

A New Topical Formulation of Minoxidil and Finasteride Improves Hair Growth in Men with Androgenetic Alopecia

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Abstract

Objectives: To compare the safety and efficacy of MorrF (combination of Minoxidil [5%]+Finasteride [0.1%] lipid solution) with Minoxidil (5%) solution in adult male patients suffering from Androgenetic Alopecia (AGA).

Background: AGA is one of the three most common forms of non-scarring alopecia with approximately 95% of hair loss cases in men and women. Fifty percent of men by age 50 years exhibit some degree of AGA. Currently there are two effective treatments available for the treatment of AGA in men: topical Minoxidil and oral Finasteride. Clinical studies have demonstrated that both Minoxidil and Finasteride have well established therapeutic effect in the management of AGA.

Materials and methods: Safety study in rats was carried out for 28 days with topical application of MorrF twice a day for 28 days. Human Pharmacokinetics (PK) and efficacy study was conducted in male patients suffering from Androgenetic Alopecia. PK parameters were determined after 2 weeks of MorrF administration. For efficacy study patients were randomized to receive either MorrF or Minoxidil (5%) alone for 24 weeks. Patients administered 1 mL of the either solution twice day on the effected part of the scalp.

Results: Topical treatment of MorrF was found to be well-tolerated in rats and humans. Pharmacokinetics study in human showed the steady state C_{max,ss} and exposure (AUC_{0-t,ss}) for Minoxidil to be 2.7 ng/mL and 19.3 ng.h/mL respectively whereas the steady state maximum Finasteride concentration (C_{max,ss}) was 0.6 ng/mL and exposure (AUC_{0-t,ss}) of Finasteride was found to be 6.3 ng.h/mL. Significantly more patients treated with MorrF showed greater improvement in Investigator score (65% vs. 26%), global photographic assessment (89% vs. 60%) and patient's self-assessed questionnaire as compared to Minoxidil alone.

Conclusion: Topical formulation of MorrF was shown to have clinically significant improvement in terms of hair growth as compared to Minoxidil (5%) alone.

Keywords: MorrF; Minoxidil; Finasteride; Topical; Efficacy; Alopecia

Introduction

Loss of hair is a general problem in men over 50 years old were 95% of the hair loss is attributed to Androgenetic Alopecia (AGA) [1]. In women AGA is less common with about 40% of women suffer from some degree of hair loss especially after menopause. Alopecia occurs in stages with miniaturization of the hair follicles mediated by increase in metabolism with conversion of testosterone to dihydrotestosterone (DHT) by 5 α -reductase enzyme. It has been reported that AGA does not occur in men with a genetic deficiency of the enzyme 5 α -reductase (5-AR) type II, which converts testosterone to DHT, implicating DHT in its pathogenesis. Therefore, AGA is caused by androgen-dependent miniaturization of scalp hair follicles, with DHT implicated as a contributing cause [2]. Men with AGA lose hair in the

fronto-temporal and vertex regions of the scalp in varying degrees depending on the severity of the disorder [1].

Three most common forms of non-scarring alopecias are Androgenetic Alopecia, telogen effluvium, and alopecia areata. AGA produces patterned hair loss, beginning with bitemporal recession of the frontal hair line, followed by diffuse thinning over the vertex [1]. A model for the pathogenesis of AGA must account for the histological features mentioned above, in particular the miniaturization of the hair follicle and an increase in the ratio of telogen to anagen hairs; the systemic and local effects of androgens in promoting the condition; and the familial tendency. The genetics of AGA is complex which is believed to be caused due to an autosomal dominant gene with variable penetrance, but a polygenic inheritance has not been excluded. Candidate genes are those involved in androgen production and conversion of androgen to DHT [3].

Due to the prevalence of AGA with half of the men suffering from hair loss problem, several methods have been used to restore hair loss including topical, oral, implants treatments etc. However, only two drugs have been approved by the United States Food and Drug Administration for the treatment of AGA in men: topical Minoxidil and oral Finasteride. It has been demonstrated that Minoxidil aids in enhancing the hair growth by vasodilation via providing the nutrients to the hair follicles and thus direct stimulation of the hair follicle cells [4,5].

Pharmacodynamics studies have shown that increase in the testosterone by 5 α -reductase to DHT results in loss of hairs due to the miniaturization of scalp hair follicles. Finasteride is an inhibitor of human 5 α -reductase resulting in the decrease of DHT formation that prevents the miniaturization of scalp hair follicles. Oral Finasteride have been indicted to have potential risks of gynecomastia, feminization, and impotence [3].

