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ORIGINAL ARTICLE

Assessing therapeutic effectiveness of scalp treatments for dandruff and seborrheic dermatitis, part 1: a reliable and relevant method based on the adherent scalp flaking score (ASFS)

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***Background*: Dandruff and seborrheic dermatitis (D/SD) are common and troublesome scalp conditions with the primary signs and symptoms being presence of skin flakes, pruritus, a tight feeling, and sometimes erythema. *Aim*: To demonstrate the reliability and relevance of a clinical model for the assessment of therapeutic efficacy of a treatment using the Adherent Scalp Flaking Score (ASFS) method to quantitate the flaking severity. *Methods*: Six randomized, double-blind, parallel design studies were conducted in either North America or Asia with subjects suffering from dandruff using the ASFS grading method before and after a 3-week test product treatment period. *Results*: Treatment with a commercial potentiated 1% zinc pyrithione (ZPT) shampoo resulted in statistically significant ($p < 0.0001$) improvements in total ASFS compared with the placebo cosmetic shampoo. Results were consistent across all studies, geographies, and product usage protocols (controlled on-site versus home use conditions), and were associated with statistically significant improvements in self-perception of scalp condition. *Conclusion:* The ASFS-based clinical model was demonstrated to be a reliable and proven methodology to assess the effectiveness of widely used anti-dandruff treatments. The results are consistent with patient self-assessments, establishing this methodology as relevant to patient perception of product benefits.**

Key words: adherent scalp flaking score (ASFS), anti-dandruff shampoo, dandruff, scalp, seborrheic dermatitis, therapeutics, clinical method, expert grading

Introduction

Dandruff and seborrheic dermatitis (D/SD) are scalp conditions with the primary signs and symptoms of appearance of skin flakes frequently accompanied by pruritus, a tight feeling, and sometimes erythema. While not completely understood, the etiology involves metabolic activity of commensal *Malassezia* organisms acting upon sebaceous lipids to release fatty acids that initiate inflammation, hyper-proliferation, and barrier disruption (1-5). The condition is quite common in post-pubescent adults, affecting approximately 50% of the population, irrespective of gender, race, or nationality (6,7). As bothersome as the signs and symptoms are, the psycho-social implications should not be overlooked. Accompanying this condition is frustration that it cannot be permanently cured leading to a reduced quality of life when appropriate preventative measures are not taken (8,9).

The development of effective technologies for treating D/SD requires relevant and dependable methods for the quantitation of the condition of the scalp and assessment of therapeutic resolution. There are many potential targets that may be indicative of the state of dandruff; the presence and level of skin flakes is a common approach. The benefits of this measurement include direct observation, instantaneous results, and that it represents one of the hallmark signs of the condition. However, the specific clinical design parameters and detailed method for quantitation of degree of flaking that lead to relevant and dependable results are not trivial. Critical clinical design parameters include: how to identify a relevant and sensitive population, inclusion/exclusion criteria, appropriate population size relative to the assessment sensitivity, and maintenance of blindedness. From the flaking measurement point of view, critical parameters include: the identification and training of experts skilled in quantifying their observations, an algorithm leading to a global score, qualification of the experts, and assurance that the assessment measures patient-relevant outcomes.

We report here a relevant and reliable clinical methodology for assessing the D/SD condition and the effectiveness of therapeutic products. Standardization of this methodology will benefit both the clinician and patient, assuring that products which claim efficacy will deliver the intended benefits.

Methods

The studies were conducted under good clinical practice guidelines in accordance with the US 21CFR 312.66 and the International Conference on Harmonisation guidelines (ICH). All studies received approval from Institutional Review Boards prior to study execution.

