

A dermocosmetic containing bakuchiol, *Ginkgo biloba* extract and mannitol improves the efficacy of adapalene in patients with *acne vulgaris*: result from a controlled randomized trial

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Background: *Acne vulgaris* is an inflammatory disorder of the pilosebaceous unit.

Aim: To confirm that BGM (bakuchiol, *Ginkgo biloba* extract, and mannitol) complex increases the established clinical efficacy of adapalene 0.1% gel in patients with acne.

Methods: A clinical trial was conducted in acne patients. A total of 111 subjects received adapalene 0.1% gel and BGM complex or vehicle cream for 2 months. Assessments comprised Investigator Global Assessment (IGA), global efficacy, seborrhea intensity, inflammatory and non-inflammatory lesions, and subject perception, as well as overall safety and local tolerance and quality of life.

Results: At the end of the trial, inflammatory and non-inflammatory lesions, IGA, global efficacy, and seborrhea intensity had significantly improved in both treatment groups. Differences were statistically significant ($P < 0.05$) in favor of BGM complex for inflammatory lesions as well as IGA and seborrhea intensity. Global efficacy assessments and subject perception confirmed the superiority of BGM complex-including treatment over the comparative combination. Quality of life had improved more with the active combination than with the vehicle combination. In the active group, four subjects had to interrupt temporarily BGM complex and 12 adapalene compared to seven subjects interrupting the vehicle and eleven adapalene in the vehicle group. One subject withdrew from the trial due to an allergy to adapalene. The majority of all events were mild.

Conclusion: BGM complex improves the treatment outcome of adapalene 0.1% gel in patients with *acne vulgaris*. Overall, safety and local tolerance of BGM complex were good.

Keywords: adapalene, *acne vulgaris*, bakuchiol, BGM complex, *P. acnes*, sebum

Introduction

Acne vulgaris is a multifactorial, inflammatory disorder of the pilosebaceous unit. It presents with ductal hyperkeratinization and increased cohesiveness of keratinocytes, increased sebum production, alteration of sebum lipid composition, dysregulation of the hormone microenvironment, interaction with neuropeptides, hypercolonization by *Propionibacterium acnes*, and inflammation.^{1,2}

Changes in the activity of the sebaceous gland not only result in seborrhea but also in alterations of the sebum fatty acid composition.³ Sebum lipid fractions with proinflammatory properties and inflammatory tissue cascades have been associated with the process of the development of acne lesions, while follicular keratinocytes and sebocytes, the major components of the pilosebaceous unit, act as immune-active

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cells capable of microbial recognition and abnormal lipid presentation.⁴ The latter may be activated by *P. acnes* and recognize altered lipid content in sebum, followed by the production of proinflammatory cytokines.

There is no single topical antiacne medication that acts against all four major pathophysiologic acne features. Retinoids, such as adapalene, are well known for targeting comedones, including microcomedos and precursors of both inflammatory and non-inflammatory lesions, and exerting anti-inflammatory activity on the innate immunity.⁵⁻⁷ They are more and more often applied in combination with topical antibacterials, including antibiotics and benzoyl peroxide (BPO).^{8,9} The latter is known to cause irritation, while the use of topical antibiotics is less and less recommended due to the increased development of antimicrobial-resistant bacteria.

Laboratoire Bioderma, France, developed a new dermocosmetic cream containing a triple complex (hereafter BGM complex, Sébium Global cream). This complex mimics the effect of vitamin E, allowing protection from potentially harmful effects of squalene oxidation products, such as hyperkeratinization and inflammation.¹⁰ The product contains a triple complex consisting of bakuchiol, *Ginkgo biloba* extract, and mannitol.¹¹⁻¹⁴ Bakuchiol regulates seborrhea, is antibacterial, and has antiacne properties.¹⁵⁻¹⁹ In addition to its excipients, the active formulation contains enoxolone (18 β -glycyrrhetic acid), salicylic acid, alpha hydroxy acid esters, and zinc gluconate, all of which are all well-recognized pharmacological active agents used in the treatment of acne.²⁰⁻²³

The aim of the present trial was to assess the potential of BGM complex to improve the established clinical efficacy of adapalene 0.1% gel.

