JOHNSON & JOHNSON HEALTHCARE PRODUCTS
DIVISION OF McNEIL-PPC, INC.

CLINICAL STUDY REPORT

Minoxidil, Rogaine™

Protocol Number: MINALO3005

A Phase 3, Multi-Center, Parallel Design Clinical Trial to Compare the Efficacy and Safety of 5% Minoxidil Foam Versus Vehicle in Females for the Treatment of Female Pattern Hair Loss (Androgenetic Alopecia)

Indication Studied:	Female pattern hair loss (androgenetic alopecia)
Developmental Phase of Study:	Phase 3
Study Initiation Date (First Subject Enrolled):	September 27, 2010
Study Completion Date (Last Subject Completed):	August 30, 2011
Status/Date	Final, 8 August 2012
Approvers	Melissa Israel, Associate Director, Clinical Research and Medical Affairs Carlos Quiza, MD, Associate Director, Clinical Research and Medical Affairs Dawn Jackman, Associate Director, Global Regulatory Affairs Paul Zhang, PhD, Associate Director, Biometrics US Clare Kendall, Senior Director, Clinical Research and Medical Affairs

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2. SYNOPSIS

Name of Sponsor/Company Johnson & Johnson Healthcare Products Division of McNEIL-PPC, Inc.	***Individual Study Table Referring to Part of the Dossier***	**(For National Authority Use Only)**
Name of Finished Product: 5% Minoxidil Foam	**Volume:**	
Name of Active Ingredient: Minoxidil	**Page:**	

Title of Study:
A Phase 3, Multi-Center, Parallel Design Clinical Trial to Compare the Efficacy and Safety of 5% Minoxidil Foam Versus Vehicle in Females for the Treatment of Female Pattern Hair Loss (Androgenetic Alopecia)

Investigators:
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Study Centers:
Therapeutics Clinical Research; New York University School of Medicine; David A. Whiting, MD. PA; Minnesota Clinical Study Center; Cleveland Clinic; Callender Center for Clinical Research; Derm Research Center of New York, Inc; J & S Studies Inc.; The Education & Research Foundation, Inc.; Heartland Research Associates, LLC; Michigan Center for Skin Care Research; Axis Clinical Trials (2 different sites); Service de Dermatologie Hôpital Saint Jacques; Klinik für Dermatologie, Venerologie und Allergologie (Clinical Research Center for Hair and Skin Science); Dermaticum Practice for Dermatology; Dermatology Department, The George Eliot Hospital

Publication (reference):
Not available.

Study Period:	**Phase of Development:**
Date of first enrollment: 27 September 2010 Date of last completed: 30 August 2011	Phase 3

Objective:
The objective of this study was to determine the risk/benefit profile of 5% minoxidil topical foam (MTF) formulation applied once daily (OD) for the treatment of female pattern hair loss (FPHL) in comparison to foam vehicle used OD, using objective and subjective efficacy measures and safety assessments.

This study and Study MINALO3004 are 2 pivotal studies conducted in support of the 5% MTF clinical program.

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Methodology:

A minimum of 300 subjects with FPHL were to be enrolled in this randomized, double-blind, vehicle-controlled, multi-center study that involved 17 centers. Subjects were randomized in a ratio of 1:1 to apply no more than a half capful (equivalent to 1 gm) of 5% MTF formulation OD or foam vehicle formulation OD to the scalp area for 24 weeks. Subjects had 7 scheduled visits: a Screening visit, Baseline visit, and interim visits at Weeks 1, 6, 12, 18, and a Final visit (Week 24 or early termination). During the trial, the subject applied the investigational product (IP) according to oral and written instructions.

