COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Crysalis 50 microgram/g + 0,5 mg/g, gel (calcipotriol monohydrate/betamethasone dipropionate)

NL/H/6536/001/DC

Date: 15 October 2025

This module reflects the scientific discussion for the approval of Crysalis 50 microgram/g + 0,5 mg/g, gel. The procedure was finalised at 19 April 2021 in Germany (DE/H/6739/001/DC). After a transfer on 11 September 2025, the current RMS is the Netherlands. For information on changes after the finalisation date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the data on quality, the application for Crysalis 50 microgram/g + 0,5 mg/g, gel, from Laboratoires Medgen, with the following indication:

"Topical treatment of scalp psoriasis in adults. Topical treatment of mild to moderate "non-scalp" plaque psoriasis vulgaris in adults."

is approved.

This is an application according to Art 10.3 (hybrid application). Multiple/Duplicate Applications were submitted.

The topical Crysalis gel has been developed as an alternative of the innovator product Daivobet® gel approved in the European Union for the topical treatment of scalp psoriasis in adults as well as the topical treatment of mild to moderate "non-scalp" plaque psoriasis vulgaris in adults (German authorisation no 69204.00.00, date of first authorisation: 8th of December 2008).
Pharmacotherapeutic group: Antipsoriatics.
Other: Antipsoriatics for topical use, Calcipotriol, combinations.
ATC Code: D05AX52

Calcipotriol is a vitamin D analogue. In vitro data suggest that Calcipotriol induces differentiation and suppresses proliferation of keratinocytes. This is the proposed basis for its effect in psoriasis.
Like other topical corticosteroids, betamethasone dipropionate has anti-inflammatory, antipruritic, vasoconstrictive and immunosuppressive properties, however, without curing the underlying condition. The effect can be enhanced by occlusion due to increased penetration of the stratum corneum. On the other hand, the incidence of adverse events will increase because of this. In general, the mechanism of the anti-inflammatory activity of the topical steroids is unclear.

<u>General comments on the submitted dossier</u>
Crysalis gel is a locally applied and locally acting drug product, consequently the legal base for the marketing authorisation application is Article 10 (3) of Directive 2001/83/EC.
To demonstrate that topical treatment with the proposed medicinal product is therapeutically equivalent to the innovator product Daivobet® gel in the treatment of chronic stable, mild to moderate plaque-type psoriasis as determined by the percentage reduction in psoriasis area and severity index (PASI) and to demonstrate the superiority of the proposed drug product to its vehicle, a phase III, multicentre, randomised, double-blind, parallel-group trial has been conducted.

General comments on compliance with GMP, GLP
Quality:
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substances:
Regarding the statement on GMP for the active substances, statements/declarations are provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU.
The applicant stated that the clinical trial was conducted in compliance with Good Clinical Practice (GCP) including the archiving of essential documents.

The concerned member state (CMS) involved in this procedure was France.

II. QUALITY ASPECTS

II.1 Introduction

The drug product is a gel for cutaneous application containing 50 microgram/g of Calcipotriol (as monohydrate) and 0.5 mg/g of Betamethasone (as dipropionate).
The Crysalis gel for topical treatment has been developed as an alternative to the innovator product Daivobet® gel. The excipients are polyoxypropylene stearyl ether, hydrogenated castor oil and liquid paraffin. They were selected based on the Innovator and the quality of the excipients comply with the requirements of the corresponding Ph. Eur. Monographs.

The product specification covers relevant parameters for this dosage form.

30g or 60g of Crysalis gel is packed in white cylindric HDPE tubes without membrane and seal, with white PP screw cap without pin.

II.2 Drug Substance

The drug product contains two drug substances, Calcipotriol (as monohydrate) and Betamethasone (as dipropionate). Betamethasone dipropionate is described in the Ph. Eur. monograph no. 0809. Calcipotriol monohydrate is described in the Ph. Eur. monograph no. 2284.

Manufacturing process
Betamethasone dipropionate is controlled in accordance with the Ph. Eur. monograph and the additional requirements of the CEP for residual solvents. Furthermore, acceptance criteria for

particle size distribution are specified, as micronised Betamethasone dipropionate is used for manufacture of the drug product.

Calcipotriol monohydrate is controlled in accordance with the Ph. Eur. monograph and the respective additional requirements of the CEPs for residual solvents.

Quality control of drug substance
Batch analysis results of micronised Betamethasone dipropionate from both the ASM and the drug product manufacturer have been provided.

Batch analysis results from both the ASM and the drug product manufacturer have been provided for Calcipotriol monohydrate.

II.3 Medicinal Product

Pharmaceutical development
The drug product is a water-free, oily formulation which contains the active product ingredient in dissolved (Calcipotriol monohydrate) or partially dissolved / partially suspended form (micronised Betamethasone dipropionate) in the gel matrix structure.

Quality control of drug product
Validations of the analytical methods have been presented. Batch analysis results are provided for the three process validation batches filled in both 30g and 60g tubes. The specified parameters were met.

Stability of drug product
Stability studies of the three validation batches filled in both 30g and 60g tubes are available under accelerated conditions at 40°C/75%RH for six months, and for the ongoing long term stability study at 25°C/60%RH for 24 months. The samples were stored cap down and horizontal. The batches were tested according to the updated specification. From the stability results, the proposed shelf life of 24 months under the storage conditions “Do not refrigerate” is justified. From the in-use stability data, the proposed in-use shelf life of 6 months after first opening is considered justified.

Conclusion
The DCPs are approvable from the quality point of view. There are no outstanding quality issues.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

The applicant provided a Phase I ERA for the active ingredients calcipotriol and betamethasone including PBT assessment, PECsurface water (PECsw) calculation and a detailed risk assessment for betamethasone as endocrine active substance.