ASFS grading method

Assessment of D/SD flaking severity was performed using the Adherent Scalp Flaking Score (ASFS) method by qualified graders. With this method, a subject is positioned on a swivel stool and the scalp area under examination is illuminated by lighting that mimics daylight conditions. To grade dandruff severity, the scalp is divided into eight sections (Figure 1). A comb is used to part the hair in each area to give a clear view of the scalp. Each section is assessed for the presence of dandruff flakes that are adhering to

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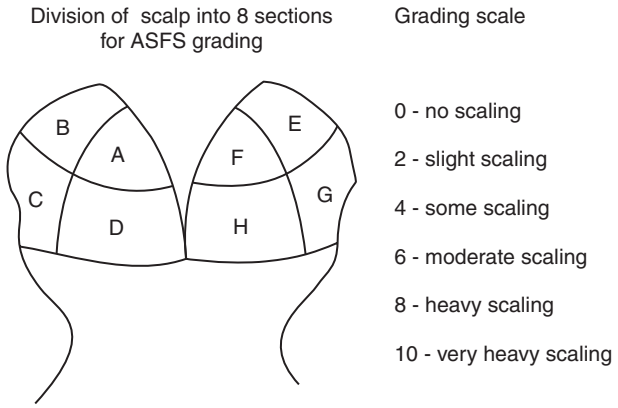

Figure 1. Adherent Scalp Flaking Score (ASFS) grading method.

the scalp skin using a 0 to 10 (increment of 2 units) scale. Loose flakes in the hair are not considered in the grading. The final, or total, ASFS is the sum of the grades for all eight scalp sections, which results in a scale ranging from 0 to 80 units. Graders were qualified on the ASFS method on the basis of high intergrader correlation with the reference grader.

The visual grading of D/SD flaking severity by expert graders using the ASFS method has been utilized successfully in several published trials to measure anti-flaking efficacy of anti-dandruff shampoos (2,10-14) and was used in the present studies at baseline and after 3 weeks of test product treatment.

Study design

Several studies using essentially the same basic study design were performed to compare the effect of treatment with the anti-dandruff shampoo versus a placebo cosmetic shampoo using the ASFS method to quantitate the dandruff condition. All were randomized, double-blind, parallel design studies conducted in subjects suffering from D/SD and included a 2-week pre-treatment washout period followed by 3 weeks of product treatment. During the washout period, subjects shampooed their hair at least three times per week using a standard placebo cosmetic shampoo. The baseline visit included ASFS measurements and self-perception assessment questionnaires designed to capture subject-relevant outcomes (e.g., severity of scalp flaking) using a categorical scale that varied from "none" to "very severe." Subjects who met the inclusion/exclusion criteria were randomized to a treatment group and used only the assigned test product for hair washing during the treatment period. Subjects were asked to refrain from shampooing and using any hair styling products prior to scheduled visits during which they underwent ASFS measurements and completed self-assessment questionnaires. Subjects were not permitted to use other anti-dandruff preparations or hair conditioners, scalp treatment products, scalp sunscreens, hair relaxers, permanent waves, bleaches, or hair colorants during the test product treatment period.

Subject population

Healthy male and female subjects from 18 to 65 (Studies 1 and 2) or 18 to 75 (Studies 3–6) years of age who suffered from dandruff were recruited from the general population at sites in North America and Asia (Table I). Potential subjects were initially screened using a medical history questionnaire then assessed by qualified dandruff graders using the ASFS measurement to quantitate D/SD flaking severity. To participate in a study, subjects had to have an ASFS ≥24 at the baseline visit. Subjects were excluded if they had concomitant skin diseases of the scalp; significant scalp scarring; a history of skin cancer; history of allergic reaction to shampoos, perfumes or topically applied hair care products; taken oral anti-fungal or immunosuppressant agents or any chronic anti-inflammatory or chronic anti-histamine drugs within 4 weeks prior to baseline; used anti-dandruff, anti-psoriatic or anti-seborrheic dermatitis shampoos and/or treatment products within 2 weeks prior to baseline; a significant medical condition or was on chronic medication considered exclusionary.

Test products

The test product used in the studies was a commercial potentiated 1% zinc pyrithione (ZPT)-based anti-dandruff shampoo (Head & Shoulders, manufactured by The Procter & Gamble Company). Zinc pyrithione (ZPT) is a commonly used anti-dandruff material throughout the world. The placebo cosmetic shampoos used was a commercial non-medicated shampoo (Pantene, manufactured by The Procter & Gamble Company) (Table I).

