

# Efficacy and Safety of a Topical Pediatric Gel in Infants with *Pityriasis capitis*: A Randomized Phase III Controlled Trial

Patrice Plantin<sup>1</sup>, Virginie Ribet<sup>2\*</sup> and Sayda Ben Becher<sup>3</sup>

<sup>1</sup>Dermatologist and Pediatrician, Head of Dermatology Unit, Centre Hospitalier de Cornouaille, France

<sup>2</sup>Head of Clinical Development, Skin Research Center, Hôtel Dieu Saint-Jacques, Pierre Fabre Dermocosmetics, Toulouse, France

<sup>3</sup>Pediatrician, Head of Pediatric Unit, Bashir Hamza Children's Hospital, Bab Saadoun Children's Hospital, Tunisia

\*Corresponding author: Virginie Ribet, Center for Skin Research, Hôtel Dieu Saint-Jacques, Pierre Fabre Dermocosmetics, Toulouse, Tel: +3356248 8594, Fax: +3356248 8507; E-mail: [virginie.ribet@pierre-fabre.com](mailto:virginie.ribet@pierre-fabre.com)

Received date: October 27, 2016; Accepted date: January 02, 2017; Published date: January 08, 2017

Copyright: © 2017 Plantin P, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## Abstract

**Objective:** Cradle cap is a multifactorial pediatric skin condition characterized by inflammation, irritation, and scalp flaking. The aim of this international, phase III, open-labeled, randomized, parallel-group study was to demonstrate the efficacy and safety of a pediatric gel (spring water, glycerol, panthenol, lactamide, PEG-60 almond glycerides, zinc sulfate), in addition to standardized hygiene, in infants suffering from cradle cap and/or mild to moderate seborrheic dermatitis.

**Methods:** During the 6 week study period, infants were randomly assigned to receive the study gel (gel group, n=65), applied before a standardized shampoo every day from the inclusion visit on Day 0 to Day 7 and every second or third day from Day 8 to Day 42, or only the daily shampoo (control group, n=62). Due to the absence of a published reference score, a total lesion score (combining measures of both the area involved and scale severity in each scalp quadrant; range 0-64) was used to evaluate efficacy.

**Results:** Significantly greater improvements in the total lesion scores were observed in infants from the gel group compared with those in the control group at D7 ( $-12.8 \pm 8.1$  versus  $-8.5 \pm 6.9$ ,  $p=0.002$ ), D21 ( $-18.9 \pm 9.8$  versus  $-14.3 \pm 9.6$ ,  $p=0.009$ ) and D42 ( $-22.3 \pm 10.8$  versus  $-17.5 \pm 9.8$ ,  $p=0.01$ ). Complete recovery was reported in 73% of infants in the gel group, compared with only 50% in the control group ( $p=0.01$ ). "Very good/Good" gel tolerance was observed in more than 98% of infants.

**Conclusion:** The cradle cap gel efficiently reduced Pityriasis capitis from the first post-inclusion visit on day 7 and tolerance was satisfactory in this specific population. This gel, in addition to a daily hygiene routine, provides a good alternative to commonly used treatments. Combined with use of a mild shampoo, it could be used for first line topical care of infants with cradle cap, with or without mild to moderate seborrheic dermatitis.

**Keywords:** Cradle cap; Infants; Mild to moderate seborrheic dermatitis; Pediatric gel; Topical treatment; Randomized controlled trial; Scalp dermatoses.

## Introduction

Dry scalp flaking, dandruff, and seborrheic dermatitis are chronic scalp manifestations of similar etiology but of differing severity. Seborrheic dermatitis (SD) is an inflammatory hyperproliferative dermatosis that affects patients of any age with an incidence of 1 to 3% in adults [1]. Cradle cap, or Pityriasis capitis, is a form of SD that occurs in newborns, most frequently around the age of 3 or 4 months [2-4]. The common etiology is a convergence of three factors: increased sebaceous gland secretions in neonates, cutaneous microflora disequilibrium (mainly involving *Malassezia* yeasts), and individual sensitivity (including a possible primary defect in corneocytes and their precursor keratinocytes favouring *Malassezia*-driven disorders) [5-7]. The pathogenic role of *Malassezia* fungi in SD is related to their ability to increase inflammatory responses through three mechanisms: i) production of lipases and phospholipases that impair epidermal barrier function, ii) an increase in the local

production of interleukins that enhances the local immune response, and iii) sensitization to cross-reactive allergens produced by *Malassezia* yeasts [7].