The provided Kow study in the updated ERA for both active ingredients is considered acceptable. Since LogP of calcipotriol exceeds the trigger value for a PBT assessment, the substance was assessed by using metabolism data and read across from cholecalciferol ECHA dossier. This approach is considered to be not appropriate for the PBT assessment. Thus a stepwise PBT assessment is considered necessary, starting with the P assessment, i.e. a study on transformation in water/sediment systems according to OECD 308 unless it can be shown that calcipotriol is readily biodegradable. To waive the PBT assessment the applicant provided a justification. containing a list of already marketed products with calcipotriol and betamethasone dipropionate as active substances, data on released amounts of calcipotriol kilograms from 2016 to 2019 in RMS and CMSs and the market share of generics in comparison to the originator. The released amounts of calcipotriol show an increase in all member states from 2016 to 2019 and the market share a domination by the originator products. More products on the market will lead to increasing consumption. Therefore, the justification cannot be accepted.
However, it seems unlikely to reach an agreement in terms of the conclusion on the potential environmental risk of this product containing calcipotriol monohydrate and betamethasone dipropionate within this procedure. Due to the fact that the present application is a generic application according to §10(3) of directive 2001/83/EC as amended, open non-clinical issues will not be pursued further.

The recalculated refinements in the PECsw calculation bases on treatment regime are acceptable. The ERA for calcipotriol can stop in Phase I. The PECsw of betamethasone is below the action limit but betamethasone is a potential endocrine active substance. Therefore, the applicant provided data which can be used for a tailored ecotoxicity assessment. The updated risk assessment of betamethasone clearly indicates a risk for the aquatic compartment which is communicated in the SmPC.

Summary of main study results

Substance (INN/Invented Name): CALCIPOTRIOL MONOHYDRATE			
CAS-number (if available): 147657-22-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log *K*ow	OECD 123	5.45	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log *K*ow	5.45	Potentially B
	BCF		B/not B
PBT-statement :	TPending		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surface water , default or refined (treatment regime)	0.000723	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

Substance (INN/Invented Name): BETAMETHASONE DIPROPIONATE					
CAS-number (if available): 5593-20-4					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log *K*ow	OECD 123	4.26			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log *K*ow	4.26			Potentially □
	BCF	Not required			B/not B
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC surface water , default or refined (treatment regime)	0.00723	□g/L			≥ 0.01 threshold (N)
Other concerns (e.g. chemical class)	Betamethasone dipropionate is a glucocorticoid and, as such, is considered a potential endocrine active substance and therefore the potential endocrine activity of this compound should be investigated in an appropriate chronic test system with relevant endpoints				(Y)
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**

Fish, Full Life Cycle *Oryzias latipes* 133 d F0 + 91 d F1, flow-through, analysis <80%	-	NOEC	0.0672	µg/L	Vestel et al., 2017 Human Ecol Risk Assessm, 23, 4, 879–894 Acceptable with restrictions, CRED 2

Conclusions on studies:
A final conclusion on potential risk of calcipotriol to the environment cannot be drawn. The PECsw of the active substance calcipotriol is below the action limit of 0.01 µg/L. Regarding the PBT assessment studies are missing to conclude on the PBT properties.
The ERA provided for betamethasone dipropionate is considered complete and acceptable. Considering the above data, betamethasone dipropionate is expected to pose a risk to the aquatic compartment. This information is included in the product information. A PBT assessment was not required as the logP value does not exceed the action limit of 4.5.

III.2 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of the individual drug substances calcipotriol and bethamethasone are well known and the topical use of the fixed combination of calcipotriol and betamethasone is well established for the treatment of psoriasis.
The strengths of the drug substances calcipotriol and betamethasone (0.05 mg and 0.5 mg per g gel) correspond to the originator. All excipients used in the final formulation are well known, monographed in the European Pharmacopoeia and are also part of the Daivobet formulation.
The applicant has not provided additional non-clinical studies and further studies are not required. Overview based on literature review is, thus, appropriate.
The provided non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

To demonstrate that topical treatment with the proposed drug product is therapeutically equivalent to the innovator product Daivobet® gel in the treatment of chronic stable, mild to moderate plaque-type psoriasis as determined by the percentage reduction in psoriasis area and severity index (PASI) and to demonstrate the superiority of the proposed drug product to its vehicle, a phase III, multicentre, randomised, double-blind, parallel-group trial has been

conducted (0155/2018). The applicant followed the scientific advice during a meeting at BfArM at 18.04.2018.

IV.2 Clinical efficacy

A total of 14 trial centres recruited subjects:
4 trial centres in Germany and 10 trial centres in Poland

Objectives:
The primary objectives were:
(a) To demonstrate that topical treatment with the Generic Calc/Bet gel is therapeutically equivalent to the originator Daivobet® gel in the treatment of chronic stable, mild to moderate plaque-type psoriasis as determined by the percentage reduction in psoriasis area and severity index (PASI)
(b) To demonstrate the superiority of the generic gel to its vehicle

Methodology:
This trial was a randomised, double-blind, parallel-group trial to evaluate the efficacy and safety of a generic Calc/Bet gel (calcipotriol + betamethasone 50 µg/g + 0.5 mg/g gel) compared to the Originator gel (Daivobet® gel) and the generic vehicle gel in the treatment of mild to moderate plaque-type psoriasis.
The trial design consists of a 28-day screening period, a 4-week comparative treatment period, and a subsequent treatment period for up to 4 weeks (8 treatment weeks in total). Each subject had 5 visits (V1-screening, V2-Day 1 [randomisation], V3-Week 2/Day 15, V4-Week 4/Day 29 [primary endpoint visit], and V5-Week 8/Day 56 [End of Treatment]), as well as unscheduled visits as needed.
Approximately 280 subjects were planned to be randomised on Day 1 to receive one of 3 treatment arms (Generic Calc/Bet gel, Originator gel [Daivobet® gel], or Generic vehicle gel) once daily for up to 8 weeks.
The treatment allocation was on a 3:3:1 ratio (120:120:40 subjects) in a blinded manner; site staff, the subject, the Sponsor, and the CRO staff did not know the identity of the study drug assigned. Subjects were randomised to one of the following 3 treatment groups:

- Generic Calc/Bet gel, 120 subjects
- Originator gel (Daivobet® gel), 120 subjects
- Generic vehicle gel, 40 subjects

Topical application of approximately 5g gel once daily (OD) for up to 8 weeks (56 consecutive days). Recruitment was competitive between the sites.
Efficacy was evaluated through PASI/mPASI, IGA, and the determination of BSA at Screening Visit, Day 1, Day 15, Day 29 and Day 56.