It has been reported that efficacy of 1mg/day oral Finasteride and 5% topical Minoxidil were found to be safe and effective. The oral Finasteride was more effective than Minoxidil in patients with mild to severe AGA [6]. There are several studies conducted where patients used both topical Minoxidil and oral Finasteride that resulted in enhance benefit to the patients compared to single treatment of either one drug indicating the synergistic effect of the combination [7-9]. However, topical formulation of Finasteride is not available in the market. In order to have enhanced treatment option for patients, we have developed a lipid based topical formulation with combination (MorrF) of Minoxidil and Finasteride. This combination would improve patient compliance because patient would not be required to take individual drugs concomitantly and combining two molecules acting on same ailment would provide faster improvement in hair growth. It will be a good replacement of oral therapy, especially in those who are more concerned about side effects of oral Finasteride. This article describes the results of preclinical and clinical study with lipid based topical formulation of MorrF.

Material and methods

Material

Minoxidil and Finasteride were obtained from Kumar Organic Limited, India and Aurobindo Pharma Limited, India respectively. Soyphosphatidylcholine was procured from Lipoid LLC (Newark, NJ). Other inactive ingredients were procured locally.

Preparation and administration of MorrF

MorrF was prepared by dissolving 50 mg/mL Minoxidil, 1 mg/mL Finasteride, and 5 mg/mL Soy Phosphatidylcholine in isopropyl alcohol-propylene glycol-water solution. The resulting homogenous clear solution was passed through 2.5 micron polypropylene filter and filled in to Amber colored 60 mL capacity bottles. The Finasteride and Minoxidil concentration in the finished product were determined by a prepacked C18 column (5 μ m particle size, 250 \times 4.6 mm i.d.) attached with Agilent 1100/1200 Series HPLC system (Agilent technology, Palo Alto, CA) and a UV detector.

A total dose of 1 mL MorrF was applied twice daily to the affected scalp, beginning at the center of the area. This dose was used regardless of the size of the affected area. MorrF was allowed to completely dry for 2 to 4 hours after applying it, including before

going to bed. MorrF topical solution was applied when the hair and scalp were thoroughly dry.

Preclinical toxicity studies

A total of four groups (3 test groups and 1 control) were used to test toxicity in rats. Placebo group (A) did not have any active ingredients (Minoxidil and Finasteride). Three test groups are identified as following. Group B (1% Minoxidil and 0.2% Finasteride), Group C (3% Minoxidil and 0.6% Finasteride) and Group D (5% Minoxidil and 1% Finasteride).

A set of 3 male (215-245 g) and 3 female (160-190 g) Sprague-Dawley Albino rats (~8 weeks old) were randomly selected for each of one control (Placebo, Group A) and three test groups (Group B, C and D). The upper dorsal area of the trunk of each rat was shaved ~24-hour before the first dose application. A volume of 1 mL of groups A, B, C and D dosing solution was applied topically drop by drop over the shaven area of each rat twice daily for 28 consecutive days. Following the 28 days of topical administration, the biological samples as stated below were collected from the study animals after sacrificing the study animals. The blood from each animal was collected in the BD Vacutainer tubes for blood chemistry determination. The gross examination of the internal tissues/organs was conducted. The tissues; heart, kidney, liver and spleen from each animal were collected, cleaned, weighed and examined for any gross abnormality. Thereafter, each tissue was saved in 10% formalin solution for histopathological examination. Animals were also observed daily for morbidity/mortality during the period of the study.

Clinical studies

Pharmacokinetics: An open label, single period study to evaluate the multiple dose pharmacokinetics of MorrF by twice daily topical application in 16 healthy adult, human male subjects with Androgenetic Alopecia was conducted.

Healthy adult human male volunteers between 18 - 60 years of age (both inclusive) and in good general physical and mental health, with Androgenetic Alopecia with II to V grade on the modified Norwood Hamilton classification, having a Body Mass Index (BMI) between 18.5 to 27.0 kg/m² (both inclusive) and having given their written informed consent were enrolled for the study. They did not have any significant diseases or clinically significant abnormal findings during screening, medical history, physical examination, clinical examination, laboratory evaluation, 12-lead ECG and Chest X-ray (postero-anterior view) recordings. Volunteers who complied with all the inclusion and exclusion criteria were only enrolled into the study.

