, blood pressure, heart rate). Overall hair assessment was made using a standardized 7 point scale (Table I). Subjects were asked to evaluate any change with respect to their current level of satisfaction with their hair.

Efficacy Measures

Efficacy measures were administered at baseline, and final visit. These were: 1) investigative staff assessed hair growth (Figure 1) and 2) patient self-assessment of treatment efficacy and satisfaction with appearance (Figure 2).

Patient Self-Assessment

The parameters assessed by study subjects in this analysis were the following questions: a) size of bald spot; b) appearance of hair; c) growth of hair; d) rate of hair loss; and e) satisfaction with appearance of hair (Table I).

Table I. Subject Self Assessment Questions and Rating of Subject Current Satisfaction.

Self Assessment Questions

1. **Since the start of the study, I can see my bald spot getting smaller.** Choice of answers: strongly agree, agree, no opinion either way, disagree, strongly disagree.

2. **Because of the treatment I have received since the start of the study, the appearance of my hair is:** Choice of answers: a lot better, somewhat better, a little better, same, a little worse, somewhat worse, a lot worse.

3. **Since the start of the study, how would you describe the growth of your hair?** Choice of answers: greatly increased, moderately increased, slightly increased, no change, slightly decreased, moderately decreased, greatly decreased.

4. **Since the start of the study, how effective do you think the treatment has been in slowing your hair loss?** Choice of answers: very effective, somewhat effective, not very effective, not effective at all.

5. **Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of: a) the hairline at the front of your head? B) the hair on top of your head? C) your hair overall?** Choice of answers: very satisfied, satisfied, neutral, dissatisfied, very dissatisfied.

Subject Current Satisfaction

1. **What is your current level of satisfaction with your hair condition**? Choice of answers: -3 very dissatisfied,
-2 moderately dissatisfied, -1 slightly dissatisfied, +1 slightly satisfied, +2 moderately satisfied, +3 very satisfied.

Investigative Staff Assessment

As recorded in the Study Protocol Case Report Forms, the primary measure utilized by the investigative staff in determination of formulation efficacy was a seven point scale starting with (-3) denoting greatly decreased hair density, ranging to (+3) marking greatly increased hair density. (Table II).

Table II. Investigator Rating Scale for Subject Assessment in the course of this study.

Assessment	**Score**
greatly decreased	-3
moderately decreased	-2
slightly decreased	-1
no change	0
slightly increased	+1
moderately increased	+2
greatly increased	+3

Toxicity and Adverse Events

Risk of toxicity in this study was considered minimal inasmuch as the LD/50 for the botanicals under investigation was far greater than the highest dosages likely to be consumed. Numerous independent BPH studies evaluating similar formulations support this observation (Carraro et al. 1996; Wilt et al. 1998; Gerber et al. 1998; Wilt et al. 1999; Wilt et al. 2000a).

Adverse events were recorded in the Study Protocol Case Report Form Manual per IRB guidelines. THE CAUSALITY OF ADVERSE EVENTS WAS based on a four (4) point scale with 1 = great probability that the adverse event was likely to be related

to use of the study drug and 4 = great probability that the adverse event was not likely to be related to use of the study drug.

The adverse events noted during the course of this study included nausea, constipation, and diarrhea. However, no adverse events occurring within this pilot were determined as likely to be related to the use of the study drug. The data are presented in accordance with the CONSORT clinical study reporting guidelines as described in the Lancet (Moher et al. 2001).

Results

Study Goals

Our primary goal in this initial pilot study was to assess if the study formulation was efficacious in arresting scalp hair loss as well as improving hair quality. Based on anecdotal and open label data, we anticipated being able to show a positive trend demonstrating a response to therapy. The two measurements utilized for this purpose were:

1) *Investigative staff assessment using a standard assessment format*

Twenty six [26] male subjects, ages 23 to 64 were enrolled in the trial between July, 1999 and October 1999. Of these 26, nineteen [19] completed the trial. Seven [7] dropped out prior to study completion, with two of these due to a perceived adverse event (Table III). Five of the seven patients who withdrew did not report an adverse event, but dropped out for reasons unrelated to the research study. A total of 19 patients were evaluated after study completion. Duration of participation in this study ranged from 18 to 24.7 weeks.

Table III. Perceived Adverse Events Arising in the Course of the Study.