Primary efficacy was assessed by the change from Baseline in the target area hair count (TAHC), as measured by macro photography at Baseline and Week 24, and subject assessment of scalp coverage from global photographs, as measured by the change from Baseline at Week 24 on a 7-point scale. Secondary efficacy was evaluated by the change from Baseline in TAHC, as measured by macro photography at Baseline and Week 12. Exploratory analyses included an expert panel review (EPR) of hair re-growth based on global photographs, as measured as the change from Baseline at Week 24 on a 7-point scale, and the change from Baseline in the total unit area density (TUAD), as measured by macro photography at Baseline, Week 12 and Week 24.

Safety was assessed at all visits through vital signs, and scalp evaluations for symptoms of irritation. Adverse events (AEs), including self-reported and observed, were recorded at Baseline and at Weeks 1, 6, 12, 18, and 24. Facial assessments were performed to observe any increases in facial hair (hypertrichosis) at Baseline and Week 24, and laboratory tests for the collection of serum minoxidil samples were obtained at screening and as-needed for serious adverse events (SAEs) of cardiac nature or unexpected SAEs.

Number of Subjects (planned and analyzed):

A minimum of 300 female subjects with FPHL were to be enrolled and randomized in the study for a total of 260 subjects to complete the study. At least 16 subjects were to be enrolled per study center across the United States and globally. A total of 404 subjects (201 on foam vehicle and 203 on 5% MTF) were randomized and 351 completed the study.

Diagnosis and Main Criteria for Inclusion:

Subjects had to meet all of the following inclusion criteria to be eligible for enrollment in the study:

- Female, aged 18 or older, in general good health;
- Exhibited FPHL based on a discernable decrease in hair density on the top of the scalp, relative to the sides and back of the scalp, with scalp hair density in involved area D3 to D6 on the Savin Density Scale;
- Women of childbearing potential (included all women unless they were one year post menopause or were previously surgically sterilized by a hysterectomy or oophorectomy, or had a bilateral tubal ligation) had to have a negative urine pregnancy test at the Screening visit;
- Willingness to maintain the same hairstyle, hair color, and hair regimen throughout the study. Hair had to remain a sufficient length to determine hair density. The subject was to discuss with study personnel before any changes were made from Baseline.

Test Product, Dose and Mode of Administration, Batch Number:

The test product used in this study was 5% minoxidil foam (Formula# FDS-W016140-0002) applied OD. Subjects were instructed to dispense no more than half of a capful (equivalent to 1 gm) of 5% MTF to the scalp at the hair thinning areas. The investigative product was applied for 24 weeks. The batch number for 5% minoxidil foam was BEG-2C.

Duration of Treatment:

Subjects were to apply 5% MTF or foam vehicle for 24 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number:

The reference product used in this study was the foam vehicle (Formula# PD-F-7430) applied OD. Subjects were instructed to dispense half of a capful (equivalent to 1 gm) of foam vehicle to the scalp at the hair thinning areas. The investigative product was applied for 24 weeks. The batch number for the foam vehicle was BGB-C.

Criteria for Evaluation:

Efficacy:

The co-primary efficacy endpoints included the following:

a. Change from Baseline in TAHC at Week 24.
b. Subject assessment of scalp coverage as measured by the change from Baseline at Week 24 on a 7-point scale.

The secondary efficacy endpoint was the change from Baseline in TAHC at Week 12.

Other endpoints which were analyzed for exploratory purposes included the following:

- EPR of hair re-growth as measured by the change from Baseline at Week 24 on a 7-point scale.
- Change from Baseline in TUAD at Week 12 and Week 24.

Safety:

The safety endpoints included the following:

- Evaluation of local intolerance.
- Evaluation of facial hypertrichosis.
- Evaluation of AEs.

Safety was assessed at all visits through vital signs, and scalp evaluations for symptoms of irritation. Adverse events, including self-reported and observed, were recorded at Baseline and at Weeks 1, 6, 12, 18, and 24. Facial assessments were performed to observe any increase in facial hypertrichosis at Baseline and Week 24, and laboratory tests for the collection of serum minoxidil samples were obtained at screening and as-needed for serious adverse events (SAEs) of cardiac nature or unexpected SAEs.

