A Nova Formulação de Calcipotriol/Dipropionato de Betametasona em Espuma Cutânea para o Tratamento da Psoríase

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RESUMO – A psoríase é uma doença inflamatória crónica da pele, imunomediada, potencialmente desfigurante e incapacitante, que afeta mundialmente mais de 100 milhões de indivíduos. A combinação fixa de calcipotriol e betametasona (0,005% Cal/ 0,064% BD) é o tratamento tópico recomendado. No entanto, os tratamentos tópicos estão associados a falta de eficácia e baixa adesão, nomeadamente devido às fracas propriedades cosméticas das formulações disponíveis. Para melhorar a aceitação e a adesão dos doentes, foi desenvolvida uma espuma cutânea de Cal/ BD para tratamento de adultos com psoríase. Os ensaios clínicos de fase II e III mostraram que a formulação fixa dos dois compostos é consistentemente mais eficaz e mais segura do que os ingredientes individuais, considerando o mesmo veículo. A espuma cutânea demonstrou maior eficácia em estudos clínicos, sendo que uma análise conjunta dos principais estudos mostrou que isso não ocorre à custa do perfil de segurança. Além disso, a espuma cutânea Cal/ BD mostrou uma melhoria significativa da eficácia em comparação com pomadas, géis e loções. O perfil de eficácia e segurança melhorado desta nova formulação, maior tolerabilidade e resposta mais rápida, aliados a uma menor frequência de tratamento (1x por dia), oferece maior conveniência e melhor aceitação do que as respetivas monoterapias (2x por dia) podendo, eventualmente, melhorar a adesão ao tratamento, conduzindo a melhorias mais significativas na qualidade de vida dos doentes, representando uma opção terapêutica mais vantajosa para os doentes. São necessários mais estudos para explorar a possibilidade desta espuma cutânea permitir a gestão da doença a longo prazo.
PALAVRAS-CHAVE – Aerossóis; Betametasona/administração e dosagem; Betametasona/antagonistas & inibidores; Calcitriol/administração & dosagem; Calcitriol/antagonistas & inibidores; Gel; Psoríase/tratamento.

New Calcipotriol/Betamethasone Dipropionate Foam Formulation for the Treatment of Psoriasis: An Overview

ABSTRACT – *Psoriasis is a chronic, inflammatory, immune-mediated, potentially disfiguring and disabling skin disorder, affecting over 100 million individuals worldwide. Calcipotriol plus betamethasone fixed-combination (0.005% Cal/0.064% BD) is the recommended topical treatment for psoriasis. However, topical treatments are associated to lack of efficacy and low adhesion rates due to poor cosmetic characteristics' formulations, and vehicle issues. To answer the need for improving patients' acceptability and adherence, an innovative Cal/BD aerosol foam formulation was developed for the topical treatment of adults with plaque psoriasis. Phase II and III clinical trials have consistently shown that the two-compound formulation is more effective and safer than its individual ingredients in the same vehicle. Cal/BD aerosol foam formulation has proved higher efficacy in clinical studies, and a pooled analysis of the main clinical studies has demonstrated that this does not occur at the safety profile expense. Furthermore, Cal/BD aerosol foam has shown a significantly improved efficacy compared with more traditional formulations, such as ointments, gels, and lotions. The improved efficacy and safety profile of this new formulation, together with the once-daily treatment, a more*

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DOI: https://dx.doi.org/10.29021/spdv.76.1.879

Recebido/*Received*
01 Janeiro/*January* 2018
Aceite/*Accepted*
07 Janeiro/*January* 2018

Artigo de Revisão

acceptable tolerability profile, and an early and rapid response, offers improved convenience and better acceptance over the twice--daily applications required for the respective monotherapies, which may improve adherence to treatment, leading to faster and greater improvements in HR-QoL, representing a useful therapeutic option to the management of patients with plaque psoriasis. Further clinical investigations to explore the possibility of Cal/BD aerosol foam treatment ability to provide long-term psoriasis' management are required.

KEYWORDS – *Aerosols; Betamethasone/administration & dosage; Betamethasone/analogs & derivatives; Calcitriol/administration & dosage; Calcitriol/analogs & derivatives; Psoriasis/drug therapy.*

INTRODUCTION

Psoriasis is a chronic, inflammatory, immune-mediated, potentially disfiguring and disabling skin disorder that affects over 100 million individuals worldwide (≈ 2% of the world's population). It affects men and women of all ages, regardless of ethnic origin.[1]

With higher rates in developed countries,[1-2] evidence suggests that psoriasis' prevalence may be increasing.[3] Published data on the prevalence of psoriasis vary between 0.09% and 11.4%.[5,4] In Portugal psoriasis prevalence ranges between 1% and 2%, affecting about 200 000 to 250 000 individuals.[5-6]

Plaque psoriasis (or psoriasis vulgaris) is the most common type (70% – 90% of cases), although it can also present as erythrodermic, guttate, inverse, nail, or pustular forms.[2-4] Psoriasis may have extracutaneous involvement (e.g. ophthalmic symptoms, psoriatic arthritis) and an increased risk of comorbidities (e.g. cardiovascular disease, malignancy, metabolic syndrome).[3,7,8]

Clinical manifestations include well-defined, erythematous plaques, covered in silvery-white scales, and common symptoms include itching and pain.[3,4] Many studies have demonstrated that even in patients with mild-to-moderate disease or even with a relatively limited body surface area (BSA) affected, the visible and highly stigmatizing nature of psoriasis can substantially impact patients' health-related quality of life (HR-QoL).[1,2,9]

As a chronic-relapsing disease, psoriasis requires long--term treatment. The selection of proper treatment is guided by patient-specific presentation (disease extent and severity), history of past treatments' response, patients' preference, and clinicians' judgment, aiming to optimize disease control and long-term management.[10-11]

1. STATE OF THE ART ON PSORIASIS TREATMENT

Therapeutic options include topical, photo and systemic therapy. Each treatment presents limitations: poor efficacy/tolerability ratio, drug interactions, patients' comorbidities, administration route, regimen inconvenience (e.g. time consuming or frequent application), high costs, which are the main reasons for non-adherence, consequently leading to an unsuccessful disease management.[3,16]