Complaint	Placebo (n=9)	Treatment (n=10)	Resolved during study	Relationship to treatment
Skin	0	1	No	Not related
GI	0	1 loss of appetite 1 flatulence 1 diarrhea	No Yes Yes	Possible Unlikely Unlikely
Neurological	1	0	Yes	Placebo
GU	1 frequent urination	0	No	Placebo
Miscellaneous	1 aware of heart beat 1 heightened sensations	0	No	Placebo

In total, there were 8 perceived adverse events reported by 7 subjects in the course of this study. One subject in the treatment group reported acne which was present at baseline and worsened during the course of the study. Three subjects in the treatment group reported gastroinestinal symptoms, including loss of appetite, flatulence and diarrhea. One subject in the placebo group reported lightheadedness with a bowel movement. One subject in the placebo group reported frequent urination, and one subject in the placebo group reported heightened sensations and awareness of heartbeat. GI, gastrointestinal; GU, genitourinary.

On the basis of the investigative staff assessment of change in the patient's scalp hair growth from baseline (Figure 1), treatment with the active study formula demonstrated 60% (6/10) subjects rated as 'improved' at the final visit as compared to baseline. In contrast, only 11% (1/9) in the placebo group were rated as 'improved'. These findings show a markedly positive response to treatment as denoted by the proportion of responders. Due to the small sample size, statistical significance and/or confidence intervals were not endpoint goals of this pilot study (n = 19) nor were they achieved, however, future large-scale studies will be designed with these definable endpoints in mind.

2) Subject self-assessment of hair condition

The study participant's self-assessment criterion reflected a time-dependent analysis of any change noted in the thinning areas of the scalp. Subject assessment of the "appearance of the bald spot" at the final visit compared to baseline were as follows: In the treatment group [0]--0% deteriorated, vs. the placebo group where [3]--33% deteriorated (Figure 2).

Discussion

As previously noted, both LSESr and ß-sitosterol represent, among other indications, first line BPH treatments in Europe and elsewhere. This is meaningful in light of the previously noted etiological similarities between these two disorders. However, to the best of our knowledge, prior to the small trial described in this study, no controlled and blinded clinical research had previously been conducted on a formula, either oral or topical, combining LSESr and ß-sitosterol, in the treatment of AGA.

The composition under discussion was designed on the basis of the excellent safety and efficacy previously demonstrated by each ingredient alone. However, the published studies were performed on each substance tested separately, but never together. Nonetheless, both LSESr and ß-sitosterol alone have established clinical efficacy against BPH.

For example, in a meta-analysis of 18 randomized controlled trials comparing LSESr to finasteride, involving 2,939 men, both magnitude of improvement and confidence interval, all tend to favor the efficacy of LSESr with less erectile dysfunction that that associated with finasteride (Millon et al. 1999). Also, in a randomized, double-blind trial, BPH patients treated with ß-sitosterol showed a significant improvement in lower tract urinary symptoms as compared with placebo recipients (Wilt et al. 1998).

Furthermore, a 26-week LSESr vs. finasteride trial involved 1,098 men led to a remarkable finding which highlights an important safety aspect of these two therapies. It was found that finasteride lowers the level of prostate specific antigen (PSA) by 30% to 50%. This test is routinely used to screen for prostate cancer and monitor prostate cancer therapy (Gerber et al. 1998). This study showed that although finasteride does

not affect the sequelae of prostate cancer, it may complicate the diagnostic process, since PSA values must be approximately doubled. In the same study, however, LSESr demonstrated no impact on PSA levels, suggesting the absence of this potentially dangerous side effect.

Moreover, in contrast to phytotherapy, where negative side effects are virtually nonexistent, finasteride has been implicated with the following adverse reactions; decreased libido (1.8%), erectile dysfunction (1.3%), and ejaculation disorder (1.2%) (Carraro et al. 1996). Resolution did occur in all men who discontinued therapy with finasteride due to these side effects. Finally, finasteride treatment is contraindicated in females as a result of its terotogenic potential. In fact, even the handling of crushed finasteride tablets by pregnant females is discouraged due to the possibility of systemic absorption, which may result in risk of feminizing birth defect to a male fetus (Wolf and Kunte, 1999).

In contrast, these warnings and contraindications have never been associated with the botanically based substances tested in this study, and in fact LSESr has been safely and widely used in women for the treatment of dysmenorrhea, genital/urinary problems, and difficulty association with lactation (Lee et al. 2000). In recognition of the safe and potentially EFFICACIOUS nature of the substances under examination, this small proof of principle trial was conducted with the goal of yielding objective data demonstrating a positive response for the active formula as measured against placebo.