It is essential to develop safe and well-tolerated measures that can efficiently reduce the morbidity associated with these common skin conditions in very young children. We have developed an anti-cradle cap gel, formulated to reduce inflammation, hyperproliferation, and skin barrier damage. The gel contains 3% lactamide as a keratolytic agent, glycerol and panthenol as moistening agents, 1.5% emollient PEG-60 almond glycerides, 1% zinc sulfate and 65% spring water (well-known for its anti-inflammatory properties both *in vitro* [8-11] and *in vivo* [11-14]). The aim of this study, conducted on French and Tunisian infants suffering from cradle cap and/or mild to moderate SD, was to assess the efficacy and safety of this anti-cradle cap gel. The gel was applied before a standardized shampoo and results were assessed by comparison with use of the shampoo alone.

## Patients and Methods

This international, 25-centre, randomized, open-labeled, parallel-group, 6-week, phase III controlled study was approved by local ethics committees (Brest in France and Tunis in Tunisia) and was conducted in accordance with the local regulations in each country and the ethical principles stated in the Declaration of Helsinki (Tokyo, 2004).

## Participants

Subjects (male or female infants aged from 1 to 12 months, suffering from cradle cap, with a total lesion score (TLS) greater than 12) were enrolled by pediatricians or dermatologists. Patients undergoing treatments affecting the skin (antifungal agents, topical corticosteroids) or those that had used cosmetic products on the scalp in the 7 days preceding the inclusion visit were excluded from the study. Other exclusion criteria were allergies to any of the components of the treatments studied and presence of erythroderma or life-threatening systemic disease. Written informed consent was obtained from the parents of all subjects prior to inclusion in the study.

## Interventions

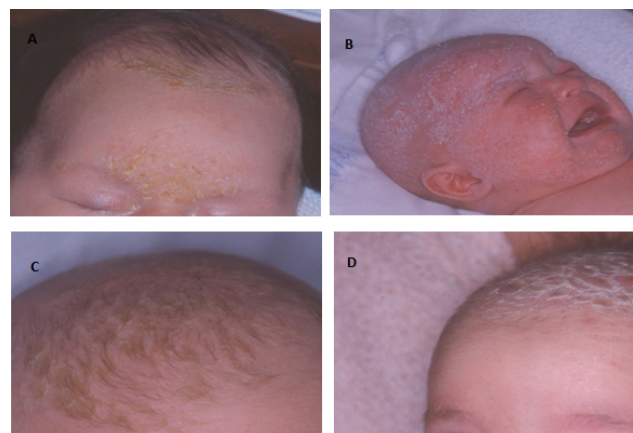
Throughout the whole study, all infants were shampooed daily in standardized conditions. This standardized shampooing consisted of the application of a small ball of study shampoo on wet hair, followed by gentle massage and careful rinsing. Parents of infants in the gel group were asked to use their fingers to spread a small ball of gel over the whole of the infant's scalp, gently massage, and allow the gel to act for 10 minutes before proceeding to the standardized shampooing. This routine was repeated every day during the initial care period from Day 0 to Day 7, and then every second or third day during the maintenance period from Day 8 to Day 42. The first gel application was performed at the inclusion visit by the investigator, in the presence of the parents. At the same visit, parents were supplied with care products for the whole study period, as well as an instruction sheet, and a diary to record any modifications in the rhythm of use of the study shampoo and/or study gel. Both the study shampoo (a mild cleansing complex: "Shampooing doux pour bébé", France) and the study gel were formulated for pediatric use. Moreover, the gel was hypoallergenic, non-comedogenic and free from perfumes, colorants and parabens (Laboratoires Dermatologiques Avène - France).

