1. TITLE PAGE

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

CLINICAL STUDY REPORT

Minoxidil, Rogaine™

Protocol Number: MINALO3004

A Phase 3, Multi-Center, Parallel Design Clinical Trial to Compare the Efficacy and Safety of 5% Minoxidil Foam Versus 2% Minoxidil Solution 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):	08 June 2010
Study Completion Date (Last Subject Completed):	13 February 2012
Status/Date	Final, 18 December 2012
Approvers	Melissa Israel, Associate Director, Clinical Research and Medical Affairs Carlos Quiza, MD, Associate Director, Clinical Research and Medical Affairs Lee Evans, 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 2% Minoxidil Solution in Females for the Treatment of Female Pattern Hair Loss (Androgenetic Alopecia)

Investigators:

Prof. Dr. Ulrike Blume-Peytavi; Maria K. Hordinsky, MD; Michael T. Jarratt, MD; Robert T. Matheson, MD; Dr. Andrew Messenger; Elise A. Olsen, MD; Dr. Pascal Reygagne; Janet L. Roberts, MD; Jerry Shapiro, MD, FRCPC; Dow Stough, MD; Leonard J. Swinyer, MD, FAAD, CPI; Eduardo Tschen, MD, MBA.

Study Centers:

Klinik für Dermatologie, Venerologie und Allergologie (Clinical Research Center for Hair and Skin Science, CRC); University of Minnesota (Department of Dermatology); DermResearch, Inc.; Oregon Medical Research Center, PC; Royal Hallamshire Hospital (Department of Dermatology, Clinical Research Facility, Pharmacy Department); Duke University Medical Center; Centre de Santé Sabouraud; NW Dermatology and Research Center; University of British Columbia (Department of Dermatology and Skin Science, The Skin Care Centre); Burke Pharmaceutical Research; Dermatology Research Center, Inc.; Academic Dermatology Associates.

Publication (reference):

Not available.

Study Period:	Phase of Development:
Date of first enrollment: 08 June 2010 Date of last completed: 13 February 2012	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 2% minoxidil topical solution (MTS) used twice daily (BID), using objective efficacy measures and safety assessments.

This study and Study MINALO3005 are 2 pivotal studies conducted in support of the 5% MTF clinical program.

Methodology:

A minimum of 300 subjects with FPHL were to be enrolled in this randomized, active-controlled, multi-center study that involved 12 centers. Subjects were randomized in a ratio of 1:1 to apply no more than a

half a capful (equivalent to 1 gm) of 5% MTF formulation OD or 2% MTS BID to the scalp area for 52 weeks. Subjects had 11 scheduled visits; a Screening visit, Baseline visit, and interim visits at Weeks 1, 6, 12, 18, 24, 32, 40, 48, and a Final visit (Week 52 or early termination). During the trial, the subject applied the investigational product (IP) of either 5% MTF OD or 2% MTS BID 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 macrophotography at Week 24. Secondary efficacy was evaluated by the change from Baseline in TAHC as measured by macrophotography at Week 12. Exploratory analyses included an expert panel review of hair re-growth based on global photographs as measured as the change from Baseline at Week 24 and Week 52 on a 7-point scale, the change from Baseline in the total unit area density (TUAD) as measured by macrophotography at Week 12, Week 24, Week 40, and Week 52, and the change from Baseline in TAHC as measured by macrophotography at Week 40 and Week 52.

Safety was assessed at all visits through vital signs, facial assessments, 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, 24, 32, 40, 48, and 52. Facial assessments were performed to observe any increases in facial hair at all scheduled visits, and laboratory tests for the collection of serum minoxidil samples were obtained at Screening, Week 24, Week 52, and as needed for serious AEs (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 270 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 322 subjects (161 on 2% MTS and 161 on 5% MTF) were randomized and 267 completed the study.