Planned: Approximately 280 subjects were to be randomised into 3 treatment groups in a 3:3:1 ratio (Generic Calc/Bet gel, Originator gel [Daivobet® gel], or Generic

vehicle gel), (120:120:40 subjects) in order to have a suitable number of evaluable subjects.

Analysed: A total of 313 subjects were screened and 286 subjects were randomised.

None of the randomised subjects were excluded from the SES. Three subjects (1 subject of the Generic Calc/Bet gel arm and 2 subjects of the Daivobet® gel arm) were excluded from the FAS and PPS due to serious violations of in- or exclusion criteria likely to invalidate the assessment of efficacy.
Further 39 subject were excluded from the PPS, mostly because the 'subject did not attend the efficacy assessments at the Week4/Day 29 visit within a window of ± 2 days' reported in a similar share across treatment arms (29 subjects in total; 7% to 13% of the subjects by treatment arm).

Diagnosis and main criteria for inclusion:
Male and female, aged 18 years or older with mild to moderate chronic plaque psoriasis, BSA score up to 20%, PASI score ≥ 5.0 to ≤ 15.0 at baseline, category "mild", "moderate" or "moderate to severe" on IGA scoring (IGA 2 to 4).

Criteria for evaluation:
The primary efficacy variable was:

1. Mean % change from baseline in PASI at Week 4/Day 29

The secondary efficacy variables were:

2. Improvement (1 or more points change on a 6-point scale) in IGA at Week 4/Day 29
3. Mean % change from baseline in mPASI at Week 4/Day 29 and at Week 8/Day 56 (calculated using values from PASI evaluation)
4. Mean % change from baseline in PSSI at Week 4/Day 29 (assessed using the same component scoring criteria and the extent (%) as for PASI evaluation)

Statistical methods:
Full analysis set
The full analysis set included all randomised subjects who received at least one IMP application. Subjects might, however, have been excluded from the FAS on individual justification in case of serious violations of inclusion or exclusion criteria. Subjects were analysed for efficacy according to the investigational treatment that they were randomised to.
Per protocol analysis set
The per protocol analysis set included all FAS eligible subjects who completed the 4-week comparative treatment period with at least 75% of the scheduled applications, attended the efficacy assessments at the Week 4/Day 29 visit within a window of ± 2 days, and had no major protocol deviations interfering with the assessment of the primary efficacy outcome measure. In a blind data review meeting (BDRM) all protocol deviations were reviewed considering their influence on the efficacy assessments that warrant exclusion from the PPS.

Efficacy analyses

Hypotheses

The primary efficacy endpoint was the mean relative (%) change from baseline of the PASI score at Week 4/Day 29. The primary (confirmatory) analyses included a test of superiority of the generic product over its vehicle as well as a test of equivalence between the generic and the originator product. For the latter comparison, an equivalence margin of δ=15 % (absolute difference) was applied.

Justifying the non-inferiority margin mainly on clinical reasoning is appropriate. Firstly, the study had a three arm design including vehicle such that providing indirect assurance that the test drug has a clinically relevant superiority over vehicle was not required as a direct comparison was possible (which also confirmed that the effect vs vehicle was substantially larger than the chosen NI margin). Secondly, the primary aim of the study was not providing evidence of efficacy but demonstration of clinical equivalence.

Primary analyses

The primary efficacy endpoint, mean relative (%) change from baseline of the PASI score at Week 4/Day 29, was compared between the treatment groups using repeated measures analyses employing a restricted maximum likelihood (REML)-based, mixed-effects model approach (MMRM)..

The confirmatory comparison was the contrast between the treatments at the Week 4/Day 29 visit.

Estimates with two-sided 95% confidence intervals and significance tests were provided based on least-squares means.

Co-primary endpoint: Equivalence between the generic and the originator product

For the assessment of equivalence of the generic and the originator product with respect to the mean % change from baseline of the PASI score at Week 4/Day 29, a two-sided 95% confidence interval was determined for the difference μg - μo, of the means μg and μo, in the generic product group and the originator group, respectively. The difference was based on the adjusted mean values determined in the MMRM model and is presented with the confidence interval.

Equivalence was concluded if the confidence interval would have been included entirely within a range of -15% to +15%. The conclusion had to be proven for both analyses, the FAS, as well as the PPS analysis.

Co-primary endpoint: Superiority of the generic product over its vehicle

For the assessment of superiority of the generic product over its vehicle with respect to the mean % change from baseline of the PASI score at Week 4/Day 29, an upper one-sided 97.5% confidence interval was determined for the difference μg - μv, of the means μg and μv, in the generic product group and the generic vehicle group, respectively. The difference was based on the adjusted mean values determined in the MMRM model and is presented with the confidence interval.

Superiority was concluded if the upper confidence interval was negative, i.e. did not include zero. The conclusion had to be proven for the FAS analysis.

As the conclusion from the interim analysis was not to increase the sample size, no adjustment of significance level was applied for the final analysis.

The MMRM analysis is an acceptable method for equivalence testing because it is a sensitive method to show differences between treatments. For demonstration of superiority vs vehicle, MMRM (or other methods based on the missing at random assumption) is usually not recommended because it addresses the hypothetical effect if all patients were fully adherent to treatment, which is usually not of primary regulatory interest. However, it is acceptable in this case where the aim of the superiority analysis was primarily the demonstration of assay sensitivity rather than establishing efficacy of the test product. In addition, it needs to be taken into account that the number of patients who discontinued the study before week 4/day 29 visit was low, particularly for the active treatment groups.
It is acknowledged that the size of most sites was small. However, the strategy for pooling sites was only based on the size of the sites, which has no obvious scientific justification. However, subgroup analyses for important demographic and baseline disease characteristics including country were provided and showed overall consistency of the results.