Neither the shampoo nor the gel was applied the day before an examination. Use of any other cosmetics (e.g. any other shampoo, sweet almond oil) onto the scalp was strictly forbidden.

## Measurements

**Assessment visits:** Following the inclusion visit (D0), three subsequent study visits were planned on Day 7 (D7), Day 21 (D21) and Day 42 (D42).

**Total lesion score (TLS):** TLS was assessed by the investigator at each visit. This score was designed specifically for this study due to the absence of a published reference score. The TLS ranged from 0-64 and was obtained from the sum of four quadrant sub-scores. The quadrant sub-scores ranged from 0 to 16 and were calculated as the product of the grade according to percentage area involved (0=[0-10%], 1=[10-30%], 2=[30-50%], 3=[50-70%] and 4=[70-100%]) and the grade according to scale severity (1=thin and sparse, 2=thin and confluent, 3=thickened and sparse, 4= thickened and confluent, Figure 1).



**Figure 1:** Four grades of scale severity; A) Grade 1: Thin and sparse scales; B) Grade 2: Thin and confluent scales; C) Grade 3: Thickened and sparse scales; D) Grade 4: Thickened and confluent scales.

## Efficacy evaluation criteria

For efficacy outcomes, every missing value at a visit was replaced by the previous visit value.

**Primary outcome:** The primary outcome measure for evaluating the efficacy of the gel was the change in TLS between D0 and D42  $\pm 9$  in the intention to treat (ITT) data set (all infants who received at least one dose of the pediatric gel with at least one post-baseline assessment of the TLS).

**Secondary outcomes:** Change in TLS between D0 and D42  $\pm 9$  assessed in a per protocol (PP) set (all subjects of the ITT set without major protocol deviation, i.e. violation of study conduct, discontinuation of gel application on a part or totality of the scalp for 9 consecutive days and/or a total of 11 days, use of forbidden concomitant treatments and/or cosmetics) was a secondary outcome measure. Other secondary outcomes were changes in erythema and discomfort signs, which were evaluated at all visits by both the investigator and the parents according to 4-point scales (0=Absent, 1=Mild, 2=Moderate and 3=Severe).

Global efficacy of the gel was also assessed by the investigator and the parents at D42 (1=Recovery, 2=Improvement, 3=Worsening with the need to treat again and 4=Not assessable).

## Tolerance

The investigator rated global tolerance at each study visit as Very good, Good, Poor, or Very Poor, and assessed compliance at each post-inclusion visit by checking the data recorded in parents' diary, and at the end of study by verifying the quantity of gel remaining in the tubes brought back by parents. Adverse events and concomitant treatments were also recorded by the investigator at each visit.

## Sample size

The sample size was determined on the basis of the expected difference in primary outcome (TLS), as follows: expected improvement of 60% in the pediatric cradle cap gel group *versus* 30%

in the control group (mild cleansing shampoo) ( $\alpha$ -risk 5%,  $\beta$  -risk 10%). The target number of subjects to be included in each group was 56, i.e. a total of 112 subjects. We chose to include 4 additional subjects in each group, i.e. 120 subjects.

## Randomization

Infants were randomized according to a computerized list of randomization, with a 1:1 ratio and in chronological order of inclusion to either the gel group or the control group.