Systemic therapy (either using traditional agents, e.g. methotrexate, cyclosporine and acitretin, or biological's, e.g. anti-TNFa, anti-IL12/23 and anti-IL17 agents) is the cornerstone for moderate-to-severe psoriasis treatment.[13,16-12] Phototherapy or topical treatments are recommended for mild or mild-to-moderate disease, which affects most patients (≈70-80%).[2,12, 13,14]

Current research is mainly focused on biologic or systemic treatment agents disregarding topicals, which have had few developments in recent years.[2,12,15,16] Nevertheless, the recommended topical treatment for psoriasis includes the use of vitamin D analogues and corticosteroids, either separate or as a fixed-combination.[13,15,19,17] A well-established fixed-dose combination of a synthetic vitamin D3 analogue (calcipotriol/calcipotriene) and a synthetic corticosteroid (betamethasone dipropionate) (0.005% Cal/0.064% BD) is the most frequently used combination product for topical treatment of plaque psoriasis in adults, either in ointment or gel formulations, in Europe and in USA.[1,18-19]

However, topical treatment is associated to lack of efficacy and success and low adhesion rates due to formulations with poor cosmetic characteristics, and vehicle issues, often reported as greasy, oily, and sticky.[3] But, even though there are no new compounds available, new topical formulations could help to overcome topical treatment-related challenges, leading to a better treatment acceptability and adherence improvement, helping to provide subsequent long-term maintenance of a disease-free state.[13]

Besides patients' adhesion rates, topical therapy's efficacy is also correlated with the skin penetration of the active ingredients. One method to augment skin penetration's rate is to increase the active ingredients' concentration beyond the normal solubility limit, to develop a stable and supersaturated formulation,[13] enhancing the thermodynamic activity of the drug.[27] To answer the need for improving patients' acceptability and adherence, an innovative Cal/BD formulation was developed, and an alcohol-free aerosol foam was approved for the once daily topical treatment of plaque psoriasis in adults by FDA in October 2015 and EMA in March 2016.[3,22-25,20]

This review article pretends to give an overview of a new calcipotriol plus betamethasone dipropionate (Cal/BD) formulation for the topical treatment of adults with plaque psoriasis.

2. CAL/BD AEROSOL FOAM PHARMACOLOGICAL PROFILE

Cal/BD aerosol foam belongs to the pharmacotherapeutic group of antipsoriatics for topical use.[21] With an innovative and renewed formulation, it is a liquid supplied in a pressurized spray can containing a vehicle-based calcipotriol and

betamethasone dipropionate dissolved in a mixture of volatile propellants, butane and dimethyl ether. When the formulation is sprayed, the propellants evaporate rapidly, and a thin layer of foam forms on the skin.[22] Cal/BD aerosol foam should be applied topically to the affected areas once daily for a maximum of 4 weeks, not exceeding 15 g daily or 60g every 4 days.[26,27,23]

Clinical and pharmacological effects of the two active agents are well known, and its action mechanism in plaque psoriasis has been approached by several authors.[2,3,26] Treatment goal is to clear the psoriatic plaques by inhibiting the underlying inflammation and normalizing skin homeostasis, keratinocyte proliferation and differentiation, and to provide immunomodulation.[13] In combination, calcipotriol and betamethasone promote greater anti-inflammatory and anti-proliferative effects than either component alone.[2,27] Its complementary anti-inflammatory and immunomodulatory effects lead to the disruption of the inflammatory loop reaction underlying psoriasis pathogenesis.[13]

2.1. Pharmacodynamic properties

A prospective, multicentre, single-group, open-label study was conducted under maximal use conditions in 35 adults with extensive psoriasis. Aiming to evaluate the effect of Cal/BD aerosol foam on hypothalamic–pituitary–adrenal (HPA) axis suppression and calcium metabolism, the foam was applied once daily on the affected areas for up to 4 weeks, mean weekly dose of 61.8 g. Adrenal response to adrenocorticotropic hormone (ACTH) was determined by measuring serum cortisol levels. Hormonal stimulation and serum and urine calcium assessments occurred at baseline and at 4 weeks. None of the patients had suppressed serum cortisol levels nor elevated serum or urine calcium levels.[27]

2.2. Pharmacokinetic properties

The extent of percutaneous absorption of the two active ingredients following topical application was determined in the above-mentioned trial that also aimed to assess the pharmacokinetic profile of the active ingredients and its main metabolites. Plasma concentrations were assessed at baseline and at week 4. Following systemic exposure, both active ingredients are rapidly and extensively metabolised. In most patients' samples, plasma concentrations of calcipotriol and betamethasone dipropionate and its metabolites were below the quantification's lower limit.[26,27] These results are consistent with those of tissue distribution's studies in rats administered with radiolabelled calcipotriol and betamethasone dipropionate, that showed that the kidney and liver had the highest radioactivity level.[27]

In vitro skin penetration and ex vivo biomarker assays were conducted to compare the skin penetration and bioavailability of Cal and BD from the aerosol foam and ointment formulations, respectively. Cal/BD foam applied to *in vitro* skin is maintained for at least 26 hours, which may explain the bioavailability increase of Cal/BD aerosol foam *versus* other formulations.[31]

3. CAL/BD AEROSOL EFFICACY AND SAFETY

3.1. Efficacy data

3.1.1. Preclinical data/ Phase I

A nonclinical, *in vitro*, skin-penetration study[24,25] was developed to establish Cal/BD aerosol foam efficacy *versus* ointment. This skin-penetration model has demonstrated enhanced drug delivery, whereby steady-state Cal/BD levels were significantly higher following aerosol foam application compared with ointment. This led to significantly more rapid absorption and higher concentration of calcipotriol ($p < 0.001$) and betamethasone dipropionate ($p = 0.002$) within the skin samples (Table 1).