Diagnosis and Main Criteria for Inclusion:

Subjects had to meet all of the following inclusion criteria to be eligible for inclusion 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 1 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 length 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 topical foam (Formula# FDS-W016140-0002) applied OD. Subjects were instructed to dispense no more than a 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 52 weeks. The batch numbers for 5% MTF were BEG-C, BEG 1C, and L0041D3A.

Duration of Treatment:

Subjects were to apply 5% MTF or 2% MTS for 52 weeks.

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

The reference product used in this study was the 2% minoxidil topical solution (Formula# EDP No. 450586) applied BID. Subjects were instructed to dispense a half of a capful (equivalent to 1 mL) of 2% MTS to the scalp at the hair thinning areas. The investigative product was applied for 52 weeks. The batch numbers for the 2% MTS were OA4TR and OA5DH.

Criteria for Evaluation:

Efficacy:

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The primary efficacy variable was the change from Baseline in the TAHC as measured by macrophotography at Week 24.

The secondary efficacy variable was the change from Baseline in TAHC as measured by macrophotography at Week 12.

Analysis of other variables for exploratory purposes was as follows:

- Expert panel review of hair re-growth based on global photographs as measured as change from Baseline at Week 24 and Week 52 on a 7-point scale.
- Change from Baseline in the TUAD as measured by macrophotography at Week 12, Week 24, Week 40, and Week 52.
- Change from Baseline in the TAHC at Week 40 and Week 52.

Safety:

The safety variables for this study included the following:

- Evaluation of local intolerance.
- Evaluation facial hypertrichosis.
- Evaluation of AEs.
- Evaluation of systemic minoxidil levels.

Safety was assessed at all visits through vital signs, facial assessments, 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, 24, 32, 40, 48, and 52. Facial assessments were performed to observe any increases in facial hair at all scheduled visits, and laboratory tests for the collection of serum minoxidil samples were obtained at Screening, Week 24, Week 52, and as-needed for 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 and safety analyses 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 difference was estimated from the analysis model and the 95% confidence interval (CI) of the treatment difference was computed from the analysis model. Non-inferiority of 5% MTF OD to 2% MTS BID was claimed if the lower limit of the 95% confidence interval of (μ_{foam} - $\mu_{solution}$) was greater than -5. 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 change from Baseline in TAHC at Week 24 was analyzed using Wilcoxon rank sum test. For this analysis, there was no adjustment for Baseline hair count, but the center was adjusted by the use of the van Elteren method.

Statistical Methods (continued):

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 difference within each center was evaluated separately to investigate whether the treatment-by-center interaction was quantitative or qualitative.

As a sensitivity analysis, change from baseline in TAHC at Week 24 was also analyzed using ANCOVA with subject's age and menopausal status as additional covariates to evaluate the impact of these 2 covariates on the hair count change.

Analysis of secondary endpoints included the change from Baseline in TAHC at Week 12 and 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.

Analysis of other endpoints included the TUAD that was measured at Baseline, Week 12, Week 24, Week 40, and Week 52. 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.

Change from baseline in TAHC at Weeks 40 and 52 was analyzed using ANCOVA separately. The analysis

model included treatment and center as factors, and the Baseline hair count as the covariate.

Expert panel review was performed at Week 24 and Week 52. The median of the 3 experts' rating of hair re-growth at Week 24 and Week 52 was analyzed using ANCOVA at each time point separately. The analysis model included treatment and center as factors and subject's age as a covariate. The treatment differences were estimated and the 95% confidence intervals of the treatment difference were calculated.

All AEs were reported by treatment group. Summary tables included the number and percentage of subjects with at least 1 AE overall, and by body system, number and percentage of subjects with at least 1 drug-related AE, number and percentage of subjects with at least 1 SAE, number and percentage of subjects who discontinued due to an AE, and the number of deaths.

The frequency of facial hypertrichosis was summarized by treatment and visit. If the hypertrichosis was considered as 'severe', it was recorded as an AE. Any hypertrichosis that was considered undesirable by the subject was also recorded as an AE.