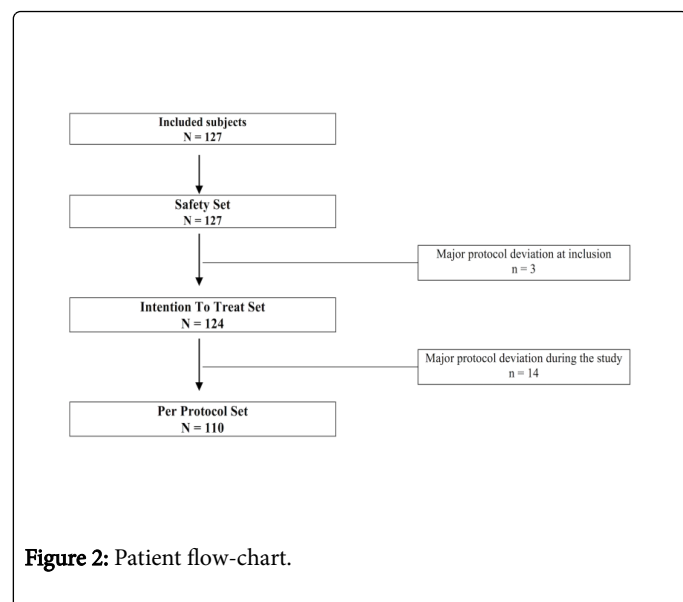
## Statistical analysis

At baseline (D0), infants' characteristics were compared using the Chi-square test or Fisher's exact test for qualitative criteria, and the Student's T-test for independent samples of quantitative variables. The TLS was assessed using the Student's T-test and Wilcoxon test due to a non-normal distribution. Between-group comparison of the change from baseline for erythema and discomfort signs was performed using the Cochran-Mantel-Haenszel test. Within groups, time effect was assessed using the Wilcoxon's test for paired samples for the TLS, and the McNemar's test for erythema and discomfort signs. The type-I error was two-sided and fixed at 0.05.

## Results

### Participants

From February to October 2005, 65 infants were randomized into the pediatric gel group and 62 to the control group (Figure 2). Three subjects from the gel group had a major protocol deviation at inclusion: 2 infants had sweet almond oil or olive oil applied to the scalp within the 7 days preceding inclusion, and one was only 15 days old at the first visit. These subjects were excluded from the ITT set.



Fourteen patients were excluded from the PP set. In the gel group, 2 infants were withdrawn after their parents decided to end the treatment prematurely after almost 1 month of care, and 5 other infants were excluded due to major protocol deviations (8-day delay to last visit, treatment with amoxicillin for rhinopharyngitis and

laryngitis). In the control group, 1 infant was withdrawn after 6 days due to a serious adverse event (independent left lobar pneumonia treated with antibiotics) and 6 others were excluded due to protocol deviations (9-day delay to last visit, treatment with oral corticosteroids for tracheitis and bronchiolitis, treatment for scabies with topical crotamiton). With regard to compliance, the gel was applied as requested in the protocol in all but 14 infants, due to complete recovery in 8 subjects, non-medical reasons for 3 subjects and adverse events in 3 subjects (rotavirus diarrhea, 2 episodes of pruritus, vaccination).

### Patient characteristics at baseline

No relevant differences in demographic data or baseline characteristics (Table 1) were observed between the gel and control groups ( $p > 0.05$  for all variables).

Characteristics	Gel group (N = 63)	Control (N=61)	group	p-value <sup>s</sup>
Gender, n (%)				
Male	33 (52.4)	39 (63.9)		0.19 <sup>a</sup>
Female	30 (47.6)	22 (36.1)		
Age (months)				
Mean ± SD	4.4 ± 2.8	4.0 ± 2.7		0.41 <sup>b</sup>
Min – Max	1-11	1-11		
Weight (Kg)				
Mean ± SD	6.5 ± 2.0	6.2 ± 1.8		0.35 <sup>b</sup>
Min – Max	3-12	3-11		
Height (cm)				
Mean ± SD	62.1 ± 7.5	60.7 ± 6.4		0.24 <sup>b</sup>
Min – Max	46 - 85	52 – 85		
Total lesion score				
Mean ± SD	23.2 ± 11.1	20.4 ± 9.9		0.13 <sup>b</sup>
Min – Max	12 - 64	12 – 56		
Erythema, n (%)				
Absent	40 (63.5)	37 (60.7)		0.98 <sup>b</sup>
Mild	12 (19.1)	12 (19.7)		
Moderate	10 (15.9)	11 (18.0)		
Severe	1 (1.6)	1 (1.6)		
Discomfort signs, n (%)				
Absent	36 (57.1)	37 (60.7)		0.37 <sup>b</sup>
Mild	14 (22.2)	11 (18.0)		
Moderate	13 (20.6)	10 (16.4)		
Severe	-	3 (4.9)		