In a Phase I (NCT01946386) study, 35 healthy volunteers received a single application of Cal/BD aerosol foam, clobetasol propionate (CP) cream, Cal/BD ointment, fluocinolone acetonide (FA) ointment and betamethasone dipropionate aerosol foam.[34,26] Skin blanching was measured to evaluate vasoconstrictor potential as a surrogate of steroid potency. Cal/BD aerosol foam proved greater vasoconstriction than Cal/BD and FA ointment, but less vasoconstriction than CP cream (Table 1).

3.1.2. Phase II

In a Phase IIa (NCT01347255), 4-week, investigator-blinded study involving 24 patients with psoriasis vulgaris, the antipsoriatic effect of Cal/BD foam was measured by assessing the decrease in mean Total Clinical Score (TCS; the sum of erythema, scaling and lesional thickness scores).[34,27] Cal/BD foam led to a greater decrease in TCS compared with Cal/BD ointment (–6.0 *vs* –5.3; $p = 0.038$), betamethasone dipropionate foam (–6.0 *vs* –5.0; $p = 0.005$) and foam vehicle (–6.0 *vs* –1.9; $p < 0.001$). Ultrasound measurements showed that reductions in total skin thickness and dermis inflammation psoriasis-associated were consistently greater with Cal/BD aerosol foam than with all other treatments (Table 1).

Cal/BD aerosol foam's systemic safety was assessed in a phase II (NCT01600222) multicentre, single-arm, open-label, maximal-use systemic-exposure trial.[28] Cal/BD foam once daily was applied to adult patients with moderate to severe, extensive psoriasis. Endpoints were week 4 abnormal adrenocorticotropic hormone (ACTH) challenge test and change in albumin-corrected serum calcium, 24-hour urinary calcium excretion, and urinary calcium-creatinine ratio. At week 4, all 35 patients exhibited normal ACTH responses and changes in calcium homeostasis were minor and not clinically relevant. No patients experienced elevations above normal. Disease severity generally improved, and 49% of patients achieved treatment success according to the Physician's Global Assessment of Disease Severity (Table 1).

In 376 patients with psoriasis vulgaris enrolled in a phase II (NCT01536886), multicentre, investigator-blind, randomized, 4-week trial, significantly more patients using Cal/BD aerosol foam achieved treatment success at week 4 versus Cal/BD ointment (54.6 *vs* 43.0%; $p = 0.025$).[34,29] Mean mPASI score was significantly improved for aerosol foam *versus* ointment by week 1 (mean difference –0.7, $p = 0.001$) and maintained

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Table 1 - Efficacy and safety results from Cal/BD clinical trials.

Clinical Trial	Study design	Study population	Treatments & formulations	Endpoints/ Outcomes	Efficacy results	Safety results
Phase I						
Queille-Roussel, 2016[35] NCT01946386	Phase I, single-centre, investigator-blinded, vehicle-controlled, intra-individual comparison vasoconstriction study.	35 healthy volunteers from 18-50 y, skin type I to IV (Fitzpatrick scale).	Single application on selected sites: Cal/BD aerosol foam, clobetasol propionate 0.5 mg/g cream (CP; very potent), Cal/BD ointment (potent), fluocinolone acetonide 0.25 mg/g ointment (FA; moderately potent), BD aerosol foam and aerosol foam vehicle. A 7th untreated site acted as a negative control.	Skin blanching was assessed by visual (primary response criterion) and colorimetric a* and L* measurements (secondary criteria), and was analysed over time (6-32 h post-application).	All active treatments led to significantly greater skin blanching than control. By visual assessment, skin blanching with Cal/BD aerosol foam was significantly less compared with CP cream [mean AUC_{0-32} 2560 *vs* 3831; mean difference=-1272; 95% confidence interval (CI): -1598, -945; $p < 0.001$], similar to BD aerosol foam (mean AUC0-32 2560 *vs.* 2595; mean difference=-35; 95% CI: -362, 292; p=0.83) and significantly greater than Cal/BD ointment (mean AUC0-32 2560 *vs* 2008; mean difference=552; 95% CI: 225, 878; $p=0.001$) and FA ointment (mean AUC0-32 2560 vs 1981; mean difference=578; 95% CI: 251, 905; $p <0.001$). Colorimetric assessments a* and L* also indicated significantly reduced skin blanching with Cal/BD aerosol foam compared with CP cream.	Throughout the study, there were no reports of AEs, serious AEs or ADRs, no clinically relevant changes in patient vital signs and no withdrawals due to AEs. Throughout the study, there were no reports of AEs, serious AEs or ADRs, no clinically relevant changes in patient vital signs and no withdrawals due to AEs.
Queille-Roussel, 2015[40] NCT01935869	Single-centre, randomized, investigator-blind, phase I study.	213 healthy volunteers, median age 44y (range 19-65) randomized to 3 test sites.	5 applications/ product/ week of Cal/BD foam, foam vehicle and white petrolatum (negative control), under semi occlusive conditions (patches) for 3 weeks (induction phase), then 1 application (challenge phase), following a 2-week rest period.	Induction phase - skin irritation analysis: MDR and MCII. Challenge phase - skin sensitization analysis: number of volunteers with positive sensitization at the end of dermal response was assessed by a 6-point scale (0, 0.5, 1, 2, 3, 4) 30' after patch removal in induction phase, and by a 5-point scale (ranging from 'no reaction' to 'extreme positive reaction') at 3 time points up to 72h after the single application in challenge phase. Following challenge phase, a certified dermatologist considered whether sensitization reactions occurred at any test site, with the scale: 0 ¼ negative, 1 ¼ equivocal, 3 ¼ positive.	During the induction phase, MDR=0 (no response) or 0.5 (questionable or faint, indistinct erythema) was reported for 79% of volunteers for Cal/BD foam treated sites *vs* 98% for vehicle and control. The highest score was 2 (erythema with slight-moderate oedema) reported in 3 volunteers, all following Cal/BD foam application. MCII (induction phase) was low for all treatments: Cal/BD foam, 0.10; vehicle, 0.02; control, 0.02; comparative analysis of Cal/BD foam vs control was statistically significant different (95% CI 0.07, 0.10; $p =0.001$). There was no indication of any equivocal/ positive sensitization reactions.	Adverse drug reactions were experienced by 22 volunteers. Cal/BD foam: folliculitis, n ¼ 20; pruritus, n ¼ 8 Vehicle: urticaria, n ¼ 2; skin irritation, n ¼ 1.