In summary, the results from this study demonstrate a trend in favor of active therapy over placebo. The Investigative Staff Assessment showed that 60% (6/10) subjects were rated as 'improved' by the investigator at the final visit as compared to baseline. This compares to 11% (1/9) in the placebo group (Figure 1). Further, the Subject Assessment analysis of the 'appearance of the bald spot' at the final visit compared to baseline showed that in the treatment group, no subjects deteriorated. In contrast however, the placebo group reported three subjects as deteriorated. Inasmuch as maintenance of hair density and hair quality is a goal for many patients, this finding is in itself noteworthy. Based upon the small number of subjects (n = 19) our data justifies the design of a larger scale study of these substances in the treatment of AGA.

In conclusion, we have observed objective evidence of EFFICACY using orally administered botanical therapy in the treatment of AGA, for the first time. The implementation of larger gender-specific clinical trials, incorporating local delivery concomitant with oral administration is planned as an appropriate next step. Research is also underway to identify additional botanical compounds which may offer useful activity against AGA.

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Figure Legends

Figure 1. Graphic representation of the results of the Investigative Staff Assessment of the study group. The blue (upper) bar represents subjects treated with active formulation, versus the green (lower) bar representing subjects in the placebo group. The X-axis represents numbers of subjects
(1-10). The results demonstrated that 6 of 10 subjects (60%) were rated as improved in the group taking the active formulation, compared to 1 of 9 subjects (11%) in the placebo control group.

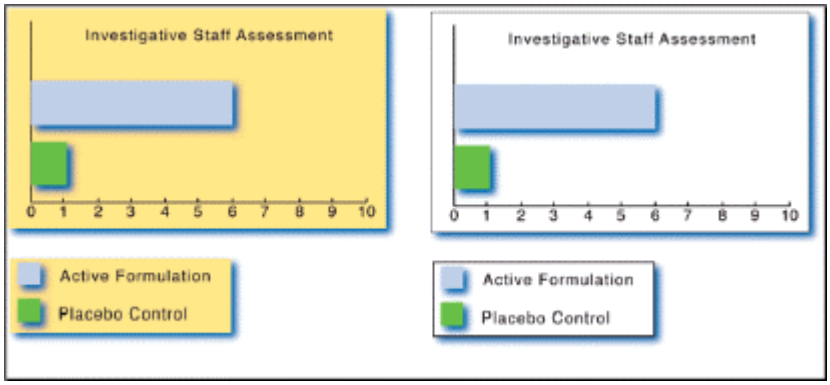

Fig. 1

Figure 2. Graphic representation of the results of the Subjects' Self-Assessment of the study group. The criterion represented here was the perceived deterioration of the bald spot. The yellow (left-hand) bar represents subjects in the treatment group, versus the blue (right hand) bar representing subjects in the placebo group. The Y-axis represents percent deterioration. The results demonstrated that 0 of 10 subjects (0%) in the group taking active formulation reported any deterioration of the bald spot, compared to 3 of 9 subjects (33%) in the placebo control group.

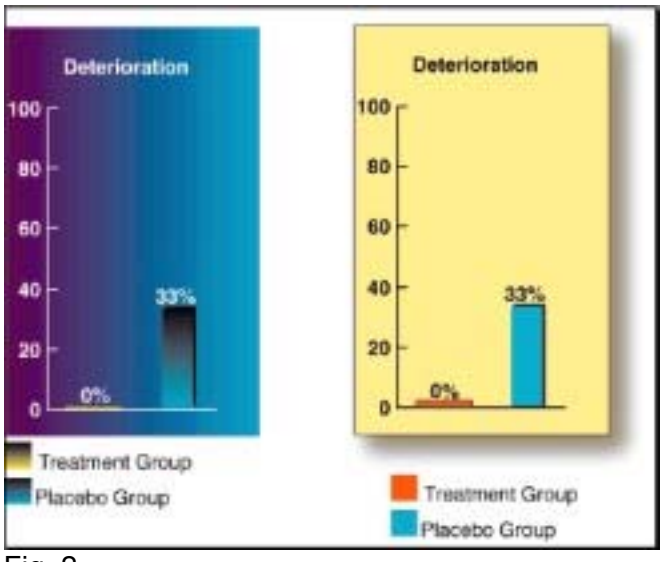

Fig. 2