**Table 1:** Demographic data and baseline characteristics in infants of the Intention To Treat set (N=124) (<sup>s</sup> Between group statistical

comparisons were performed using the following tests: a) Chi-square test; b) Student's T-test for independent samples; c) Fisher's exact test).

## Efficacy

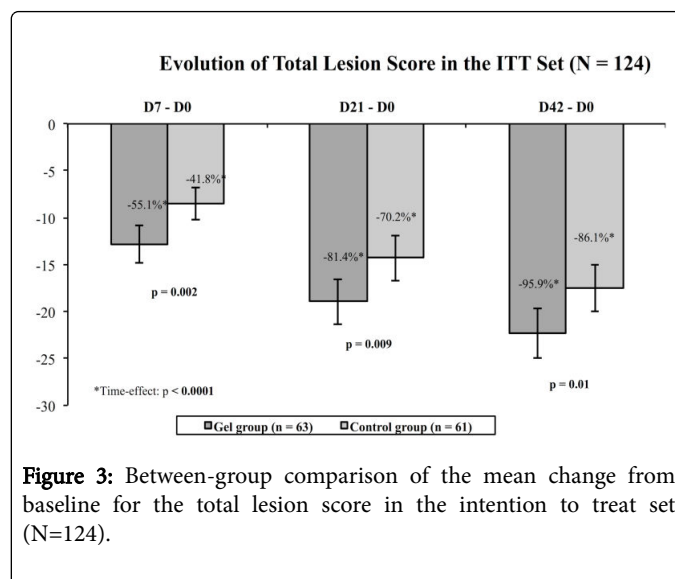
A TLS decrease was observed at each visit in both groups, in comparison with baseline. A statistically significant greater improvement in TLS was observed in the gel group compared with the control group (Figure 3). The efficacy of the gel over hygiene alone was confirmed when each component of the TLS was considered individually. Statistically significant greater decreases in the global affected area score were observed in the gel group as compared to the control group at D7, D21 and D42 (Table 2). The scale intensity score decreased in both groups during the course of the study, with a statistically significant greater decrease in the gel group compared to the control group at D21 and D42 (Table 2). By the end of the study, complete resolution of the lesions was observed in 44 infants (69.8%) in the gel group compared to 29 infants (47.5%) in the control group ( $p=0.01$ ).

Component Score Δ (Mean ± SD)	Gel group N=63	Control group N=61	p value <sup>\$</sup>
Global affected area score			
D7-D0	-3.6 ± 2.7	-2.3 ± 2.2	0.04
D21-D0	-6.5 ± 3.2	-4.5 ± 2.8	0.0003
D42-D0	-8.2 ± 2.6	-6.3 ± 3.1	0.0004
Global scale intensity score			
D7-D0	-3.4 ± 2.4	-2.8 ± 3.0	0.18
D21-D0	-6.1 ± 3.9	-4.7 ± 3.6	0.04
D42-D0	-8.3 ± 3.6	-6.9 ± 3.8	0.04

**Table 2:** Changes in global components of the total lesion score (TLS) between assessment visits in the ITT set (N=124). Global affected area and scale intensity scores were measured as the sum of the affected area and intensity scores of each segment (<sup>\$</sup> Between-group comparisons for changes between visits from D0 were analysed using the student's T-test.  $P>0.05$  was considered as not significant).