ACTH - Adrenocorticotropic hormone; ADRs – Adverse reactions; AEs – Adverse events; AUC – Area under the curve; DLQI - Dermatology Life-Quality Index; DTT – Difficult to treat; HR-QOL – Health-related quality of life; MDR - maximal dermal response; MCII - mean cumulative irritation index; mPASI – modified psoriasis area and severity index; pts – Patients; SAES – Serious adverse events; SD – Standard deviation; TCS - Total clinical score; y - Years

Table 1 (Cont.) - Efficacy and safety results from Cal/BD clinical trials.

Clinical Trial	Study design	Study population	Treatments & formulations	Endpoints/ Outcomes	Efficacy results	Safety results
Phase II						
Queille-Roussel, 2015[36] NCT01347255	Phase IIa, single-centre, investigator-blinded, exploratory study, with intra-individual comparison using a modified psoriasis plaque test.	24 patients, median age 52.5y (range 21-75).	Cal/BD foam, Cal/BD ointment, BD foam and Cal/BD foam vehicle once daily (6 days/ week) for 4 weeks, randomized to 4 plaque test sites (5 cm^2 each).	Primary efficacy endpoint: change in TCS (sum of erythema, scaling and lesional thickness). Secondary endpoints: ultrasonographic changes in total skin thickness and echo-poor band thickness, and adverse events.	At week 4, test sites treated with Cal/BD foam had a significantly greater decrease in mean (±SD) TCS (-6.00 ± 1.27) *vs* those treated with Cal/BD ointment (-5.25 ± 1.78; difference -0.75; 95 % CI -1.46 to -0.04; p=0.038), BD foam (-4.96 ± 1.85; difference -1.04; 95 % CI -1.75 to -0.33; p=0.005) or foam vehicle (-1.88 ± 1.12; difference -4.13; 95 % CI -4.83 to -3.42; p<0.001). Total skin thickness and echo-poor band thickness of Cal/BD foam-treated sites were reduced to a greater extent than those treated with comparators.	Eleven patients reported 17 adverse events, the most frequent being headache (five patients). There were no lesional/ perilesional AEs or adverse drug-related events.
Taraska, 2016[37] NCT01600222	Phase II, multicentre, single-arm, open-label, maximal-use systemic-exposure trial.	37 adult patients (mean age 48y; 46% female) with moderate to severe, extensive psoriasis (15%-30% of body surface area, including ≥30% of scalp).	Cal/BD foam once daily.	Endpoints were week 4 abnormal ACTH challenge test and change in albumin-corrected serum calcium, 24-hour urinary calcium excretion, and urinary calcium-creatinine ratio.	35 patients reaching week 4 exhibited normal ACTH responses. At week 4, changes in calcium homeostasis were minor and not clinically relevant; no patients experienced elevations above normal. Disease severity generally improved, and 49% of patients achieved treatment success according to the Physician's Global Assessment of Disease Severity.	Safety analysis set included 37 patients. Four patients (11%) reported 6 AEs of mostly mild or moderate intensity, and no specific AE was experienced by more than 1 patient. One of the events, severe erythema, which occurred within 4 days of treatment, was considered related to treatment. The other 5 AEs were considered not related to treatment. There were no clinically significant changes in hematologic, biochemical, or urinalysis parameters.
Koo, 2016[38] NCT01536886	Phase II, multicentre, investigator-blind, 4-week trial.	376 adult patients with psoriasis were randomized.	Cal/BD aerosol foam (141 pts), Cal/BD ointment (135 pts), aerosol foam vehicle (49 pts) or ointment vehicle (51 pts) (3:3:1:1).	Primary efficacy endpoint: proportion of patients at week 4 who achieved treatment success (clear or almost clear with at least a two-step improvement) according to the physician's global assessment of disease severity.	54.6% patients using Cal/BD aerosol foam achieved treatment success *vs.* 43.0% ointment (p=0.025); mean mPASI score was significantly different between Cal/ BD aerosol foam and Cal/BD ointment (mean difference -0.6; p=0.005). Rapid, continuous itch relief occurred with both active treatments.	One adverse drug reaction was reported with Cal/BD aerosol foam (application site itch).

ACTH - Adrenocorticotropic hormone; ADRs – Adverse reactions; AEs – Adverse events; AUC – Area under the curve; DLQI - Dermatology Life-Quality Index; DTT – Difficult to treat; HR-QOL – Health-related quality of life; MDR - maximal dermal response; MCII - mean cumulative irritation index; mPASI – modified psoriasis area and severity index; pts – Patients; SAES – Serious adverse events; SD – Standard deviation; TCS - Total clinical score; y - Years

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Table 1 (Cont.) - Efficacy and safety results from Cal/BD clinical trials.