Methods

Settings

This multicenter and comparative double-blind clinical trial was conducted according to the Declaration of Helsinki of 1973 and all its amendments and its successive updates, to good clinical practices for the conduct of clinical trials and to local regulatory requirements. The trial was performed from January to June 2013 at 13 sites in Slovakia.

Trial population

Subjects had to be 12–25 years of age, present with mild-to-moderate acne (grades 2–3 on the Investigator Global Assessment [IGA] scale), and had to be prescribed adapalene 0.1% gel for at least 2 months.

Treatments

Subjects were randomized at investigational sites in a 1:1 ratio to either an association of BGM complex cream and adapalene 0.1% gel, hereafter active association, or to an association of vehicle cream and adapalene (hereafter vehicle association).

Adapalene was prescribed by the investigators on the day of inclusion and had to be used as per the instructions.

BGM complex or the vehicle, containing water (aqua), glycerin, hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer, isohexadecane, titanium dioxide, phenoxyethanol, chlorphenesin, polysorbate 60, alumina, and stearic acid, was to be applied on the entire face in the morning, after the face had been cleaned with a gentle cleanser. Adapalene was to be applied in the evening on the cleaned skin.

Make-up, except foundation cream, was permitted, while no other topical skin care product or treatment was authorized on the face during the trial. Oral contraception for women of childbearing potential had to remain unchanged during the course of the trial.

Assessments

Clinical evaluations of inflammatory and non-inflammatory lesions count, seborrhea intensity on a visual scale (from 0: nil to 3: high), global acne severity using the IGA score (from 0: none to 4: severe), and global efficacy assessed on a scale (from 0 [lowest score] to 10 [highest possible score]) were performed on D0, D28, and D56 (D standing for day). Quality of life using the Cardiff Acne Disability Index²⁴ was assessed on D0 and D56.

Safety was assessed through adverse event reporting; local tolerance signs and symptoms comprising erythema, desquamation, pruritus, burning, prickling, tightness, vesicles, papules, and edema were assessed on D28 and D56 by the investigator on a scale from 0 to 3 (0= none, 1= light, 2= average, 3= high).

Statistics

Statistical analyses were performed on data from subjects who completed the trial. Quantitative criteria were expressed by sample size, mean, and standard deviation. Qualitative criteria were expressed in percentage. The Student's *t*-test on paired data or paired Wilcoxon test was applied to compare the number of non-inflammatory and inflammatory lesions, IGA and intensity of seborrhea between D0 and D28, and D0 and D56 in each group. Differences between groups for lesion count, intensity of seborrhea and IGA were calculated using

the Student's *t*-test or Mann–Whitney test. The chi-square test was used to compare global efficacy between groups. A two-sided significance level of 0.05 was chosen. IGA was compared between each time point.

Results

Demographics and baseline data

A total of 111 subjects participated in this trial, 55 in the active association and 56 in the vehicle association group (Table 1). Three patients presented with an acne severity of less than mild (IGA grade 1) at inclusion. The investigator decided to maintain these subjects in the trial.

Efficacy

Lesion count

After 56 days of treatment, the mean number of non-inflammatory lesions had decreased from 34.4 ± 23.5 to 15.2 ± 13.5 lesions in the active association group and from 29.3 ± 20.3 to 14.6 ± 8.5 lesions in the vehicle association group. The percent decrease at D56 from D0 reached 56% and 50.2% in the active association and the vehicle association groups, respectively (Figure 1A). These reductions were statistically significant ($P < 0.005$) for each group and sustained from D28. The difference between both groups was not statistically significant.