Assigned products were applied using a home washing regimen (Studies 1 and 2) or an on-site controlled washing regimen (Studies 3–6). For the home washing regimen, subjects were instructed to shampoo their hair according to clinical label instructions. For the on-site regimen, a fixed amount of test product was applied to the subject's scalp by study personnel at the clinical site three times per week on specified days for 3 weeks. After product application, each subject massaged the shampoo into their scalp and rinsed as directed. Subjects who participated in the on-site regimen were not permitted to wash their hair at home.

Statistical analysis

The change from baseline in total ASFS was compared between the treatment groups using an analysis of covariance (ANCOVA). Appropriate study design parameters were included in the model. Two-sided p-value < 0.05 was considered significant. All statistical analyses were conducted using SAS (SAS Institute Inc., Cary, North Carolina, USA). The reproducibility between graders was compared using the intraclass correlation coefficient.

Results

ASFS method reliability: reproducible demonstration of the efficacy of a 1% potentiated ZPT shampoo

A summary of the change from baseline ASFS data for all six studies is summarized in Table I and Figure 2. For each study, the potentiated ZPT treatment was significantly more effective ($p < 0.0001$) than the placebo control for that study. As expected for clinical studies, there is variability in absolute responses, likely related to population and environmental differences between studies, necessitating the appropriate comparative controls within a study.

ASFS method relevance: self-perception assessments

Representative data from self-perception assessment questionnaires completed for Studies 3 and 4 revealed statistically significant reductions (Study 5 achieved a p-value of 0.056) in the severity of self-perceived scalp flaking at week 3 in subjects who used the 1% ZPT shampoo compared with the placebo cosmetic shampoo (Table II). Studies 1, 2, and 6 did not include flaking severity self-assessments. These reductions coincided with the improvements observed in dandruff severity based on the ASFS grading method.

ASFS method reproducible across graders: intraclass correlation coefficient

To demonstrate the reproducibility of the ASFS method, we evaluated the correlation between the reference grader and

Table I. Study design, demographic, and total Adherent Scalp Flaking Score (ASFS) data.

Study	Region	Washout procedure	Baseline mean (SD) age (years)	Treatment regimen	Treatment	Baseline sample size (female/male)	ASFS week 3 mean change from baseline (SE)	*p*-Value
1	North America	Placebo for at least 2 weeks	43.1 (12.5)	At home at least 3×/wk	1% ZPT shampoo	146 (54/92)	−18.6 (0.89)	< 0.0001
					Placebo	25 (13/12)	−3.4 (1.92)	
2	North America	Placebo for at least 2 weeks	40.6 (11.9)	At home every time you shampoo	1% ZPT shampoo	133 (45/88)	−12. 8 (1.08)	< 0.0001
					Placebo	21 (10/11)	−2.1 (2.20)	
3	Asia	Placebo 3×/week for 2–3 weeks	42.0 (8.3)	On site 3×/wk	1% ZPT shampoo	120 (99/21)	−19.6 (0.76)	< 0.0001
					Placebo	60 (51/9)	−10.9 (1.01)	
4	Asia	Placebo 3×/week for 2–3 weeks	44.3 (8.1)	On site 3×/wk	1% ZPT shampoo	90 (77/13)	−18.2 (0.80)	< 0.0001
					Placebo	45 (37/8)	−11.4 (1.01)	
5	Asia	Placebo 3×/week for 2 weeks on site wash	44.1 (9.7)	On site 3×/wk	1% ZPT shampoo	77 (59/18)	−16.0 (0.73)	< 0.0001
					Placebo	75 (58/17)	−10.3 (0.72)	
6	Asia	Placebo 3×/week for 2 weeks	38.9 (9.0)	On site 3×/wk	1% ZPT shampoo	120 (107/13)	−14.8 (1.03)	< 0.0001
					Placebo	60 (54/6)	−6.6 (1.30)	

SD = standard deviation; SE = standard error; ZPT = potentiated 1% zinc pyrithione shampoo.
p-Values are based on analysis of covariance comparing treatment groups.