Secondary analyses
There was no confirmatory testing on secondary endpoints, and hence any p-values resulting from tests on secondary endpoints were considered descriptive.
Multiple imputations (MI) were applied for the evaluation of the secondary endpoints. Secondary endpoints included treatment group comparisons for the PASI (except for the Week 4/Day 29 visit which was the primary endpoint), the mPASI, the IGA and the PSSI scores.
Secondary analyses included the following treatment group comparisons:

- Improvement (1 or more points change on a 6-point scale) in IGA at Week 4/Day 29
- Mean % change from baseline in mPASI at Week 4/Day 29 and at Week 8/Day 56
- Mean % change from baseline in PSSI at Week 4/Day 29:

The other secondary analyses, namely comparisons of treatments group comparisons with respect to

- improvement in IGA at Week 2/Day 14 and at Week 8/Day 56,
- mean % change from baseline in mPASI at Week 2/Day 14,
- mean % change from baseline in PSSI at Week 2/Day 14 and at Week 8/Day 56 were performed following the methods given above.

Sensitivity analyses
Since MMRM assumes missing data to be missing at random, sensitivity analyses were performed to assess the validity of the missing at random assumption.
The sensitivity of the primary analysis with respect to the missing data was assessed by evaluation of the co-primary endpoints in the FAS with missing values imputed by MI. However, as the multiple imputation analyses as conducted were also based on the missing at random assumption, these are not suitable for this purpose. As the number of missing values is low, assessing the validity of MAR is not considered a relevant issue.

Interim analysis

Due to uncertainty regarding the variability of the primary outcome variable, an unblinded interim analysis was performed by an independent, external statistician (Psy Consult Scientific Services) after about 80% of the pre-planned number of subjects had completed the 4-week PASI assessment. The purpose of the interim analysis was to verify the assumptions underlying the initial sample size estimation laid down in the trial protocol, and to increase the sample size, should this have been required to maintain the pre-defined target power.

Although a blinded sample size re-assessment is usually preferred, the applicant's justification that deriving a reasonable estimate of the variance based on the pooled patient population is not possible in a study including a vehicle arm is accepted.

The procedures for ensuring confidentiality of interim results are considered appropriate.

Efficacy results

This phase III, multicentre, randomised, double-blind, parallel-group trial (n=286) demonstrated equivalence between the Generic Calc/Bet gel and the Daivobet® gel and as well superiority of the Generic Calc/Bet gel over the Generic vehicle gel with respect to the mean % change from baseline of the PASI score at Week 4/Day 29.

Results are presented in the following tables:

Analysis Population

Table 2 Analysis populations overall

	Generic Calc/Bet gel N (%)	Daivobet® gel N (%)	Generic vehicle gel N (%)	Total N (%)
Number of subjects screened				N=313
Number of subjects randomised	N=124	N=123	N=39	N=286
Subjects included in SES[1]	124 (100)	123 (100)	39 (100)	286 (100)
Subjects included in FAS[1]	123 (99)	121 (98)	39 (100)	283 (99)
Subjects included in PPS[1]	109 (88)	103 (84)	32 (82)	244 (85)

Calc/Bet: calcipotriol-betamethasone, FAS: full analysis set, PPS: per protocol analysis set, SES: safety evaluation set .

[1] Percentages calculated on number of subjects randomised

The main reason for patients being excluded from the PP analysis was 'Deviations regarding visit completion'. On the other hand, the number of patients who discontinued study before visit 4/day 29 was small. Particularly, it was smaller than the number of patients with deviations regarding visit completion. However, this issue is explained by Week 4 / Day 29 visits that were completed but not within the +/- 2 day window that was pre-specified as requirement for subjects to be included in the PPS.

Primary analyses

Table 3 Relative (%) change from baseline of PASI – MMRM analysis Week 4/ Day 29 (FAS)

Relative change from baseline in PASI[1]	Generic Calc/Bet gel	Daivobet®	Generic vehicle gel
Subjects in FAS	(N=123)	(N=121)	(N=39)
Week 4/Day 29			
n[2]	123	120	33
Mean ± SE[3]	-58.1 ± 2.2	-59.8 ± 2.3	-21.8 ± 4.2
95%-CI[3]	-62.5, -53.7	-64.2, -55.3	-30.0, -13.5
Mean difference[4] ± SE[3]		1.7 ± 3.2	-36.3 ± 4.7
Mean difference[4] 95%-CI[3]		-4.6, 7.9	-45.7, -27.0
Conclusions[5,6]		Equivalence	Superiority

[1] Relative change from baseline [%] determined as 100 * (post-baseline assessment - baseline assessment) / baseline assessment.
[2] Number of observed cases.
3 Estimates determined using a REML (restricted maximum likelihood) based MMRM (mixed-effects model approach) model of relative (%) change from baseline to Week 4/Day
29, including fixed, categorical effects of treatment, visit, treatment-by-visit interaction and analysis site as well as the baseline PASI score as a continuous, fixed covariate. Within subject errors modelled using an unstructured covariance matrix and Kenward-Roger correction used for the denominator degrees of freedom.
[4] Difference of relative change vs. Generic Calc/Bet gel, determined as Generic Calc/Bet gel minus Daivobet® gel and Generic Calc/Bet gel minus Generic vehicle gel, respectively.
[5] Equivalence of Generic Calc/Bet gel and Daivobet® gel concluded, if the confidence interval is included entirely within the equivalence range of -15% to +15%.
[6] Superiority of Generic Calc/Bet gel vs. Generic vehicle gel concluded, if the upper limit of the confidence interval is negative, i.e. does not include zero.
Calc/Bet: calcipotriol-betamethasone, CI: confidence interval, FAS: full analysis set, MMRM: mixed-effects model approach, PASI: psoriasis area severity index, REML: restricted maximum likelihood, SE: standard error.