At D56 compared to D0, the mean number of inflammatory lesions had decreased in both groups: from 18.4 ± 10.9 to 6.9 ± 6.6 and from 17.3 ± 11.5 to 10.1 ± 10.4 lesions in the active association and vehicle association groups, respectively. At the end of the trial, the percent decrease from D0 was 62.7% for the active association group and 41.5% for the vehicle association group (Figure 1B). These reductions were statis-

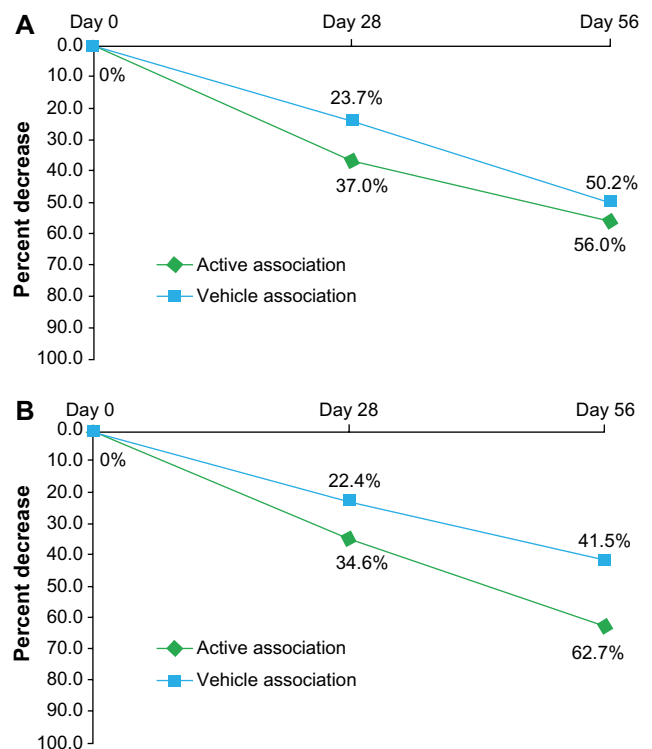


Figure 1 Percent decrease over time of acne lesions: (A) non-inflammatory and (B) inflammatory lesions.

Notes: At D56, the difference to D0 was statistically significant ($P < 0.005$) for both groups. The between-treatment group difference was not significant for non-inflammatory lesions, while it was significant for inflammatory lesions ($P < 0.05$).

Abbreviation: D, day.

tically significant ($P < 0.005$) and sustained from D28. The difference between both groups was statistically significant ($P < 0.05$) and in favor of the active association group.

Table 2 shows results for seborrhea intensity, IGA, global efficacy evaluation, and quality of life at D0 and D56.

Safety

In the active association group, 23 subjects reported at least one local adverse event (burning sensation, erythema, desquamation, and pruritus). In 15 subjects, they were considered related to adapalene and in four subjects, related to BGM complex. The majority of all local adverse events were mild in intensity.

A total of 12 subjects had to stop adapalene and four had to stop BGM complex. The interruption of applications was temporary in all subjects except for one subject who experienced an allergy considered to be related to adapalene.

In the vehicle association group, 17 subjects reported at least one local adverse event (erythema, burning sensation, pruritus, and desquamation). Of those, 12 were related to adapalene. The majority of all local adverse events were mild in intensity.

Table 1 Demographics and baseline data

	Active association	Vehicle association
Number of subjects	55	56
Age (years)		
Mean \pm SD	18.7 \pm 3.4	18.7 \pm 3.0
Min/max	13/25	12/25
Sex		
Male	17 (30.9%)	16 (28.6%)
Female	38 (69.1%)	40 (71.4%)
Acne severity		
Almost none	1 (1.8%)	2 (3.7%)
Mild	25 (45.4%)	33 (58.9%)
Moderate	28 (50.9%)	18 (32.1%)
Severe	1 (1.8%)	3 (5.3%)
Seborrhea intensity score	2.1 \pm 0.6	1.8 \pm 0.6
IGA	2.5 \pm 0.6	2.3 \pm 0.6

Abbreviation: IGA, Investigator Global Assessment.