Serum minoxidil level was summarized by descriptive statistics at each collection time point.

Change in body weight from pre-treatment and post-treatment was also summarized by descriptive statistics.

The frequency of topical irritation of application site was summarized by treatment and visit.

SUMMARY - CONCLUSIONS

Efficacy Results:

The 5% MTF re-grew 23.9 hairs/cm^2 after 24 weeks of treatment and was clinically equivalent to 2% MTS which re-grew 24.2 hairs/cm^2 after 24 weeks of treatment. The 95% confidence interval of the treatment mean difference was (-6.0, 5.4).

The 5% MTF improved scalp coverage after 24 weeks of treatment based on the Expert Panel Review of scalp coverage. The adjusted mean scores were 0.66 and 0.60 for the 5% MTF and 2% MTS groups, respectively; treatment difference of 0.06 (95% CI: -0.12, 0.24).

The 5% MTF increased the total non-vellus hair diameters by 1660 uM/cm^2 after 24 weeks of treatment, while the 2% MTS increased the same by 1948 uM/cm^2. The 95% confidence interval of the treatment mean difference was (-697, 120).

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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 2% MTS.

The most commonly (≥5.0% of subjects) experienced AEs in the 5% MTF group were nasopharyngitis (14.3%), weight increased (12.4%), upper respiratory tract infection (9.9%), sinusitis (6.2%), headache (5.6%), urinary tract infection (5.0%), and bronchitis (5.0%). The most commonly experienced AEs in the 2% MTS group were nasopharyngitis (13.7%), headache (9.9%), weight increased (8.7%), sinusitis (7.5%), and upper respiratory tract infection (5.0%).

The percentage of subjects with at least 1 drug-related AE was 10.6% in the 5% MTF group and 11.8% in the 2% MTS group. The most commonly (≥1.0% of subjects) experienced drug-related AEs in the 5% MTF group were pruritus (2.5%), alopecia (2.5%), and hypertrichosis (1.9%). The most commonly experienced drug-related AEs in the 2% MTS group were headache (3.7%), pruritus (1.9%), alopecia (1.2%), and weight increased (1.2%).

Most AEs in both the 5% MTF and 2% MTS groups were mild or moderate in severity.

Hypertrichosis was recorded as an AE for 3 subjects in the 5% MTF group.

No deaths occurred during the study within 30 days after the last dose of IP. However, 1 subject in the 2% MTS group experienced an SAE of metastatic neoplasm that led to death 140 days after the last dose of IP. A larger percentage of subjects in the 2% MTS group (5.0%) compared to subjects in the 5% MTF group (1.2%) experienced at least 1 SAE within 30 days after the last dose of IP, and none were considered by the investigator to be related to IP.

Similar percentages of subjects in the 5% MTF group (2.5%) and the 2% MTS group (3.7%) withdrew from study due to AEs.

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

A low incidence of scalp irritation and hypertrichosis was observed, with no clinically important differences between 5% MTF and 2% MTS.

Conclusions:

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

- Promotion of hair re-growth

  The 5% MTF re-grew 23.9 hairs/cm^2 after 24 weeks of treatment and was clinically equivalent to 2% MTS, which re-grew 24.2 hairs/cm^2 after 24 weeks of treatment. The 95% confidence interval of the treatment mean difference was (-6.0, 5.4).

- Improvement in scalp coverage

  The 5% MTF improved scalp coverage after 24 weeks of treatment based on the Expert Panel Review of scalp coverage. The adjusted mean scores were 0.66 and 0.60 for the 5% MTF and 2% MTS groups, respectively; treatment difference of 0.06 (95% CI: -0.12, 0.24).

- An increase in hair density

  The 5% MTF increased the total non-vellus hair diameters by 1660 uM/cm^2 after 24 weeks of treatment, while the 2% MTS increased the same by 1948 uM/cm^2. The 95% confidence interval of the treatment mean difference was (-697, 120).

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

Date of the Report: 21 September 2012