Table 4 Relative (%) change from baseline of PASI – MMRM analysis Week 4/ Day 29 (PPS)

Relative change from baseline in PASI[1]	Generic Calc/Bet gel	Daivobet®	Generic vehicle gel
Subjects in PPS	(N=109)	(N=103)	(N=32)
Week 4/Day 29			
n2	109	103	28
Mean ± SE[3]	-57.7 ± 2.4	-59.6 ± 2.5	-23.2 ± 4.6
95%-CI[3]	-62.5, -53.0	-64.4, -54.7	-32.2, -14.2
Mean difference[4] ± SE[3]		1.8 ± 3.4	-34.5 ± 5.2
Mean difference[4] 95%-CI[3]		-4.9, 8.6	-44.7, -24.3
Conclusions[5,6]		Equivalence	Superiority

[1] Relative change from baseline [%] determined as 100 * (post-baseline assessment - baseline assessment) / baseline assessment.
[2] Number of observed cases.
[3] Estimates determined using a REML based MMRM model of relative (%) change from baseline to Week 4/Day 29, including fixed, categorical effects of treatment, visit, treatment-by-visit interaction and analysis site as well as the baseline PASI score

as a continuous, fixed covariate. Within subject errors modelled using an unstructured covariance matrix and Kenward-Roger correction used for the denominator degrees of freedom.
[4] Difference of relative change vs. Generic Calc/Bet gel, determined as Generic Calc/Bet gel minus Daivobet® gel and Generic Calc/Bet gel minus Generic vehicle gel, respectively.
[5] Equivalence of Generic Calc/Bet gel and Daivobet® gel concluded, if the confidence interval is included entirely within the equivalence range of -15% to +15%.
[6] Superiority of Generic Calc/Bet gel vs. Generic vehicle gel concluded, if the upper limit of the confidence interval is negative, i.e. does not include zero.
Calc/Bet: calcipotriol-betamethasone, CI: confidence interval, MMRM: mixed-effects model approach, PASI: psoriasis area severity index, PPS: per protocol set, REML: restricted maximum likelihood, SE: standard

Co-primary endpoint: Equivalence between the generic and the originator product
The mean % change from baseline of the PASI score at Week 4/Day 29 was comparable for the Generic Calc/Bet gel and the Daivobet® gel. The confirmatory analyses proved equivalence of the Generic Calc/Bet gel to the Daivobet® gel with respect to the mean % change from baseline of the PASI score at Week 4/Day 29 for both analysis data sets (FAS and PPS), since the CIs were included entirely within a range of -15% to +15%. The sensitivity analyses showed similar results which support the outcome of the primary analyses based on the FAS and PPS.

Co-primary endpoint: Superiority of the generic product over its vehicle
A greater mean % change from baseline of the PASI score at Week 4/Day 29 was noted for the Generic Calc/Bet gel when compared to the Generic vehicle gel for the FAS (primary analysis population).

The confirmatory test showed superiority of the Generic Calc/Bet gel over its vehicle gel with respect to the mean % change from baseline of the PASI score at Week 4/Day 29, since the upper CI was negative. The sensitivity analyses showed similar results which support the outcome of the primary analysis based on the FAS.

Secondary analyses
PASI
The mean % changes from baseline of the PASI score were comparably high for the Generic Calc/Bet gel and Daivobet® gel in the FAS and the PPS at Week 2/Day 15 and at Week 8/Day 56.
No statistically significant differences were found between the two active treatment arms. The mean % changes from baseline of the PASI score were statistically significantly lower for the Generic vehicle gel in the FAS and the PPS at Week 2/Day 15 and at Week 8/Day 56.
Over the trial period, the mean absolute PASI scores decreased distinctly for the Generic Calc/Bet gel and the Daivobet® gel arm with the greatest mean changes of -5.27 and -5.59 (FAS), respectively, at Week 8/Day 56. The PASI scores of the Generic vehicle gel arm also decreased during the course of the trial but to a less distinctive degree with the greatest mean change of -2.80 at Week 8/Day 56. Similar results were observed for the PPS.

IGA
The proportion of responder subjects for IGA were comparable for the active treatment arms (Generic Calc/Bet gel and the Daivobet® gel arm) and this proportion increased during the course of the trial (from Week 2 to Week 8), i.e., showed improvement by at least 1 point in

the 6-point IGA scale, for the FAS (Week 2: 57% and 64%, Week 4: 77% and 78%, Week 8: 83% and 82%, respectively). A statistically significantly less increase was seen in the percentage of IGA responders in the Generic vehicle gel arm. The highest responder rate was assessed at Week 8 with 42%.
An improvement from an initial 'mild' to 'moderate to severe' (scores 2 to 4) disease severity was already noted for both active treatment arms (Generic Calc/Bet gel and Daivobet® gel arm) at Week 2 while no distinct improvement was noted for the subjects of the Generic vehicle gel arm.
At Week 4, a further improvement to 'clear' (score 0) or 'almost clear' (score 1) was rated for 43% and 44% and to 'mild' for 43% and 47% of the subjects of the Generic Calc/Bet gel or the Daivobet® gel arm, respectively. On the contrary, 'mild' or 'moderate' were rated for most of the subjects (45%, each) in the Generic vehicle gel arm.
At Week 8, 'almost clear' or 'clear' were rated for most of the subjects (57% and 54%) of the Generic Calc/Bet gel arm and the Daivobet® gel arm, respectively; next frequently 'mild' was rated (30 % and 38%, respectively). A slight trend to an improvement in disease severity was seen in the Generic vehicle gel arm with 'mild' rated most frequently (52%); 'moderate' was rated in 35% of the subjects. Similar results were observed for the PPS.

mPASI and PSSI
In the mPASI and PSSI subgroups, the mean % changes from baseline of the mPASI/PSSI scores were comparably high for the Generic Calc/Bet gel and Daivobet® gel at Week 2/Day 15, Week 4/Day 29 and at Week 8/Day 56 (FAS and PPS). No statistically significant differences were found between the two active treatment arms. Whereas, statistically significantly lower mean % changes from baseline were seen for the Generic vehicle gel when compared to the Generic Calc/Bet gel at each assessment point (FAS and PPS).
Over the trial period, the mean absolute mPASI scores decreased distinctly for the Generic Calc/Bet gel and the Daivobet® gel arm with the greatest mean changes of -4.73 and -5.30, respectively, at Week 8/Day 56 (mPASI subgroup in FAS). The mPASI scores of the Generic vehicle gel arm decreased to a less distinctive degree with the greatest mean change of -2.45 at Week 8/Day 56. Similar results were observed for the mPASI subgroup in the PPS.