Table 2 Results for seborrhea intensity, IGA, global efficacy evaluation, and quality of life after 56 days of use of BGM complex or vehicle in combination with adapalene 0.1% gel

Criterion	Active association		Vehicle association		P-value (between groups)
	D0	D56	D0	D56	
Seborrhea intensity	2.1±0.6	1.0±0.6 (-51.9%)	1.8±0.6	1.3±0.6 (-26.4%)	P<0.005*
IGA	2.5±0.6	1.5±0.6 (-40.3%)	2.3±0.6	1.7±0.8 (-26.9%)	P<0.01*
Global efficacy evaluation					
Investigator					
Cleared		8.2%		4.1%	P<0.05*
Improved		91.8%		75.5%	
Subject					
Cleared		18.4%		2%	P<0.05*
Improved		75.5%		77.6%	
Quality of life	4.9±2.6	2.3±2.0 (-54%)	4.7±2.3	3.2±2.8 (-31.2%)	P<0.005*

Note: *P-values in favor of the active association.

Abbreviations: BGM, bakuchiol, *Ginkgo biloba* extract, and mannitol; D, day; IGA, Investigator Global Assessment.

In eleven subjects, adapalene had to be interrupted temporarily; vehicle had to be interrupted temporarily in seven subjects.

Discussion and conclusion

After 2 months of combined use with adapalene, BGM complex improved significantly the clinical outcome for inflammatory lesions when compared to the vehicle. The fact that BGM complex enhances the anti-inflammatory potential of adapalene may be due to its antibacterial properties on *P. acnes* as well as its anti-irritation potential. Results observed for the non-inflammatory and inflammatory lesion counts were confirmed by the IGA, the seborrhea intensity, and the global efficacy rated by the investigator and the subject, which at the end of the trial were all significantly in favor of the BGM complex/adapalene regimen; quality of life of subjects had significantly improved. Even though results are not shown, the excellent subjects' perceptions of BGM complex may have contributed to making them adhere to their treatment, especially in the light of acne being a chronic disease.²⁵ One may argue that subjective evaluation is secondary to objective clinical assessments. However, disfigurement from inflamed lesions, post-inflammatory hyperpigmentation, and scars often causes embarrassment and frequently undermines confidence and lowers self-esteem. Hence, adherence to treatment, reducing sequels from acne is crucial for a positive treatment outcome.

The fact that bakuchiol, one of BGM complex agents, has antibacterial properties may open new perspectives in the issue of *P. acnes* strains, becoming more and more resistant to antibiotics. Indeed, to limit the use of topical antibiotics, retinoids such as adapalene are more and more

combined with BPO. However, BPO may cause irritation and is hence contraindicated in a certain number of patients. As for BPO, bakuchiol does not lead to antibiotic resistance. Hence, in such patients, BGM complex may be considered an alternative to BPO. To confirm this, future clinical trials may be conducted to evaluate the efficacy of BGM complex combined to a topical retinoid compared to a combination of topical retinoids and topical antibacterials.

A similar number of subjects reported mild and transient local adverse events with BGM complex and with the vehicle cream; the majority of local adverse events were caused by adapalene, even though known to be the less-irritating topical retinoid.^{26,27}

A missing treatment arm with adapalene in monotherapy and the short treatment duration, treatment of adapalene should last 3 months, may raise concerns for limitations. However, we feel that the results obtained from the active and the vehicle groups confirmed the expected treatment outcome of adapalene. Therefore, we consider that the trial is robust enough to show that BGM complex improves the treatment outcome of adapalene in patients with *acne vulgaris*.

In conclusion, the dermocosmetic containing BGM complex improves the treatment outcome of adapalene in patients with *acne vulgaris* and is well tolerated.

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Disclosure

Dr Katarína Poláková has no financial interest to disclose. Eric Jourdan, Aurélie Fauger, and Michèle Sayag are employees of Laboratoire Bioderma, France.

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