Clinical Trial	Study design	Study population	Treatments & formulations	Endpoints/ Outcomes	Efficacy results	Safety results
Phase II						
Lebwohl, 2016[39] NCT01536938	Randomized, Double-blind, Multicentre, Three-arm, Phase II Study.	302 patients (≥18 years) with psoriasis vulgaris (≥mild disease severity by physicians' global assessment). Most patients (76%) had moderate psoriasis of the body (66% for scalp).	Patients were randomized (100:101:101) to receive Cal/BD foam, Cal foam, or BD foam once daily for 4 weeks.	Treatment success of the body ("clear"/"almost clear" from baseline moderate/severe disease; "clear" from baseline mild disease). Involved scalp treatment success was an additional endpoint.	At week 4, 45% of Cal/BD foam patients achieved treatment success, significantly more than Cal foam (14.9%; OR 4.34 [95%CI 2.16,8.72] $p<0.001$) or BD foam (30.7%; 1.81 [1.00,3.26] $p=0.047$). Mean mPASI (population baseline 7.6) improved in all groups, with statistically significant differences in Cal/BD foam score (2.37) *vs* Cal foam (4.39; mean difference -2.03 [-2.63] [-1.43] $p<0.001$) and BD foam (3.37; -1.19 [-1.80] [-0.59] $p<0.001$).	Four (Cal/BD), 10 (Cal), and 8 (BD) adverse drug reactions were reported.
Queille-Roussel, 2017[40] NCT02518048	Phase IIa, randomized, single-centre, investigator-blinded, 4-week study.	35 adult patients with psoriasis were included.	Cal/BD foam and BV-medicated plaster were applied once daily to 6 test sites (3 for each treatment).	The primary efficacy endpoint was absolute change in total clinical score (TCS; sum of erythema, scaling, and infiltration); secondary endpoints were changes from baseline in each individual clinical score, ultrasonographic changes (total skin and echo-poor band thickness), and safety. Post hoc analysis was change from baseline in TCS on DTT areas.	Least-squares mean change in TCS from baseline was significantly greater for Cal/BD foam (-5.8) than BV-medicated plaster (-3.7; difference -2.2; 95% confidence interval -2.6 to -1.8; $p<0.001$); greater changes for Cal/BD foam were observed from day 8 for each clinical sign. Absolute total skin and echo-poor band thickness change was significantly greater for Cal/BD foam than for BV-medicated plaster (both $p<0.001$). Post hoc analyses showed that Cal/BD foam was significantly more effective than BV-medicated plaster on DTT areas after 4 weeks ($p<0.001$).	Both treatments were well tolerated.

ACTH - Adrenocorticotropic hormone; ADRs – Adverse reactions; AEs – Adverse events; AUC – Area under the curve; DLQI - Dermatology Life-Quality Index; DTT – Difficult to treat; HR-QOL – Health-related quality of life; MDR - maximal dermal response; MCII - mean cumulative irritation index; mPASI – modified psoriasis area and severity index; pts – Patients; SAES – Serious adverse events; SD – Standard deviation; TCS - Total clinical score; y - Years

at week 4 (mean difference – 0.6, $p = 0.005$). Both active treatments led to rapid and marked itch relief within the first week and maintained throughout the study. Itch severity, measured using a visual analogue scale (VAS), decreased from 52.7 to 13.5 at baseline and at week 4, respectively, in patients using Cal/BD aerosol foam, and from 52.1 to 14.5 in ointment-treated patients. Combination foam treatment was considered more effective and with the same tolerability as ointment (Table 1).

A phase II (NCT01536938), randomized, double-blind, multicentre, three-arm study enrolled 302 patients, randomized to receive Cal/BD foam, Cal foam, or BD foam once daily for 4 weeks.[30] Endpoints included treatment success of the body and scalp. At the end of the study, 45% of Cal/BD foam patients achieved treatment success, significantly more than Cal or BD foam (14.9%; OR 4.34 [95%CI 2.16,8.72] $p < 0.001$) (30.7%; 1.81 [1.00,3.26] $p = 0.047$). Mean mPASI score improved in all groups, with statistically significant differences in week 4 Cal/BD foam score (2.37) *versus* Cal foam (4.39; mean difference -2.03 [-2.63] [-1.43] $p < 0.001$) and BD foam (3.37; -1.19 [-1.80] [-0.59] $p < 0.001$) (Table 1).

Aiming to compare the efficacy of Cal/BD foam with betamethasone 17-valerate 2.25 mg (BV)-medicated plasters (recommended for treating psoriasis plaques localized in

Table 1 (Cont.) - Efficacy and safety results from Cal/BD clinical trials.

Clinical Trial	Study design	Study population	Treatments & formulations	Endpoints/ Outcomes	Efficacy results	Safety results
Phase III						
Leonardi, 2015[25] PSO-FAST NCT01866163	Phase III, double-blind, randomized PSO-FAST (Cal/BD foam in PSOriasis vulgaris, a Four-week, vehicle-controlled, efficacy And Safety Trial)	426 with ≥ mild severity psoriasis of the trunk and/or limbs from 27 US outpatient sites.	426 patients were randomized (3:1) to Cal/BD foam or vehicle once-daily for 4 weeks (Cal/BD foam, N=323; vehicle, N=103).	Primary outcome: Proportion of patients at week 4 who achieved treatment success according to physician's global assessment. Secondary outcomes: Modified (excluding head) psoriasis area and severity index (mPASI) and patient's assessment of itch (visual analogue scale). Safety was monitored by adverse events/calcium homeostasis.	At week 4, significantly more patients using Cal/BD foam achieved treatment success versus vehicle (53.3 *vs* 4.8%; OR 30.3, 95% CI 9.7,94.3; $p<0.001$) and mean mPASI score was significantly lower for patients using Cal/BD foam than vehicle (2.0 *vs* 5.5; adjusted difference -3.3, $p<0.001$). Significantly greater itch relief was observed for patients using Cal/BD foam than vehicle ($p=0.010$ at day 3, $p<0.001$ from day 5).	Adverse drug reactions were reported in 10 Cal/BD foam patients (3.1%) and two vehicle patients (1.9%); events occurred in one patient each except application site pain (Cal/BD foam, two patients; vehicle, one patient). Cal/BD foam-related AEs: Discolouration, irritation, pruritus (all application-site events), application-site reaction, folliculitis, psoriasis, skin irritation and increased blood calcium (one patient each). Application-site pain was reported by two patients. Foam vehicle-related AEs: Application-site dryness, erosion, erythema and oedema, and application-site pain (one patient each). AEs did not lead to treatment discontinuations. Two SAEs (single occurrences of bipolar disorder and substance-induced psychotic disorder) were reported in Cal/BD foam recipients. Whether these events were treatment-related was not stated.
Leonardi, 2016[41] PSO-FAST HR-QOL NCT01866163		426 patients with ≥ mild severity psoriasis of the trunk and/or limbs.	Patients were randomized (Cal/BD foam, N=323; vehicle, N=103). Baseline mean DLQI scores were 9.9 (Cal/BD foam) and 10.3 (vehicle).	To compare the impact on HR-QOL of Cal/BD foam vs. vehicle in patients with mild-to-severe psoriasis. HR-QoL was assessed by DLQI at baseline, weeks 1, 2, 4 and EQ-5D-5L at baseline and week 4 questionnaires. A DLQI score of 0 (range, 0-30) indicates no effect on the patient's life; an EQ-5D utility score of 1 (range, 0-1) and an EQ-5D visual analogue scale (VAS) score of 100 (range, 1-100) indicate perfect health.	The impact of psoriasis on HR-QOL (EQ-5D utility score) at baseline was primarily driven by pain/discomfort (Cal/BD foam: 69.9%; vehicle: 65.0%) and anxiety/depression (Cal/BD foam: 45.3%; vehicle 44.7%). There was a greater improvement from baseline in DLQI score for Cal/BD foam vs vehicle at week 4 (-7.0 *vs* -4.4; $p<0.001$); increased improvement was also seen in EQ-5D scores. At week 4, 48.1% of Cal/BD foam patients reported no effect of psoriasis on their lives (DLQI=0/1), and of patients using Cal/BD foam with baseline DLQI scores ≥5, 81.2% achieved a ≥5-point improvement.	