Statistical Methods:

The primary analysis population was the intent-to-treat (ITT) population, which included all randomized subjects who received dispensed IP. All efficacy analysis and safety analysis were based on the ITT population.

Change from Baseline in TAHC at Week 24 was analyzed using analysis of covariance (ANCOVA). The analysis model included treatment and center as factors, and Baseline hair count as the covariate. The treatment differences were estimated, and the 95% confidence intervals of the treatment difference were calculated. The normality assumption of the ANCOVA model was checked using the Shapiro-Wilk test based on the residuals from the model at the significance level of 0.01. If the normality assumption was not satisfied, change from Baseline in TAHC at Week 24 was analyzed using the Wilcoxon rank sum test. For this analysis, Baseline hair count was not adjusted but the center was adjusted using the van Elteren method. The heterogeneity of treatment effects across the centers was explored by including the treatment-by-center interaction in the model. If this interaction effect was significant at the significance level of 0.10, the treatment effects were evaluated within each center separately. The change from Baseline in TAHC at Week 24 was also analyzed by adding the subject's age and menopausal status to the ANCOVA model as covariates to evaluate the sensitivity of the model specifications.

Statistical Methods (continued):

The 7-point scale of subject assessment of scalp coverage at Week 24 was analyzed using ANCOVA. The analysis model included treatment and center as factors, and the subject's age as a covariate. The treatment differences were estimated, and the 95% confidence intervals of the treatment difference were calculated. The normality assumption of the ANCOVA model was checked using the Shapiro-Wilk test based on the residuals from the model at the significance level of 0.01. If the normality assumption was not satisfied, the median scores of subject rating were compared using the Wilcoxon rank sum test. The subject's age was not adjusted, but the center was adjusted using the van Elteren method. The heterogeneity of treatment effects across the centers was investigated by including the treatment-by-center interaction in the model and assessed at the significance level of 0.10. Additionally, the 7-point scale subject assessment score was dichotomized into success (rating of 1, 2, 3) or failure (rating of -3, -2, -1, and 0) and analyzed using logistic regression analysis, with treatment and center as factors and subject's age as a covariate.

Sensitivity analysis was performed to evaluate the impact of missing data on the efficacy results, which included no imputation, single imputation, and multiple imputation of missing data. The change from Baseline in TAHC at Week 12 was analyzed using ANCOVA. The analysis model included treatment and center as factors, and the Baseline hair count as a covariate. The treatment differences were estimated and the 95% confidence intervals of the treatment difference were calculated.

Total unit area density (measured as the total non-vellus hair diameters in 1 cm^2 area) was measured at Baseline, Week 12, and Week 24. The change from Baseline in TUAD was analyzed using ANCOVA at each time point separately in a similar way as for the change from Baseline in TAHC. The analysis model included treatment and center as factors, and the Baseline TUAD as the covariate. EPR was performed at Week 24. The median of the 3 experts score was used as the final assessment score. EPR score was analyzed using ANCOVA. The analysis model included the treatment and center as factors, and the subject's age as the covariate.

Safety data included the subject's weight, blood pressure and pulse, as well as any evident abnormalities by body system and spontaneous reports of AEs collected at each study visit. Particular attention was directed to the site of application for evidence of irritation (erythema, dryness/scaling, sting/burning, folliculitis, and itching) in the treatment area, and the condition was rated as none, mild, moderate or severe, as well as evidence of facial hypertrichosis. All AEs were reported by treatment group. Summary tables included the number and percentage of subjects with at least one AE overall, and by body system, number and percentage of subjects with at least one drug-related AE, number and percentage of subjects with at least one SAE, number and percentage of subjects who discontinued due to an AE, and the number of deaths. The frequency distribution was provided for local intolerance parameters by study visit and by treatment group.