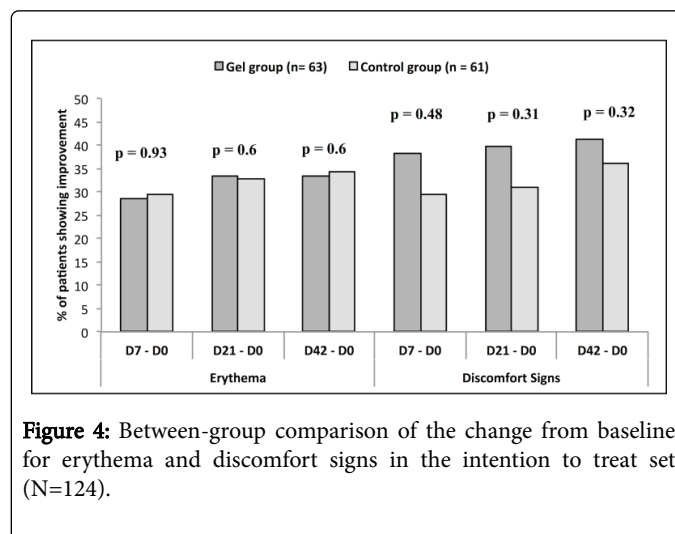
Results were confirmed by the PP set analysis, where a significantly greater decrease in TLS was also observed in infants of the gel group ( $n=56$ ) compared to those in the control group ( $n=54$ ), at D7 ( $-12.4 \pm 8.3$  versus  $-8.7 \pm 6.9$ ,  $p=0.01$ ), D21 ( $-19.2 \pm 10.3$  versus  $-14.8 \pm 10.0$ ,  $p=0.02$ ) and D42 ( $-22.6 \pm 11.2$  versus  $-18.1 \pm 10.1$ ,  $p=0.03$ ). Moreover, at the end of study, complete recovery was obtained in 73.2% of infants in the gel group versus 50.0% in the control group ( $p=0.01$ ).

A similar proportion of infants in both groups of the ITT set had improved erythema at D7, D21 and D42 (Figure 4). A slightly higher proportion of infants in the gel group had improved discomfort signs at D7, D21 and D42 (Figure 4), without reaching statistical significance. In both groups, global scores of erythema and discomfort signs showed statistically significant improvements starting from D7 (data not shown) ( $p<0.05$ ).



**Figure 3:** Between-group comparison of the mean change from baseline for the total lesion score in the intention to treat set (N=124).

At D42, one infant (1.6%) in the gel group and 3 subjects (4.9%) in the control group presented with worsening of erythema, whereas 5 (7.9%) and 2 (3.3%) subjects had worsening of discomfort signs. The investigator and the parents graded global efficacy of the pediatric gel as “recovery” in 51 (81.0%) and 50 (79.4%) infants, respectively, and as “improvement” in 12 (19.0%) and 13 (20.6%) infants, respectively.



**Figure 4:** Between-group comparison of the change from baseline for erythema and discomfort signs in the intention to treat set (N=124).

## Global tolerance

Global tolerance was estimated as “Very good/Good” in more than 96% of infants in both groups at all examination visits. Tolerance was reported as “Poor” for one infant in the control group at all study visits and as “Very Poor” for one infant in the gel group at the D21 visit (due to pruritus that completely resolved after a 2 day gel discontinuation, then relapsed moderately on D36, and completely resolved after treatment discontinuation one week before the end of the study).

## Discussion

Despite progress in understanding the mechanisms involved in the development of SD, no consensus treatment strategy has been clearly



established. The most commonly used treatments are topical preparations (soaps, shampoos, creams) containing antifungal agents (i.e. ketoconazole, ciclopirox), anti-inflammatory drugs (mainly corticosteroids and calcineurin inhibitors) and moisturizing creams, in an attempt to control skin oiliness and restore the skin barrier [15]. These treatments were developed for adult use and development of safe pediatric treatments, which take into account the systemic absorption risk, is needed. Recently, a study by David et al assessed the efficacy of a non-steroidal cream (applied twice daily over 14 days in 42 children) as a treatment for cradle cap [16]. In this pilot study, the only significant difference between treatment groups was for percentage reduction in scaling at the end of treatment, with a 90% reduction in the non-steroidal cream group compared with a 58% reduction in the placebo cream group.