ACTH - Adrenocorticotropic hormone; ADRs – Adverse reactions; AEs – Adverse events; AUC – Area under the curve; DLQI - Dermatology Life-Quality Index; DTT – Difficult to treat; HR-QOL – Health-related quality of life; MDR - maximal dermal response; MCII - mean cumulative irritation index; mPASI – modified psoriasis area and severity index; pts – Patients; SAES – Serious adverse events; SD – Standard deviation; TCS - Total clinical score; y - Years

difficult-to-treat areas) in patients with plaque psoriasis, a phase IIa (NCT02518048), randomized, single-centre, investigator-blinded, 4-week study was performed.[31] Cal/BD foam and BV-medicated plaster were applied once daily to six test sites. Primary efficacy endpoint was absolute change in TCS; secondary endpoints were changes from baseline in each individual clinical score, ultrasonographic changes, and safety. Thirty-five patients were included. Least-squares mean change in TCS from baseline was significantly greater for Cal/BD foam (-5.8) than BV-medicated plaster (-3.7; difference -2.2; 95% CI -2.6 to -1.8; $p < 0.001$); greater changes for Cal/BD foam were observed from day 8 for each clinical sign. Absolute total skin and echo-poor band thickness change was significantly greater for Cal/BD foam than for BV-medicated plaster ($p<0.001$). Post hoc analyses showed that Cal/BD foam was significantly more effective than BV-medicated plaster on DTT (difficult-to-treat) areas after 4 weeks ($p < 0.001$) (Table 1).

3.1.3. Phase III

Cal/BD foam versus vehicle

The PSO-FAST (*Psoriasis vulgaris, a Four-week, vehicle-controlled, efficacy And Safety Trial*) study compared the

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Table 1 (Cont.) - Efficacy and safety results from Cal/BD clinical trials.

Clinical Trial	Study design	Study population	Treatments & formulations	Endpoints/ Outcomes	Efficacy results	Safety results
Phase III						
Paul, 2017[43] PSO-ABLE NCT02132936	Randomized, parallel-group, investigator-blinded Phase III, 12-week - PSO-ABLE study.	A total of 463 patients aged ≥18 years with mild-to-severe psoriasis were randomized 4:4:1:1 to Cal/BD foam (n = 185), Cal/BD gel (n = 188), foam vehicle (n = 47), gel vehicle (n = 43) Overall completion rate was 90%.	Patients were randomized to once-daily Cal/BD foam, Cal/BD gel, foam vehicle or gel vehicle.	The primary efficacy endpoint was the proportion of patients who were clear/almost clear with a ≥ 2 grade improvement according to the physician's global assessment of disease severity (i.e. treatment success) at week 4 for Cal/BD foam vs. week 8 for Cal/BD gel. Secondary efficacy endpoints included: proportion of patients achieving at least a 75% reduction in modified psoriasis area and severity index(mPASI75), and time to treatment success (TTTS). Safety was monitored throughout.	Cal/BD foam achieved higher treatment success rates (38% vs 22%; $p<0.001$) and mPASI75 (52% vs 35%; $p<0.001$) by week 4 than Cal/BD gel by week 8. Median TTTS with Cal/BD foam was 6 weeks; this could not be determined for Cal/BD gel as 50% treatment success was not achieved ($p<0.001$).	Adverse drug reactions were reported in 14 (7.6%) Cal/BD aerosol foam patients and 7 (3.7%) Cal/BD gel patients; all were single events except for itch with Cal/BD aerosol foam (n=5; 2.7%) and worsening psoriasis with Cal/BD gel (n=3; 1.6%). No SAEs were reported.
Paul, 2017[44] PSO-ABLE Sub-Group Analysis NCT02132936		159 patients with moderate-to-severe psoriasis from the PSO-ABLE study.	Cal/BD foam and Cal/BD gel (77 and 82 patients, respectively).	To assess the response to Cal/BD foam and gel in patients with moderate-to-severe psoriasis enrolled in the phase III, 12-week PSO-ABLE study.	A greater proportion achieved mPASI75 and mPASI90 with Cal/BD foam than gel at weeks 4, 8, and 12 (57.1 *vs* 35.4%; $p=0.006$ and 15.6 *vs*12.2% at week 12, respectively). The overall reduction in mPASI from baseline to week 12 was 64% with the foam *vs* 51% with the gel. Overall reduction in body surface area at week 12 was 50% with the foam and 39% with the gel. Treatment success rates were higher with the Cal/BD foam than the gel at weeks 1, 2, 4, 8 ($p=0.0089$), and 12, and a greater proportion of foam patients achieved a DLQI score of 0/1 at weeks 4 ($p=0.004$), 8, and 12 ($p=0.001$).	