During the housing period, compliance to dosing was assessed by examination of application site by trained study personnel immediately after dosing. For other dose applications, subjects were instructed to abide by the requirements and compliance to dosing was assessed through subject diary.

A total of twenty-one (21) samples were collected from each subject to analyse the pharmacokinetic profile of the test product. Prior to morning dose (Day 01 and Days 13 to 15) and evening dose (Day 12 to Day 14): 12 mL blood samples were withdrawn prior to morning Dose on Day 01 and 10 mL each was withdrawn prior to morning dose (Day 13 to 15) and evening dose (Day 12 to Day 14). Post-dose samples: Day 15 (after morning dose): Venous blood samples of 10 mL each were withdrawn at 0.500, 1.000, 1.500, 2.000, 3.000, 4.000, 5.000, 6.000,

8.000, 12.000, 16.000, 24.000, 36.000 and 48.000 hours post-dose application.

The pharmacokinetic parameters were calculated and reported from the drug concentration vs. time profile by non-compartmental model using WinNonlin Professional Software Version 5.3 (Pharsight Corporation, USA) for Minoxidil and Finasteride.

Efficacy study: A total of 120 patients were enrolled in the study. All the patients willing to participate in the trial were screened prior to their enrolment, in order to assess their eligibility by satisfying all of the inclusion and the exclusion criteria. Male patients of 18 to 45 years of age with Androgenetic Alopecia with II to V grade on the modified Norwood Hamilton classification were enrolled in this clinical study provided they were willing to maintain the same hair style, approximate length, and hair colour throughout the study and willing to provide written informed consent.

Patients with concomitant dermatological disorders on the scalp other than AGA, serious cardiovascular diseases, renal diseases, hepatic diseases, history of drug hypersensitivity, breast disorders, clinically significant abnormalities on baseline physical examination or laboratory tests (i.e. DHT) and other conditions such as wearing a wig, history of surgical treatment for hair loss, shaved scalp were not eligible for the study.

Subjects were given patient screening ID, underwent clinical examination and specified laboratory investigations at screening visit. Subjects fulfilled all eligibility criteria at screening were enrolled, assigned a patient randomization ID. Patients were supplied study medication for four weeks at a time. Patients were instructed to topically apply study medication every day to the bald area on scalp as per the Investigator's advice.

The day of entry in the study was considered Day 1 for all enrolled subjects and all subsequent assessment time points (i.e., visit days) was designated on this basis. Patients were randomized to receive either MorrF or Minoxidil alone. Drugs were dispensed with the help of dropper packed with them. Dropper was marked to dispense 1 ml quantity of study drugs.

At each time point of assessment (viz., screening visit, study entry, follow-up on five occasions (after every 4 weeks) and end-of-study (total 24 weeks), the subject had to visit the trial site as instructed and his vital signs, body weight, findings of systemic examination and investigations, concomitant illness, ongoing medication, and adverse events, if any, were recorded in the case record form (CRF).

Additionally, during each visit, effect on hair growth and scalp coverage was assessed by the investigator by using 5 point scale as following.

- Markedly improved: dense hair growth (bald area almost entirely covered with hair of density almost identical to that in the non-bald area).
- Moderately improved: moderate hair growth (bald area partly covered with newly growing hair, of density lower than that in the non-bald area).
- Slightly improved: minimum hair growth (hair growth present, but bald area clearly visible)
- Unchanged: no visual hair growth
- Worsened: decreased hair growth

Effect on the hair growth was also assessed by the patient using hair growth questionnaire except baseline visit. A total of 68 patients

completed the self-assessment in the study. The respective scores were recorded in the CRF.

Further global photographic assessment was done by the Investigator at baseline, at end of 12 weeks and at the end of study visit at 24 weeks [10]. The vertex and superior-frontal area of the scalp was photographed on specified visit. The specified laboratory investigations were done at screening, at end of 12 weeks and at the end of the study (24 weeks).

Primary efficacy criteria was comparison of change in the investigator assessment score for hair growth and scalp coverage in the two treatment groups compared to baseline and secondary efficacy criteria was comparison of the change in patient's assessment score for hair growth and loss by hair growth questionnaire and change in global photographic assessment for hair growth by 7 point scale at the end of the study compared to baseline. Proc Univariate of SAS was used to test normality assumption and Shapiro –Wilk test was used to assess normality for both treatment groups.

The proportion of patients at the end of treatment categorized by the Investigator score and by global photographic assessment score were compared between MorrF and Minoxidil alone using the chi-squared test.