Our study was conducted on a larger number of infants (n=127) and assessed the efficacy of a cosmetic gel, used in combination with a mild daily shampoo applied in standardized conditions. We compared outcomes in infants with cradle cap and/or mild to moderate SD treated with both the gel and shampoo, with those treated with the shampoo alone. The TLS decreased significantly in both groups from the first week of care; the benefits of the gel over use of the shampoo alone were statistically significant at the first visit ( $p=0.002$ ), and persisted after 3 and 6 weeks of care. Moderate to severe erythema and/or discomfort signs (experienced at inclusion by about 20% of the infants in both the gel and control groups) significantly improved from D7 compared with baseline, but without any significant difference between groups. This finding underlines the efficacy of gentle daily hygiene measures in the care of infants with these scalp conditions. However, the value of the gel as an adjunct to daily shampooing is highlighted by the complete resolution of scalp dermatitis observed at the end of study in 69.8% of infants (44 subjects) treated with the gel in addition to the shampoo, compared with complete resolution in only 47.5% of infants (29 subjects) treated with the shampoo alone ( $p=0.01$ ). Compliance to the pediatric cradle cap gel application was satisfactory: 77.8% of parents followed the study protocol schedule and most of those who terminated treatment before the end of the trial did so because of complete recovery. One limitation of our study lies in the fact that we did not use a placebo in our control group. However, we clearly demonstrated that use of the gel led to a significantly greater improvement than use of the standard shampoo alone, which confirms the value of this adjunct treatment compared with standard hygiene measures. A second limitation is the short duration of the study period; further long-term evaluations would be required to determine the rate of relapse after cessation of treatment. The efficacy of the gel is probably related to both an emollient and an anti-inflammatory effect, the respective contributions of which cannot be determined. The anti-inflammatory effect can be attributed to the main gel component, the spring water [8-14], in conjunction with zinc sulphate, also known for its role in tissue repair and regeneration [17]. Furthermore, moisturizing agents and keratolytic agents in the gel likely contributed to its efficacy by regulating skin barrier function and helping to dislodge flakes.

We suggest that application of this gel, in addition to daily hygiene measures, is a good alternative to commonly used treatments. Corticosteroids are well-known for their side effects when used in the long-term and on a large surface area [15]. Antifungal agents can be used safely in infants [1], but their widespread use in general practice might induce the emergence of resistant *Malassezia* fungi. Thus, these drugs should be reserved for infants in whom validated cosmetic care

has failed or for those with frequent relapses, or for severe cases in premature new-borns or infants with immunodeficiency.

Our study suggests that the cradle cap gel, in addition to a mild daily shampoo, can be used for first line topical care of infants aged at least 1 month and suffering from cradle cap, with or without associated mild to moderate SD. Its capacity to decrease scale intensity and reduce the size of the areas of scalp affected, combined with satisfactory tolerance levels, may be especially valuable in a population of infants in whom alternative care options are poorly efficient and signs of discomfort persist, or in those with severe lesions.

## Acknowledgments

This clinical trial was funded by the Pierre Fabre Group. Patrice Plantin and Saayda Ben Becher received fees from Pierre Fabre Dermocosmétique for their participation in the study.

Virginie Ribet is an employee of Pierre Fabre Group. We would like to thank the Avène study group and Amel Ben Osman, Bruno Carbon, Françoise Ceccato, Pierre Delbast, Nejig Doss, Philippe Esteve, Bernard Fongauvier, Georges Fregeville, Francis Geffroy, Arnaud Gerbay, Jean-François Hocquet, Geneviève Hui Bon Hoa, Khaled Kabbous, Ridha Kamoun, Hélène Kempf, Benoît Logre, Alain Marty, Insaf Mokhtar, Rafiaa Nouira, Jean-Claude Oilleau, Patrick Pacoret, Emmanuel Pichot, Jean-François Pujol, Françoise Rembert and Geneviève Sivel for their involvement, as well as Emma Pilling and Marielle Romet, from Santé Active Edition, who provided medical writing assistance on behalf of Pierre Fabre Laboratory.