The mean absolute PSSI scores also decreased distinctly for the Generic Calc/Bet gel and the Daivobet® gel arm with the greatest mean changes of -11.5 and -10.9, respectively, at Week 8/Day 56 (PSSI subgroup in FAS). The PSSI scores of the Generic vehicle gel arm decreased to a less distinctive degree with the greatest mean change of -6.3 at Week 8/Day 56. Similar results were observed for analysis of the PPS in both active treatment arms, whereas the mean change in PSSI was lower for the Generic vehicle gel arm in the PPS than in the FAS.

Table 5 IGA Improvement OC/MI (FAS)

IGA Improvement	**Generic Calc/Bet gel**	**Daivobet gel**	**Generic vehicle gel**
Subjects in FAS	(N=123)	(N=121)	(N=39)
Week 2/Day 15			
n	122	121	38

Responder[1] [N (%)]	69 (57)	78 (64)	6 (16)
Non-responder[1] [N (%)]	53 (43)	43 (36)	32 (84)
Responder[1,3] [%]	56	64	16
Odds Ratio[3,4]	0.697	7.093	
Odds Ratio 95%-CI[3,4]		0.413, 1.176	2.731, 18.422
p-value[3,5]		0.1754	< 0.001
Week 4/Day 29			
n	123	120	33
Responder[1] [N (%)]	95 (77)	93 (78)	10 (30)
Non-responder[1] [N (%)]	28 (23)	27 (23)	23 (70)
Responder[1,3] [%]	77	78	29
Odds Ratio[3,4]		0.959	8.667
Odds Ratio 95%-CI[3,4]		0.517, 1.778	3.496, 21.487
p-value[3,5]		0.8618	< 0.001
Week 8/Day 56			
n	122	19	31
Responder[1] [N (%)]	101 (83)	97 (82)	13 (42)
Non-responder[1] [N (%)]	21 (17)	22 (18)	18 (58)
Responder[1,3] [%]	83	81	40
Odds Ratio[3,4]		1.118	9.250
Odds Ratio 95%-CI[3,5]		0.575, 2.172	3.425, 24.982
p-value[3,5]		0.7338	< 0.001

[1] IGA Improvement responder: Subjects, who have at least one score of improvement on the 6-point IGA scale in comparison to the baseline (Visit 2/Day 1) assessment.
[2] Observed cases.
[3] Multiple imputation.
[4] Comparison vs. Generic Calc/Bet gel using Mantel-Haenszel (MH) estimate and confidence interval.
[5] Comparison vs. Generic Calc/Bet gel using Cochran-Mantel-Haenszel (CMH) test, with stratification by (pooled) site.
Calc/Bet: calcipotriol-betamethasone, CI: confidence interval, FAS: full analysis set, IGA: Investigator's global assessment, MI: multiple imputations, OC: observed cases.

IV.3 Clinical safety

Safety parameter were monitored from the signing of the informed consent form (ICF) until the last FU Visit.
Safety was assessed through physical examination at Screening Visit and on Day 56, vital signs and safety laboratory at Screening Visit, Day 29 (serum creatine and serum calcium only), Day 56, and at each visit through adverse events (AE) monitoring (including serious AEs [SAEs] and treatment-emergent AEs [TEAEs]). A serum pregnancy test was done for all female subjects at Screening Visit and a urine pregnancy test on Day 1 and Day 56.

Safety populations
All randomised subjects who received at least one dose of the study medication were included in the SES. Subjects were analysed for safety according to the investigational treatment that they have actually received.

Safety analyses

Descriptive summaries of adverse events, vital signs and laboratory measurements are presented by treatment group in the SES. Subjects were analysed according to the investigational treatment that they have actually received.

The assessment of safety was based on the incidence of TEAEs, SAEs, local AEs in the treatment area (dermal safety) and on the frequency of clinically notable abnormal vital signs and laboratory values.

Descriptive summaries of adverse events, vital signs and laboratory measurements are presented by treatment group in the SES. Subjects were analysed according to the investigational treatment that they have actually received.

Safety results

Treatment with topically administered Generic Calc/Bet gel, Daivobet® gel or Generic vehicle gel were safe and generally well tolerated. This was confirmed by evaluation of AEs, laboratory results, vital signs, and physical findings. Safety results of Generic Calc/Bet gel and Daivobet® gel vs. Generic vehicle gel can be summarized as follows:

Table 6 TEAEs by MedDRA term and intensity: Summary - SOCs and PTs in ≥3.5%(SOCs) or >1.7% (PTs) of the subjects in total (SES)

TEAEs[1] by MedDRA terminology and intensity Incidence[2] (Incidence rate %[3])	Intensity[4]	Generic Calc/Bet gel N=124 N (%)	Daivobet® gel N=123 N (%)	Generic vehicle gel N=39 N (%)	Total N=286 N (%)
SOC/PT[5]					
Overall	Severe	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.7)
	Moderate	8 (6.5)	10 (8.1)	5 (12.8)	23 (8.0)
	Mild	13 (10.5)	15 (12.2)	5 (12.8)	33 (11.5)
General disorders and					
administration site conditions	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	3 (2.4)	1 (0.8)	1 (2.6)	5 (1.7)
Application site erythema	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	0 (0.0)	0 (0.0)	1 (2.6)	1 (0.3)
Application site pruritus	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	0 (0.0)	0 (0.0)	1 (2.6)	1 (0.3)
Infections and infestations	Severe	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
	Moderate	2 (1.6)	2 (1.6)	1 (2.6)	5 (1.7)
	Mild	4 (3.2)	6 (4.9)	2 (5.1)	12 (4.2)
Cholecystitis infective	Severe	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)