ACTH - Adrenocorticotropic hormone; ADRs – Adverse reactions; AEs – Adverse events; AUC – Area under the curve; DLQI - Dermatology Life-Quality Index; DTT – Difficult to treat; HR-QOL – Health-related quality of life; MDR - maximal dermal response; MCII - mean cumulative irritation index; mPASI – modified psoriasis area and severity index; pts – Patients; SAES – Serious adverse events; SD – Standard deviation; TCS - Total clinical score; y - Years

two-compound aerosol foam versus vehicle in a phase III (NCT01866163), multicentre, double-blinded, randomized, vehicle controlled, 4-week trial.[25] From the 426 randomized patients, 53.3% achieved treatment success with Cal/BD foam *versus* 4.8% with vehicle only ($p < 0.001$). PASI score was lower in the combination group (2.0 *vs* 5.5, $p < 0.001$). At the end of the study, 82.3% of Cal/BD aerosol foam patients achieved at least a 50% reduction in mPASI (PASI50) compared with 28.0% using vehicle ($p < 0.001$); 52.9% achieved at least a 75% reduction in mPASI (PASI75) compared with 8.2% of vehicle patients ($p < 0.001$). Patients receiving Cal/BD aerosol foam reported a rapid and significantly greater reduction in itch severity and improvement in itch-related sleep loss compared with vehicle, which was maintained throughout the study. These are very important findings because itch and itch-related sleep loss are common and distressing aspects of psoriasis that can aggravate the lesions and negatively impact patients' daily productivity.[34,32] Psoriasis' impact on HR-QoL was also assessed. Baseline Dermatology Life-Quality Index (DLQI)[33] for Cal/BD aerosol foam and vehicle groups were

9.9 and 10.3, respectively, indicating a substantial impact on HR-QoL.[25] Mean baseline EQ-5D utility index scores indicated that the impaired QoL in these patients was due to significantly pain/discomfort and anxiety/depression compared with general population.[25] A significant improvement in DLQI was observed with Cal/BD foam *versus* vehicle at week 4 (–7.0 *vs* –4.4; $p < 0.001$). Approximately 50% of Cal/BD foam patients reported that psoriasis had no effect on their lives at week 4 (DLQI score of 0 or 1) (Table 1).[34]

Cal/BD foam *versus* Cal/BD gel

The randomized, investigator-blinded, 12-week PSO-ABLE (*Psoriasis - the effect of prolonged use of calcipotriol and betamethasone dipropionate combination therapy, a randomised, active- and vehicle-controlled 12-week trial*) (NCT02132936) study[34] compared Cal/BD aerosol foam with Cal/BD gel for 4 and 8 week-treatment periods, respectively. Cal/BD foam achieved treatment success (38 *vs* 22%; $p < 0.001$) and mPASI75 (52 vs 35%; $p < 0.001$) in significantly more patients by week 4 than gel at week 8. Median time to achieve treatment success with Cal/BD foam was 6 weeks, which could not be determined for Cal/BD gel as <50% of patients achieved treatment success ($p < 0.001$). Mean mPASI was significantly lower at week 4 for Cal/BD aerosol foam compared to gel at week 8 (2.2 *vs* 2.8; $p = 0.028$), and a significant difference was observed as early as week 1 (4.5 *vs* 5.2; $p < 0.001$). Regarding the impact on HR-QoL, DLQI scores improved by week 12 with both Cal/BD foam and gel. At weeks 4 and 12, significantly more patients using Cal/BD foam achieved DLQI scores of 0/1 than gel (week 4: 46% *vs* 32%, $p = 0.013$; week 12: 61% *vs* 44%; $p=0.03$) (Table 1).

A sub-group analysis aiming to assess the response to Cal/BD foam and gel in patients with moderate-to-severe psoriasis from the PSO-ABLE study (77 and 82 patients, respectively)[35] showed that a greater proportion of patients achieved mPASI75 and mPASI90 with foam than gel at weeks 4, 8, and 12 (57.1 *vs* 35.4%; $p = 0.006$ and 15.6 *vs* 12.2% at week 12, respectively). The overall reduction in mPASI from baseline to week 12 was 64% with foam vs 51% with gel. Overall reduction in BSA at week 12 was 50% with Cal/BD foam and 39% with gel. Treatment success rates were higher with Cal/BD foam than gel at weeks 1, 2, 4, 8 ($p = 0.0089$), and 12, and a greater proportion of foam-treated patients achieved a DLQI score of 0/1 at weeks 4 ($p = 0.004$), 8, and 12 ($p = 0.001$) (Table 1). This analysis came to prove that although moderate-to-severe psoriasis is typically treated with systemic/biologic therapies, Cal/BD foam is efficacious in these patients and may be a cost-saving alternative to systemic therapy.[44]

3.2. Safety data

Safety profile of Cal/BD fixed combination is well established. Although long-term continuous use of topical corticosteroids can lead to skin atrophy, recent studies have demonstrated that the addition of calcipotriol reduces the early signs of treatment-induced skin atrophy by modulating key extracellular matrix (ECM) components.[2,13,36] Calcipotriol opposing effects on matrix metalloproteinases counteracts the betamethasone-induced suppression of collagen 1 and hyaluronic acid synthesis.[2,45] As local skin irritation calcipotriol--related are attenuated by betamethasone addition, most likely due to its anti-inflammatory properties, the fixed combination has a more favourable tolerability profile compared with individual monotherapies.[2,13,37] Moreover, the presence of calcipotriol may increase the effect of the steroid within the combination without affecting the tolerability profile.[16,38] Overall, adverse drug reactions were seen in 3.1% - 14% of patients regarding the two-compound treatment ointment or gel formulations.[2] A long-term safety study of Cal/BD fixed combination for psoriasis' treatment (a 52-week international, multicentre, randomized, double-blinded, long-term study) proved that the two-compound product has a safe and good tolerability profile.[39]