The study was carried out according in accordance with declaration of Helsinki and CDSCO "Good Clinical Practice" guidelines after approval from IEC/IRB at eight trial sites. Approvals were obtained from respective ethics committees as applicable at each study center. The study was registered with the CTRI (Clinical trial registry of India). Reg. No. CTRI/2009/091/000896 (Dt. 02/02/2010).

Result and Discussion

A combination of Minoxidil and Finasteride solution (MorrF) was developed for topical application in patient suffering from Androgenetic Alopecia. The product was well characterized and was found to be stable at 25°C/60% RH for 2 years.

Animal toxicity study was conducted using low, mid and high doses of MorrF topically applied to rats. The general condition of the rats was monitored for any clinical signs within 1 hour post each topical application. The skin area of the rats was observed for erythema, oedema, and eschar formation before each topical application. No such signs were observed in any treated rat. The clinical signs such as changes in motor activity, skin/fur, eye and mucous membranes, respiratory system, central nervous system and behaviour patterns were monitored, but no such signs were observed in rats of Groups A, B, C and D. A dose dependent effect of reduced body weight gain between 28 days of treatment period in male rats of Groups B (47.3%), C (39.4%) and D (33.0%) was observed in comparison to control Group A (59.1%). In female rats a lower body weight gain effect was observed compared to male rats.

All male and female rats were free of signs of toxicity throughout the study period of 28 days. No apparent difference in food intake was observed in male and female animals compared to control group and all the male and female animals survived through the study period. There was also no noticeable difference in serum clinical chemistry values was observed between the treated groups. The histopathology of liver, kidney, heart and spleen showed no significant pathological changes. The results showed that all doses tested were safe and well-tolerated.

Clinical Studies

Pharmacokinetics study: Human male subjects with Androgenetic Alopecia were treated with MorrF and pharmacokinetic parameters were determined for Minoxidil and Finasteride after multiple dose application (twice daily for two weeks).

The pharmacokinetic parameters were computed after the completion of study and are presented in Tables 1 and 2.

Parameters (Units)	Mean ± SD
	(un-transformed data)
	Test Product
T _{max,ss} (h)*	4.000 (0.000 – 12.050)
C _{min,ss} (pg / mL)	1740.672 ± 753.8738
C _{max,ss} (pg / mL)	2701.228 ± 793.7069
AUC _{0-τ,ss} (pg.h / mL)	19278.993 ± 6162.2488
C _{av,ss} (pg / mL)	1603.907 ± 511.9263
%Fluctuation	62.476 ± 36.0118
%Swing	68.691 ± 50.4714
AUC _{0-t} (pg.h / mL)	43678.209 ± 13048.4362
AUC _{0-∞} (pg.h / mL)	71710.614 ± 28235.0966
AUC_%Extrap_obs (%)	32.589 ± 20.7769
Iz (1 / h)	0.032 ± 0.0129
t _{1/2} (h)	27.240 ± 20.0709

Table 1: Pharmacokinetics parameters of Minoxidil after topical administration of MorrF to subjects with Androgenetic Alopecia

Note: *T_{max} is represented as median (min-max) value

Parameters (Units)	Mean ± SD
	(un-transformed data)
	Test Product
T _{max,ss} (h)*	2.500 (0.000 – 12.050)
C _{min,ss} (pg / mL)	421.104 ± 225.7914
C _{max,ss} (pg / mL)	636.962 ± 321.5293
AUC _{0-τ,ss} (pg.h / mL)	6340.593 ± 3308.5467
C _{av,ss} (pg / mL)	527.873 ± 276.0305
%Fluctuation	33.156 ± 20.6475
%Swing	41.694 ± 33.0579
AUC _{0-t} (pg.h / mL)	15260.864 ± 8475.4908
AUC _{0-∞} (pg.h / mL)	18301.469 ± 11160.4722
AUC_%Extrap_obs (%)	14.288 ± 6.9938
Iz (1 / h)	0.045 ± 0.0126

t _{1/2} (h)	16.485 ± 4.6635
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Table 2: Pharmacokinetics parameters of Finasteride after topical administration of MorrF to subjects with Androgenetic Alopecia