SUMMARY – CONCLUSIONS

Efficacy Results:

The 5% MTF re-grew 10.8 hairs/cm^2 more than the foam vehicle at Week 12 ($p<0.0001$) and re-grew 9.1 hairs/cm^2 more than the foam vehicle at Week 24 ($p<0.0001$).

The 5% MTF improved scalp coverage, confirmed by both subject self-assessment and the EPR. After 24 weeks of treatment, a 0.69 point improvement over the foam vehicle was observed by subject self-assessment ($p<0.0001$) and a 0.36 point improvement over the foam vehicle was observed by the EPR ($p<0.0001$).

The 5% MTF increased the total non-vellus hair diameters by 657.5 $\mu M/cm^2$ more than the foam vehicle after 12 weeks of treatment ($p<0.0001$) and by 644 $\mu M/cm^2$ more than the foam vehicle after 24 weeks of treatment ($p<0.0001$).

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Safety Results:

Overall, the 5% MTF was well tolerated and no safety issues were identified. The incidence, severity, and nature of AEs were similar to those observed with foam vehicle.

The most commonly experienced AEs (occurring in ≥5.0% of subjects) in the 5% MTF and foam vehicle groups were weight increase (8.4% and 7.0%, respectively) and nasopharyngitis (5.4% and 6.5%, respectively).

The percentage of subjects with at least one drug-related AE was 8.9% in the 5% MTF group and 4.5% in the foam vehicle group. The most commonly experienced drug-related AEs in the 5% MTF group were pruritus (3 subjects), weight increased (3 subjects), dry skin (2 subjects), and eczema (2 subjects). The most commonly experienced drug-related AEs (occurring in ≥2 subjects) in the foam vehicle group were weight increase (4 subjects) and pruritus (3 subjects).

Most AEs in both the 5% MTF and foam vehicle groups were mild or moderate in severity.

Hypertrichosis was recorded as an AE for one subject in both the 5% MTF group and foam vehicle group.

Similar percentages of subjects in the 5% MTF group (3.0%) and the foam vehicle group (2.0%) experienced at least one SAE. No SAE was considered by the investigator to be related to IP.

Two subjects in the 5% MTF group died during the study due to non-IP-related cause.

A slightly larger percentage of subjects in the 5% MTF group (3.9%) compared to subjects in the foam vehicle group (<1.0%) withdrew from the study due to AEs.

One 5% MTF subject and one foam vehicle subject had cardiovascular SAEs reported during the study. Serum minoxidil levels were <0.250 ng/mL for each of these subjects at Screening and after the reported SAEs.

No clinically significant vital signs were observed in either treatment group during the study.

A low incidence of scalp irritation and hypertrichosis was observed, with no clinically significant differences between 5% MTF and foam vehicle.

Conclusions:

This study demonstrated that 5% MTF formulation applied OD provided clinically relevant benefits to the subjects who suffered from FPHL. These benefits included:

- Promoted hair re-growth
  The 5% MTF re-grew 10.8 hairs/cm^2 more than the foam vehicle after 12 weeks of treatment ($p<0.0001$) and 9.1 hairs/cm^2 more than the foam vehicle after 24 weeks of treatment ($p<0.0001$).
- Improved scalp coverage
  Improved scalp coverage was observed by both subject self-assessment and the EPR. After 24 weeks of treatment, the 5% MTF demonstrated a 0.69 point improvement over the foam vehicle by subject self-assessment ($p<0.0001$) and a 0.36 point improvement over the foam vehicle by the EPR ($p<0.0001$).
- Increased hair density
  The 5% MTF increased the total non-vellus hair diameters by 657.5 μM/cm^2 more than the foam vehicle after 12 weeks of treatment ($p<0.0001$) and by 644 μM/cm^2 more than the foam vehicle after 24 weeks of treatment ($p<0.0001$).

The 5% MTF was well tolerated and no safety issues were identified.

Date of the Report: 11 May 2012

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