Clinical trials involving Cal/BD aerosol foam have demonstrated that this formulation is safe and well tolerated. Once that the application frequency is reduced by the combination treatment foam, a significant reduction of both active ingredients monotherapies-related adverse events (AEs) is also observed.[13] AEs were generally of mild or moderate severity,[2,3,25,37- 39,43] mostly lesional or perilesional, rarely leading to treatment discontinuation.[3,25,38,39] Skin atrophy, adrenal suppression based on ACTH stimulating test, clinically relevant changes to HPA axis or calcium homeostasis were rarely reported (Table 1).[3,25,38,39,43]

In a pooled safety analysis set including PSO-FAST patients[25] and from two other trials of 4 weeks' duration,[38,39] (N = 1099) at least one treatment-related AE was reported in 2.7% of Cal/BD foam recipients, 3.0% of Cal/BD ointment recipients, 6.1% of calcipotriol foam recipients and 7.1% of betamethasone foam recipients.[3] In patients receiving Cal/BD foam, the most common treatment-related AEs (occurring in at least two patients) were application-site pruritus and pain (0.4% and 0.5%, respectively). Hypersensitivity (occurring in one patient) was the only serious AE that was considered possibly related to treatment. Two patients (0.4%) receiving Cal/BD foam discontinued treatment because of AEs, but they were not reported as treatment-related.[3]

4. CONCLUSION

In recent years, clinical research has been focused on biologic or systemic treatment agents, which respond to the needs of a psoriatic patients' minority (20%). Still, Cal/BD association is the mainstay of treatment for mild-to-moderate psoriasis (80%). Ointment and gel formulations' efficacy is well established in this population, however, many of these patizzents are not optimally controlled with available topical therapies and adherence to treatment remains a significant clinical challenge. Patients' dissatisfaction regarding regimen inconvenience and treatment formulation, contributes to poor adherence to these therapies and lack of efficacy. As such, an effective, easy-to-use formulation should lead to an improved adherence in clinical practice.

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Cal/BD aerosol foam was developed to overcome these limitations and to further increase patients' therapeutic options. This alcohol-free foam, with a non-skin-drying emollient paraffin-based vehicle, is applied once daily to the affected areas using a pressurized spray can, is rapidly effective for treating psoriasis, with a consistent and clinically relevant higher efficacy than ointment and gel formulations. Enhanced efficacy is related to the improved skin penetration of the active ingredients. Several studies have demonstrated that a stable supersaturated solution of the active ingredients is formed when its solvent rapidly evaporates after application on the skin. This phenomenon increases the solubility of the active ingredients and leads to greater skin penetration and increased bioavailability, which in turn leads to greater efficacy of Cal/BD aerosol foam compared with other formulations. Clinical studies have showed growing patients' satisfaction towards this optimized formulation, which has the potential for greater acceptability, leading to a higher adherence and treatment success than formulations that do not offer these characteristics, helping to address the unmet medical needs of patients with mild-to--moderate psoriasis.

Cal/BD aerosol foam formulation has proved a higher efficacy in clinical studies, without disregarding safety profile. A pooled analysis of the main clinical studies has demonstrated that this greater efficacy does not occur at the expense of the safety profile. Phase II and III clinical trials have consistently shown the two-compound formulation to be more effective and safer than its individual ingredients in the same vehicle for treating body psoriasis. Furthermore, Cal/BD aerosol foam has shown a significantly improved efficacy compared with more traditional formulations, such as ointments, gels, and lotions.

Targeting specific molecules involved in the disease pathophysiology, as observed in fixed-dose combination treatment, results in an early and rapid response. This increases patients' confidence in the treatment and adherence to it, which, in turn, contributes to a greater effectiveness. Research has shown that if patients believe a treatment is effective and easy to use they are more likely to be adherent, which similarly leads to better treatment's outcomes. So, besides overcoming some of the limitations related with other topical treatments, Cal/BD foam is also a cost saving formulation. Once duration of therapy course is shorter and onset of action is faster, a reduced amount of Cal/BD foam would be required.

The PSO-ABLE study showed that >75% of patients felt that Cal/BD aerosol foam was more effective, easier to apply and more tolerable than other topical and systemic therapies they had previously experienced. One possible future initiative that could be considered is patient education regarding the importance of adherence to topical therapies. By combining appropriate patient education and the use of more effective topical therapies, it might be possible to control mild-to-moderate psoriasis and avoid or delay systemic treatment introduction.

As the aim of any pharmacological intervention is to induce disease remission and to prevent relapses, after achieving a free-disease state, its maintenance becomes the therapeutic goal. Inflammation tends to recur in previously affected locations, which may be caused by the expression and reactivation of inflammatory cytokines present in the apparently normalized, plaque-free skin after treatment. Once that most topical therapies are approved for short-term use only (≤ 8 weeks), there is a clinical need for a topical therapy that can be effectively used for long-term maintenance. Further clinical investigations to explore the possibility of Cal/BD aerosol foam treatment ability to provide long-term psoriasis' management are required.

The improved efficacy and safety profile of the new formulation of Cal/BD fixed-dose combination treatment, together with the once-daily treatment, a more acceptable tolerability profile, and an early and rapid response, offers improved convenience and better acceptance over the twice-daily applications required for the respective monotherapies, which may improve adherence to treatment, and subsequently lead to faster and greater improvements in patients' QoL, representing a useful therapeutic option to the management of patients with plaque psoriasis.

Acknowledgements/Agradecimentos:

Editorial assistance was provided by Maria João Santos, from Pharma Research.

Conflicts of interest/Conflitos de interesse: *Tiago Torres was a speaker, Advisory Board member, investigator of observational studies/clinical trials supported by: Abbvie, Amgen, Boehringer Ingelheim, Janssen-Cilag, Leo-Pharma, LillyEli, Merck-Serono, Merck Sharp & Dohme, Novartis, and Pfizer.*
Paulo Filipe was a speaker, Advisory Board member, investigator of observational studies/clinical trials supported by: Abbvie, Amgen, Boehringer Ingelheim, Janssen-Cilag, Leo-Pharma, LillyEli, Merck-Serono, Merck Sharp & Dohme, Novartis, and Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Financing Support/ Suporte financeiro: *Financial support has been granted by LEO Pharma.*

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