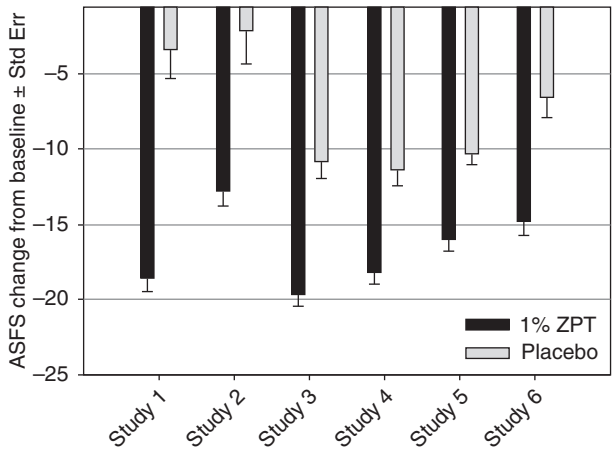

Figure 2. Change from baseline in total ASFS after 3 weeks of treatment with potentiated ZPT shampoo. The results are reported as mean ± SE.

secondary graders, if present. Study 3 was one of the studies used for this purpose using the statistical measure of intraclass correlation. In this case, high intraclass correlation coefficients between the graders at baseline (0.78), week 3 (0.85), and week 3 change from baseline (0.80) were observed. Similarly, Study 6 demonstrated high intraclass correlations: baseline (0.84), week 3 (0.78), and week 3 change from baseline (0.75). These findings demonstrate the dependability of the ASFS grading method.

Sample sizing considerations based on the ASFS method

Proper sample size is an essential component of designing a good clinical study. A conventional clinical trial with a single primary endpoint sets the probability of Type I error at 5% ($\alpha = 0.05$) and Type II error at 10–20% (15). In the studies we conducted, the average standard deviation for ASFS scores was approximately 9. Using this standard deviation value together with required α (0.05), desired power (80%) and the expected ASFS difference allows for the calculation of the minimum sample size that takes into account both Type I and Type II errors. Such upfront statistical consideration is a hallmark of a well designed clinical study. Figure 3 depicts minimum base size required per treatment group to detect a range of ASFS differences based on these parameters. A specific choice of ASFS difference depends on the anticipated treatment difference with larger sample size needed to discriminate a smaller difference in ASFS.

Discussion

In these studies, we demonstrated the development of a robust, reliable, and relevant clinical methodology for assessing the severity of D/SD based on the ASFS grading method and the effectiveness of therapeutic products designed to alleviate this troublesome condition. In particular, statistically significant improvements in ASFS were observed in D/SD sufferers who used the commercial potentiated 1% ZPT shampoo compared with the placebo shampoo. These results were consistent across all six studies, geographies (North America and Asia), and product exposure regimens (controlled on-site versus home use conditions) providing strong evidence for the robustness of the reliability of the method.

As with most clinical methods, placebo effects were observed. Such effects are frequently the result of changes from normal

Table II. Self-perceived scalp dandruff (flaking) at week 3 from representative studies.

	Treatment	*n*	Week 3 adjusted mean	Week 3 adjusted mean change from baseline	Standard error	*p*-Value
Study 3						
How would you rate severity of your flaking today?	1% ZPT shampoo	119	1.39	−1.02	0.072	0.035
	Placebo	60	1.62	−0.79	0.096	
Study 4						
Rate severity of your scalp flaking over last 24 h	1% ZPT shampoo	89	1.28	−1.45	0.117	0.0002
	Placebo	45	1.91	−0.82	0.15	
Study 5						
Rate severity of your scalp flaking over last 24 h	1% ZPT shampoo	75	1.34	−1.02	0.118	0.0563
	Placebo	77	1.65	−0.71	0.117	

ZPT: potentiated 1% zinc pyrithione shampoo.
In Study 3, a categorical scale was used in which 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. In Study 4 and 5, a categorical scale was used in which 0 = none, 1 = slight, 2 = slight to moderate, 3 = moderate, 4 = moderate to severe, 5 = severe, and 6 = very severe. *p*-Values are based on analysis of covariance.

routine in habits and practices of the subjects following study-related instruction and procedures. In these studies, subjects may have increased their typical shampoo frequency resulting in a scalp care benefit even if it was an unmedicated shampoo. Even though placebo controls will, in some cases, demonstrate activity, this method has sufficient sensitivity to regularly discriminate the active treatment from the placebo.