Note: *T_{max} is represented as median (min-max) value

These parameters were derived individually for each analyzed subject from the concentration vs. time profiles of Minoxidil and Finasteride. Actual time-points of the sample collection were used for the pharmacokinetic analysis. The steady state C_{max,ss} and exposure (AUC_{0-τ,ss}) for Minoxidil was found to be 2.7 ng/mL and 19.3 ng.h/mL respectively. This indicates a low topical absorption similar that reported with single administration of Minoxidil [5]. Finasteride pharmacokinetics parameters were also determined after MorrF administration in patients. The steady state maximum Finasteride concentration (C_{max,ss}) was 0.6 ng/mL and exposure (AUC_{0-τ,ss}) of Finasteride was found to be 6.3 ng.h/mL. The pharmacokinetic studies with oral Finasteride (1 mg/day) resulted in maximum Finasteride plasma concentration of 9.2 ng/mL, and (AUC_{0-τ,ss}) was 53 ng.hr/mL [11]. Thus, the Finasteride concentration observed were found about ten-fold lower compared to Finasteride administered orally at similar dose. This was expected as systemic exposure after topical administration is generally lower compared to oral. However, topical administration of Finasteride have indicated no significant statistical differences in the number of terminal hairs, total hair count, and size of alopecia area compared to oral Finasteride after 6 months [12].

Clinical Efficacy Study: Treatment with only oral Finasteride (1 mg/day) indicated progression of hair loss was decreased and hair growth increased in 2 years [13]. The factors other than the number of hairs, such as increased growth rate (length) and thickness of hairs, also contributes to the beneficial effects of Finasteride in treated men [14]. Similarly, treatment with topical 5% Minoxidil solution resulted in increase in scalp coverage of 60% in patients after 48 weeks compared to 23% in those who received vehicle alone. Minoxidil 5% resulted in faster onset and greater degree of hair regrowth than through the use of Minoxidil 2% [5].

A randomized, open label, multicenter, interventional clinical trial was conducted in adult male patients suffering from Androgenetic Alopecia classified as grade II to V by modified Norwood-Hamilton scale. Eligible subjects were randomized to receive either MorrF or Minoxidil alone as per the dosage schedule.

The end-of-treatment data was compared with the baseline data within the group and between the treatment groups for the assessment of efficacy. Absolute changes of Investigator's assessment, patient's assessment and global photographic assessment scores from the baseline after administration of trial medication over the study period were reported on specified visits for each evaluable patient. The Investigator assessment was based on 104 patients (53 patients in MorrF and 51 patients in Minoxidil alone) who completed Investigator assessment score at the end point. It was observed that significantly more number of patients treated with MorrF showed greater improvement in Investigator score as compared to those treated with Minoxidil alone (64.7% in MorrF group versus 25.5% in Minoxidil alone group; p =0.0006) (Figure 1).

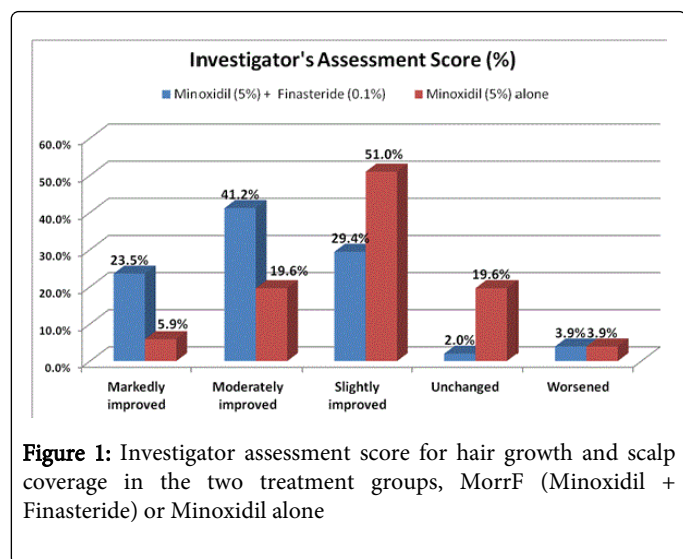


Figure 1: Investigator assessment score for hair growth and scalp coverage in the two treatment groups, MorrF (Minoxidil + Finasteride) or Minoxidil alone

Global photographic assessment seven-point scale was used to assess the pre and post treatment appearance of the scalp in Androgenetic Alopecia patients by photography of vertex and superior-frontal area of the scalp. Global Photographic assessment was based on 52 patients (27 patients in MorrF and 25 patients in Minoxidil alone) who completed global photographic assessment score at end point. Significantly more patients treated with MorrF showed greater improvement (Slightly increased, Moderately increased and Greatly increased) in global photographic assessment for hair growth score as compared to those treated with Minoxidil alone (88.9% in MorrF group versus 60.0% in Minoxidil alone group) (Figure 2). The difference between treatment groups was statistically significant treatment ($p < 0.05$) indicating that MorrF had better treatment benefit compared with Minoxidil alone.