	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal viral infection	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
	Mild	1 (0.8)	3 (2.4)	1 (2.6)	5 (1.7)
Oral herpes	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
Pulpitis dental	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	1 (2.6)	1 (0.3)
	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)

Table 7 TEAEs by MedDRA term and intensity: Summary - SOCs and PTs in ≥3.5%(SOCs) or >1.7% (PTs) of the subjects in total (SES) (continued)

TEAEs[1] by MedDRA terminology and intensity Incidence[2] (Incidence rate %[3])	Intensity[4]	Generic Calc/Bet gel N=124 N (%)	Daivobet® gel N=123 N (%)	Generic vehicle gel N=39 N (%)	Total N=286 N (%)
SOC/PT[5]					
Skin and subcutaneous tissue Disorders					
Pruritus	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	1 (0.8)	1 (2.6)	2 (0.7)
	Mild	1 (0.8)	0 (0.0)	1 (2.6)	2 (0.7)
Pruritus generalised	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psoriasis	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	1 (0.8)	3 (7.7)	4 (1.4)
	Mild	0 (0.0)	0 (0.0)	1 (2.6)	1 (0.3)
Skin burning sensation	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	2 (1.6)	0 (0.0)	0 (0.0)	2 (0.7)
Skin irritation	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	1 (2.6)	1 (0.3)
	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	0 (0.0)	0 (0.0)	1 (2.6)	1 (0.3)
Tooth extraction	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	0 (0.0)	0 (0.0)	1 (2.6)	1 (0.3)

[1] AEs not seen before treatment or, if already present before treatment, worsened after start of treatment.
[2] Incidence was determined as the number of subjects with respective adverse event.
[3] Incidence rate was determined as the incidence divided by the number of subjects at risk, i.e. size of the SES.
[4] Subjects counted once under the highest intensity
[5] Coded using MedDRA dictionary (Version 21.1 from September 2018), sorted alphabetically.

Calc/Bet: calcipotriol-betamethasone, MedDRA: medical dictionary for regulatory activities, PT: preferred term, TEAE: treatment-emergent adverse event, SES: safety evaluation set, SOC: system organ class.

Adverse Events

- Five SAEs were reported in 5 subjects. One of the 5 SAEs belonged to the Generic Calc/Bet gel arm and 4 of the 5 SAEs belonged to the Daivobet® gel arm. All SAEs were

considered to be 'not related' or 'unlikely' related to IMP and study procedure. No SAE occurred in the Generic vehicle gel arm.

- Eighty-five non-serious TEAEs were reported in 53 subjects (18.5%) over the trial. The incidence of TEAEs was lowest in the Generic Calc/Bet gel arm, followed by the Daivobet® gel arm and highest in the Generic vehicle gel arm (17.7%, 21.1%, and 25.6%, respectively).
- Most of the TEAEs in both active treatment arms were 'unlikely' or 'not related' to IMP. A 'possible' relationship to Generic Calc/Bet gel arm was reported for 4 TEAEs in 3 subjects (skin burning sensation [N=2], pruritus [N=1] and headache [N=1]) and to Daivobet® gel for 2 TEAEs in 1 subject (erythema and pruritus). In the Generic vehicle gel arm, 9 TEAEs were assessed with a 'certain', 'probable' or 'possible' relationship reported in 6 subjects, while 6 TEAEs in 4 subjects were regarded as 'not related'.
- 12 local cutaneous TEAEs were recorded in 2 of the subjects in the Generic Calc/Bet and in 6 subjects in the Generic vehicle gel arm. The local TEAEs were of mild or moderate intensity and 'certainly', 'probably' or 'possibly' related to the IMP.
- Six cutaneous TEAEs with 'possible' relationship to IMP or study procedure were also observed (2 TEAEs in 1 subject of each treatment arm).
  Most of the 90 TEAEs were of 'mild' intensity, less TEAEs were assessed with 'moderate' intensity. 'Severe' TEAEs were reported only in 1 subject each in the Generic Calc/Bet and the Daivobet® gel arm (both were SAEs).
- Most of the TEAEs including 4 of the 5 SAEs had 'recovered/resolved' or were 'recovering/resolving' at the end of the trial. The outcome of the fifth SAE was 'unknown' as the investigator was unable to contact the subject.

The incidence, intensity, relationship to IMP, and causality to IMP for TEAEs seen in this trial were lower for both treatment arms with active treatment (Generic Calc/Bet gel arm and Daivobet® gel arm) as compared to the Generic vehicle gel arm.

- In total, 7 subjects discontinued the trial due to TEAEs: 1 subject of the Daivobet® gel arm (ischaemic stroke [SAE]) and 6 subjects of the Generic vehicle gel arm (psoriasis [i.e. worsening/aggravation of psoriasis, exacerbation of psoriasis or of the skin condition in the course of psoriasis], application site erythema and application site pruritus). There were no dropouts in the Generic Calc/Bet gel arm due to TEAEs.
- The highest number of TEAEs treated with a concomitant medication was noted in the Daivobet® gel arm, followed by the Generic Calc/Bet gel arm and the lowest number was observed in the Generic vehicle gel arm:
  23 TEAEs in 17 subjects (incl. 1 SAE),25 TEAEs in 17 subjects (incl. 2 SAEs) and 7 TEAEs in 5 subjects for the Generic Calc/Bet gel arm, Daivobet® gel arm and Generic vehicle gel arm, respectively.