The robustness and reliability of the method are only useful if the method quantifies attributes relevant to the desired outcome of the users of the treatment. The hallmark characteristic of the D/SD condition is the presence of flakes or scales (16). The ASFS data coincided with statistically significant improvements in self-perception of the degree of flaking and therapeutic benefits of the treatment. The ASFS results reported here are consistent with improvements in biomarkers of scalp condition (11,12) as well as other previously published studies quantifying improvements in the dandruff condition after treatment based on the ASFS method (10).

A reliable procedure for objectively quantifying the D/SD condition is required for evaluation of therapeutic activity of treatment products. We believe that the ASFS method of scoring the degree of scalp scaling and the rigor in which it is applied is more sensitive and more able to detect changes in dandruff severity than other measures. The graders used in these studies underwent a rigorous training program and were qualified on the basis of high intergrader correlation with the reference grader using total ASFS as one of the endpoints for comparison. This method results in a global score that can reliably detect changes in the dandruff condition and differentiate between treatment effects and placebo as well as between other therapeutic products (10). The ASFS method is highly reliable if properly applied, providing the reproducible results on independently repeated trials under the same dandruff conditions, and is not dependent on a specific grader, site of evaluation, or time of year. Moreover, as ASFS scores improve with treatment, improvements in self-reported scalp flaking severity are also observed, providing evidence of the validity of this grading method in measuring patient-relevant outcomes. When this method is used as part of a clinical program that focuses attention on critical design elements, such as identification of a relevant and sensitive population, control of product usage, maintenance of blinded treatment assignment, and proper estimation of sample size, sound assessment of anti-dandruff therapeutic technologies can be devised.

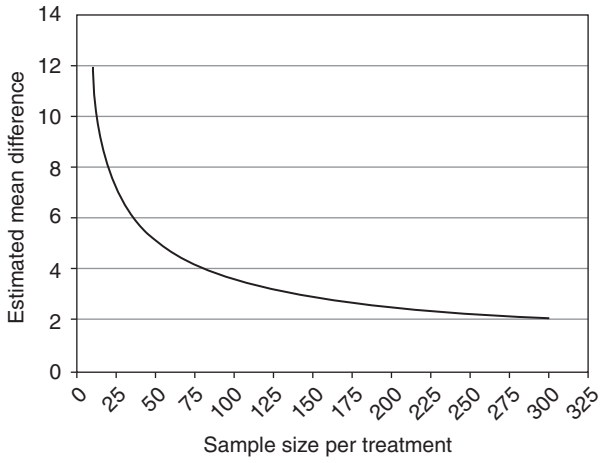

Figure 3. Sizing considerations as a function of expected magnitude of difference in ASFS between treatments. Proper parameters are 80% power, $\alpha = 0.05$, two-sided.

A critical clinical design element is the number of people per treatment enrolled in the study. This number should always be large enough to provide a reliable answer to the question addressed. Too few subjects increases the probability of Type II error, potentially resulting in a false-negative result. On the other hand, a positive result in an under-sized study is vulnerable to generating a conclusion that is at risk of not being repeatable. Grading of flakes by this, or any other approach, has an inherent variability; in these studies, a typical standard deviation is approximately 9. Knowing this variability and the typical clinical design characteristics (80% power with two-sided $\alpha = 0.05$) allows one to gauge the number of subjects required for a given predicted ASFS difference between treatment groups. A sufficient sample size is especially important when evaluating the difference between two relatively effective treatments which often require base sizes in excess of 250 per treatment.