## References

1. Dessinioti C, Katsambas A (2013) Seborrheic dermatitis: etiology, risk factors, and treatments: facts and controversies. Clin Dermatol 31: 343-351.
2. Wananukul S, Chindamporn A, Yumyourn P, Payungporn S, Samathi C, et al. (2005) Malassezia furfur in infantile seborrheic dermatitis. Asian Pac J Allergy Immunol 23: 101-105.
3. Cantarutti A, Donà D, Visentin F, Borgia E, Scamarcia A, et al. (2015) Epidemiology of frequently occurring skin diseases in Italian children from 2006 to 2012: a retrospective, population-based study. Pediatr Dermatol 32: 668-678.
4. Plantin P (1999) Mucosa and skin anomalies of the newborn. Ann Dermatol Venereol 126: 927-932.
5. DeAngelis YM, Gemmer CM, Kaczvinsky JR, Kenneally DC, Schwartz JR, et al. (2005) Three etiologic facets of dandruff and seborrheic dermatitis: Malassezia fungi, sebaceous lipids, and individual sensitivity. J Invest Dermatol Symp Proc 10: 295-297.
6. Pierard GE, Xhaufaire-Uhoda E, Pierard-Franchimont C (2006) The key role of corneocytes in pityrospores. Dermatology 212: 23-26.
7. Harada K, Saito M, Sugita T, Tsuboi R (2015) Malassezia species and their associated skin diseases. J Dermatol 42: 250-257.
8. Joly F, Galoppin L, Bordat P, Cousse H, Neuzil E (2000) Calcium and bicarbonate ions mediate the inhibition of mast cell histamine release by avène spa water. Fundam Clin Pharmacol 14: 611-613.
9. Boissic S, Branchet-Gumila MC, Segard C (2001) Inhibitory effect of Avène spring water on vasoactive intestinal peptide-induced inflammation in surviving human skin. Int J Tissue React 23: 89-95.
10. Castex-Rizzi N, Charveron M, Merial-Kieny C (2011) Inhibition of TNF- $\alpha$  induced-adhesion molecules by avène thermal spring water in human endothelial cells. J Eur Acad Dermatol Venereol 1: 6-11.
11. Portales P, Aries MF, Licu D, Pinton, J, Hernandez-Pion C, et al. (2001) Immunomodulation induced by avène spring water on Th1- and Th2-

- 
- dependent cytokine production in healthy subjects and atopic dermatitis patients. Skin Pharmacol Appl Skin Physiol 14: 234-242.
12. Casas C, Ribet V, Alvarez-Georges S, Sibaud V, Guerrero D, et al. (2011) Modulation of Interleukin-8 and staphylococcal flora by Avène hydrotherapy in patients suffering from chronic inflammatory dermatoses. J Eur Acad Dermatol Venereol 1: 19-23.
13. Merial KC, Mengual X, Guerrero D, Sibaud V (2011) Clinical efficacy of Avène hydrotherapy measured in a large cohort of more than 10,000 atopic or psoriatic patients. J Eur Acad Dermatol Venereol 1: 30-34.
14. Merial-Kieny C, Castex-Rizzi N, Selas B, Mery S, Guerrero D (2011) Avène thermal spring water: an active component with specific properties. J Eur Acad Dermatol Venereol 1: 2-5.
15. Clark GW, Pope SM, Jaboori KA (2015) Diagnosis and treatment of seborrheic dermatitis. Am Fam Physician 91: 185-190.
16. David E, Tanuos H, Sullivan T, Yan A, Kircik LH (2013). A double-blind, placebo-controlled pilot study to estimate the efficacy and tolerability of a nonsteroidal cream for the treatment of cradle cap (seborrheic dermatitis). J Drugs Dermatol 12: 448-452.
17. Vallee BL, Falchuk KH (1993) The biochemical basis of zinc physiology. Physiol Rev 73: 79-118.