Laboratory examinations

- One clinically significant clinical chemistry finding in 1 subject of the Generic Calc/Bet gel arm was considered as non-serious, mild TEAE (GGT increased), not related to IMP and not leading to premature trial discontinuation. A high GGT value (out of range) of clinical relevance has already been noted for this subject at Screening.

Vital signs

- A clinically relevant abnormal diastolic blood pressure value was observed in 1 subject in the Generic Calc/Bet gel arm first time at Visit 5 (Week 8). Abnormal diastolic and systolic blood pressure values, however not considered to be of clinical relevance, were already noted at Visit 1 (Baseline) and hypertension was documented as non-serious, moderate TEAE on relative trial day 6. This TEAE was considered to be not related to IMP and not leading to premature trial discontinuation.

Physical examination

- In the physical examination, 5 clinically significant findings, reported first time post-dose and were recorded as 5 non-serious TEAE noted in 4 subjects (N=1, 2 and 1 for the Generic Calc/Bet gel, Daivobet® gel and Generic vehicle gel arm, respectively) at Visit 5 (EoT or ETV). Most of these AEs concerned the skin (1 event each of worsening of psoriasis, psoriatic arthropathy, pruritus generalised, new plaque-type psoriasis lesions on right elbow, sciatica). Worsening of psoriasis (Generic vehicle gel arm) was considered to be possibly related to IMP and led to trial discontinuation, all other AEs were considered to be not related to IMP and did not lead to trial discontinuation.

There were no other clinically relevant observations related to safety in this trial.

It can be summarized, that the purpose of this phase III, multicentre, randomised, double-blind, parallel-group trial was

- to demonstrate equivalence between the Generic Calc/Bet gel and the Daivobet® gel and
- to demonstrate superiority of the Generic Calc/Bet gel over the Generic vehicle gel with respect to the mean % change from baseline of the PASI score at Week 4/Day 29.

The confirmatory evaluation of both primary endpoints demonstrated both for the Generic Calc/Bet gel: equivalence to Daivobet® gel and superiority over the Generic vehicle gel. The respective sensitivity analyses led to similar results that support the outcome of the primary analyses.
All assessment including PASI, IGA, mPASI, and PSSI correlated and demonstrated amendment in disease severity in both active treatment arms, already at Week 2 and further improving towards Weeks 4 and 8. An improvement, however, less pronounced, was also seen in the Generic vehicle gel arm.

Overall, the safety evaluation revealed that the Generic Calc/Bet gel, the Daivobet® gel and the Generic vehicle gel were generally well tolerated.
Most of the TEAEs (including the 5 SAEs) were 'unlikely' or 'not related' to IMP in all 3 treatment arms. A 'possible' relationship to Generic Calc/Bet gel arm was reported for 4 TEAEs in 3 subjects (skin burning sensation: 2x; pruritus and headache: 1x) and to Daivobet® gel for 2 TEAEs in 1 subject (erythema and pruritus). In the Generic vehicle gel arm, 9 TEAEs were assessed with a certain', 'probable' or 'possible' relationship reported in 6 subjects. All of these possibly, probably or certainly drug-related TEAEs, except for the headache, concerned the skin. Six of the cutaneous TEAEs with 'possible' relationship to IMP were also considered to be 'possibly' related to the study procedure (2 TEAEs in 1 subject of each treatment arm).
In general, no systemic side effects were observed, however, 6 of the local cutaneous TEAEs led to withdrawal in 5 subjects (6%) of the Generic vehicle gel arm (psoriasis [in 4 subjects], application site erythema/pruritus). All of these 'possibly/probably/certainly drug-related' TEAEs had recovered/were resolved at the end of the trial.
The evaluation of TEAEs, clinical laboratory parameters, physical findings and vital signs raised no concerns about safety. In summary, the results represent that the Calc/Bet gel is safe and generally well tolerated. There were no trends detected indicating any specific treatment related reactions.

It can be concluded, that the Generic Calc/Bet gel can be regarded as therapeutically equivalent to the Daivobet® gel and superior over the Generic vehicle gel in the treatment of chronic stable, mild to moderate plaque-type psoriasis. Generic Calc/Bet gel was in general well tolerated with a comparable safety profile comparable like Daivobet® gel and the Generic vehicle gel when applied for up to 8 weeks of treatment (EoT).

IV.4 Legal Status

Medicinal product subject to medical prescription.

IV.5 Summary Pharmacovigilance system

The applicant has submitted a signed Summary of the applicant's and/or Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and

interventions designed to identify, characterise, prevent or minimise risks relating to the medicinal product(s) applied for authorisation.

Safety specification
According to the applicant the safety specification is in full accordance with the current safety specification agreed and published for a similar product which is acceptable.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise

specified in the EURD list.

- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

V. USER CONSULTATION

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Clinical:
Therapeutic equivalence between the Generic Calc/Bet gel and Daivobet® gel and superiority over placebo (vehicle gel) has been demonstrated in a phase III trial in patients with chronic stable, mild to moderate plaque-type psoriasis on body and scalp. Generic Calc/Bet gel was principally well tolerated with a similar safety profile like Daivobet® gel and the Generic vehicle gel when applied for up to 8 weeks of treatment.
Moreover, the medicinal product under discussion and the referenced product are rather similar with regard to their non-active ingredients.
From the clinical-dermatological point of view an approval could be granted. SmPC and PIL have been revised accordingly.

Quality:
The DCPs are approvable from the quality point of view.
The application is approved. For intermediate amendments see current product information.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
DE/H/6739/001 /IA/001	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/interm ediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	No	5-12-2022	Approved	N.A.
DE/H/6739/001 /IA/002/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/interm ediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already	No	12-12-2023	Approved	N.A.

	approved manufacturer				
DE/H/6739/001 /IB/003	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan - Other variation: Update of risk management plan	No	10-3-2024	Approved	N.A.
DE/H/6739/001 /IB/004	Change in the shelf-life or storage conditions of the finished product - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	Yes	4-4-2024	Approved	N.A.