In conclusion, the ASFS-based clinical protocol was proven to reliably demonstrate the effectiveness of a commercial potentiated 1% ZPT shampoo against D/SD. The results are consistent with patient self-assessments, establishing this methodology as relevant to patient perception of product benefits. Experience with this method enables a good prediction of expected variability and anticipated treatment difference upon which sufficiently powered clinical designs can be devised to yield reproducible results.

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References

1. Ashbee H, Evans E. Immunology of diseases associated with Malassezia species. Clin Microbiol Rev. 2002;15:21–57.
2. Warner R, Schwartz J, Boissy Y, Dawson TL Jr. Dandruff has an altered stratum corneum ultrastructure that is improved with zinc pyrithione shampoo. J Am Acad Dermatol. 2001;45:897–903.
3. Harding C, Moore A, Rogers J, Medrum H, Scott AE, McGlone FP. Dandruff: a condition characterized by decreased levels of intercellular lipids in scalp stratum corneum and impaired barrier function. Arch Dermatol Res. 2002;294:221–230.
4. Rogers J, Moore A, Meldrum H, Harding CR. Increased scalp skin lipids in response to antidandruff treatment containing zinc pyrithione. Arch Dermatol Res. 2003;295:127–129.
5. Suszcynsky-Meister E, Kincaid E, Copas M, Burton DE, Mills KJ, Ceramide insufficiency in dandruff/seborrheic dermatitis is reversed by potentiated micronized platelet pyrithione zinc shampoo treatment. J Am Acad Dermatol. 2008;58:AB41.
6. Schwartz J, Cardin C, Dawson T Jr. Dandruff and seborrheic dermatitis. In: Barran R, Maibach H, editors. Textbook of cosmetic dermatology. 3rd ed. New York: Taylor & Francis; 2005. p 259–272.
7. Saint-Leger D. Dandruff (pityriasis capitis simplex): of yeasts and men. In Bouillion C, Wilkinson J, editors. The Science of hair care. 2nd ed. New York: Taylor & Francis; 2005. p 609–631.
8. Szepietowski J, Reich A, Weslowska-Szepietowska E, Baron E. Quality of life in patients suffering from seborrheic dermatitis: influence of age, gender and education level. Mycoses. 2008;52:357–363.
9. Misery L, Touboul S, Vincot C, Dutray S, Rolland-Jacob C, Consoli SG, et al. Stress and seborrheic dermatitis. Ann Dermatol Venereol. 2007; 134:833–837.
10. Billhimer W, Bryant P, Murray K, Coffindaffer TW, Rains GY, Amon RB, Hickman JG, Reed BR. Results of clinical trial comparing 1% pyrithione zinc and 2% ketoconazole shampoos. Cosmet Dermatol. 1996;9:34–39.
11. Kerr K, Darcy T, Henry J, Fieno A, Wehmeyer K, Szepietowski J, Mills KJ. A description of epidermal changes associated with symptomatic resolution of dandruff: biomarkers of scalp health. Int J Dermatol. 2011;50:102–113.
12. Kerr K, Schwartz J, Filloon T, Mizoguchi H, Schwartz JR, Morrall S, Filloon T, Mills KJ. Scalp stratum corneum histamine levels: Novel sampling method reveals correlation to itch resolution in dandruff/seborrheic dermatitis. Acta Derm Venereol. 2011;91:404–408.
13. Gemmer C, DeAngelis Y, Theelen B, Boekhout T, Dawson TL Jr. Fast, noninvasive method for molecular detection and differentiation of Malassezia yeast species on human skin and application of the method to dandruff microbiology. J Clin Microbiol. 2002;40:3350–3357.
14. Perkins M, Cardin C, Osterhues M, Robinson MK. A non-invasive tape absorption method for recovery of inflammatory mediators to differentiate normal from compromised scalp conditions. Skin Res Technol. 2002;8:187–193.
15. Anonymous. Guidance for industry. E9 statistical principles for clinical trails. Fed Regist. 1998;63:49583–49598.
16. Schwartz R, Janusz C, Janniger C. Seborrheic dermatitis: an overview. Am Fam Physician. 2006;74:125–130.