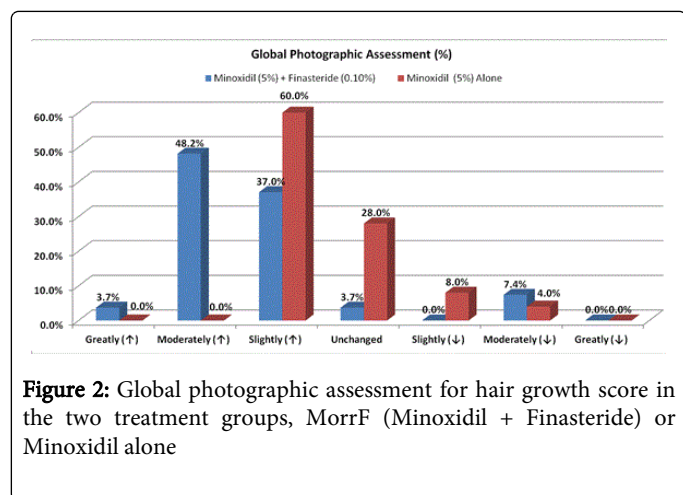


Figure 2: Global photographic assessment for hair growth score in the two treatment groups, MorrF (Minoxidil + Finasteride) or Minoxidil alone

Patients' self-assessment score was also determined. Significantly more patients (30) treated with MorrF showed strongly agree and agree response to balding getting smaller for hair growth and loss by hair growth questionnaire as compared to patients (15) treated with Minoxidil alone. The assessment was based on a total of 36 patients in MorrF group versus 34 patients in Minoxidil group ($p = 0.0008$). The results are presented in Table 3.

Treatment	Bald Score (Balding Getting Smaller)
MorrF	30
Minoxidil	15

	Strongly Agree	Agree	Disagree	No Opinion	Total
MorrF	9	21	2	4	36
Minoxidil	0	15	8	11	34
Total	9	36	10	15	70

Table 3: Patient Assessment of Balding area getting smaller after treatment with MorrF (Minoxidil + Finasteride) or Minoxidil alone

In addition, patients treated with MorrF showed greater satisfaction of the hairline at the front ($p = 0.0023$) and overall ($p = 0.0004$) for hair growth and loss by hair growth questionnaire as compared to those treated with Minoxidil alone. Tables 4 and 5 present patients self-assessment score based on hair growth and slowing down of hairs loss when treated with MorrF or Minoxidil alone.

Treatment	Growth of Hairs Score					
	Greatly increased	Moderately increased	Slightly increased	No change	Moderately decreased	Total
MorrF	14	19	11	5	2	51
Minoxidil	6	16	18	10	1	51
Total	20	35	29	15	3	102

Table 4: Patient's Assessment score of Hair Growth in the two treatment groups, MorrF (Minoxidil + Finasteride) or Minoxidil alone

Treatment	Slowing down hair loss score				
	Very Effective	Effective	Partial Effective	Not effective at all	Total
MorrF	9	23	15	4	51
Minoxidil	5	23	20	3	51
Total	14	46	35	7	102

Table 5: Patient's Assessment score of slowing down of Hair loss in the two treatment groups, MorrF (Minoxidil + Finasteride) or Minoxidil alone

Majority of the patients did not have any adverse event during the trial with MorrF, clinically significant abnormalities during laboratory assessments, vital recordings, ECG recordings etc. No deaths, serious adverse events were reported during the course of the trial. The major side effects of oral Finasteride treatment have been found to be impotence, decreased libido, erectile dysfunction, ejaculation disorders (decreased volume of ejaculate or delayed ejaculation), breast enlargement or tenderness, hypersensitivity reactions (including skin rash, pruritus, urticaria, and swelling of lips and face) and testicular pain [5]. The decreased in the side effects by topical application may be related to lower systemic exposure (ten-fold) compared to oral administration of Finasteride. The topical formulation of Finasteride also prevents the undesirable side effects resulting from greater systemic exposure of Finasteride. With greater efficacy observed with combination of Minoxidil and Finasteride compared to Minoxidil alone, MorrF could be a good replacement of individual therapy by

Minoxidil and Finasteride in patients who are more concerned about the side effects of oral Finasteride.

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