Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Silkis ointment

(calcitriol 3 µg/g)

NL/W/0049/pdWS/002

Marketing Authorisation Holder: Galderma International

Rapporteur:	The Netherlands
Finalisation procedure (day 120):	13 May 2020

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Silkis 3 mcg/g ointment
INN (or common name) of the active substance(s):	calcitriol
MAH:	Galderma Benelux B.V.
Currently approved Indication(s)	Topical treatment of mild to moderately severe plaque psoriasis (psoriasis vulgaris) with up to 35% body surface area involvement.
Pharmaco-therapeutic group (ATC Code):	D05AX03
Pharmaceutical form(s) and strength(s):	Ointment containing Calcitriol 3 µg/g

I. EXECUTIVE SUMMARY

Changes are proposed in SmPC section 5.1.

II. RECOMMENDATION

It is agreed with the MAH that no posology advice for children can be made based on the results of submitted study 18131. Addition of description of this study to section 5.1 of the SmPC is agreed, but changes to the text are proposed.

III. INTRODUCTION

On 10 October 2019, the MAH submitted a completed paediatric study for Silkis ointment, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

An updated Clinical Overview and a Clinical Study Report have been provided.

Following the US approval of Calcitriol 3 mcg/g ointment (Vectical ointment) on 23 January 2009, a paediatric clinical program had been designed to address three Post-Marketing Requirements. Primarily due to enrolment difficulties, in November 2015 the FDA agreed to release Galderma from Post-marketing Requirements RD.06.SPR.18104 and RD.06.SPR.18132. The Post-marketing Requirement was amended in order to combine all age cohorts from studies RD.06.SPR.18104, RD.06.SPR.18132 and RD.06.SPR.18131 into the single study referred to as RD.06.SPR.18131.

The Clinical Study Reports for abovementioned studies RD.06.SPR.18102 and RD.06.SPR.18104 (pharmacokinetics) and RD.06.SPR.18132 (efficacy and safety) were submitted in Europe to RMS Netherlands in May 2017 (NL/W/0049/pdWS/001). Accordingly, SmPC sections 4.2 and 4.4 and the PIL were changed to reflect that, instead of absence of data, a limited amount of data in the paediatric population is available. Consequently, a description of design and data of study RD.06.SPR.18132 was added to SmPC section 5.1, with the conclusion that due to the very small sample size, any observed numerical difference in treatment groups is most likely due to chance.

The MAH now proposes to update the SmPC section 5.1 with a description of design and data of finalised observational extension cohort study RD.06.SPR.18131

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation is an ointment containing Calcitriol 3 µg/g (0,0003%). It is applied twice daily on the affected skin excluding facial, scalp or intertriginous areas.

IV.2 Clinical aspects

IV.2.1 Introduction

The MAH submitted the final report for the following study:

- **RD.06.SRE.18131:** A multicentre open-label uncontrolled study of the long-term safety and efficacy of calcitriol 3 mcg/g ointment applied twice daily for 26 weeks in paediatric subjects (2 to 16 years and 11 months of age) with mild to moderate plaque psoriasis.

IV.2.2 Clinical study

RD.06.SRE.18131

Description

This was an 26-week study in paediatric subjects with mild to moderate plaque psoriasis being treated with calcitriol ointment. This study was part of a post-marketing commitment to the American Food and Drug Administration (FDA).

The original intent of the study was to include 100 subjects and to perform pharmacokinetic assessments in 9 of them. Due to slow study enrolment and in agreement with the FDA, the study was closed to enrolment in November 2017. At that time, 54 subjects were enrolled and 41 subjects had completed the study (including 1 PK subject).

Methods

Objectives

The objectives of this study were to evaluate the safety, plasma levels, and efficacy of up to 26 weeks of treatment with calcitriol ointment in paediatric subjects with mild-moderate plaque psoriasis.

Study design

This was an open-label, uncontrolled, multicentre 26-week study in paediatric subjects from 2 years of age or older, with mild to moderate plaque psoriasis, who received calcitriol 3 mcg/g ointment twice daily without occlusion for a period of up to 26 weeks. Evaluation for safety and efficacy was performed at baseline, and weeks 4, 12, and 26, and at follow-up week 30.

Study population /Sample size

No formal sample size calculation had been performed. It was planned to include 100 subjects, including 9 subjects for the planned pharmacokinetic assessments.

Treatments

Calcitriol 3 mcg/g ointment was applied twice daily for a period of up to 26 weeks. It was applied by the subject or parent/guardian as a thin film to all involved areas, without exceeding a maximum of 0.5 g/kg of body weight or 28 g daily, whichever was lower. If complete clearing of psoriasis per physician assessment was achieved (IGA of 0), calcitriol was discontinued but the subject remained in the study. Treatment with calcitriol was resumed if skin manifestations of psoriasis reappeared (IGA score >0).

Systemic treatment for psoriasis and topical treatments other than the study medication were not allowed by the protocol, but emollient use (provided by the sponsor) on healthy skin areas was permitted.

Outcomes/endpoints

The safety assessments were Adverse Events (AEs), laboratory safety tests, physical examination, and vital signs, performed at the scheduled study visits.

The main efficacy outcome was the percentage of subjects with an IGA Score of 0 (clear) or 1 (almost clear). The other outcomes were Body Surface Area (BSA) involved and pruritis assessment on a scale from 0 ('no itching') to 4 ('very severe itching with pronounced discomfort during night and daily activities'). Plasma concentration of calcitriol was assessed as pharmacokinetic parameter.

Statistical Methods

The Safety Population was defined as all subjects who have applied the study drug at least once. The statistical analyses were based on the safety population. No inferential statistical analysis was planned for safety or efficacy or pharmacokinetic outcomes.

The study appears to be reasonably well designed, in agreement with its primary (safety) objective. Due to the lack of a control arm, it is difficult to draw conclusions regarding efficacy.

While concomitant treatments for psoriasis were not allowed, according to the protocol these were recorded and could be a reason to exclude a patient from the remainder of the study (protocol violation).

Results

Recruitment/Number analysed

It had been planned to include 100 subjects, at study closure there were 54 patients included of whom 41 (76%) had completed the 26 weeks of study. There was one subject included for the pharmacokinetic assessments.

Table 1 Disposition of subjects

Completion Status	Calcitriol 3 µg/g (N=54) n (%)
Number of subjects enrolled[a]	54 (100.0%)
Number of subjects who completed the study	41 (75.9%)
Number of subjects who prematurely discontinued	13 (24.1%)
Reason for discontinuation	
Lack of efficacy	2 (3.7%)
Adverse Event	0
Subject request	6 (11.1%)
Protocol violation	1 (1.9%)
Lost to follow-up	4 (7.4%)

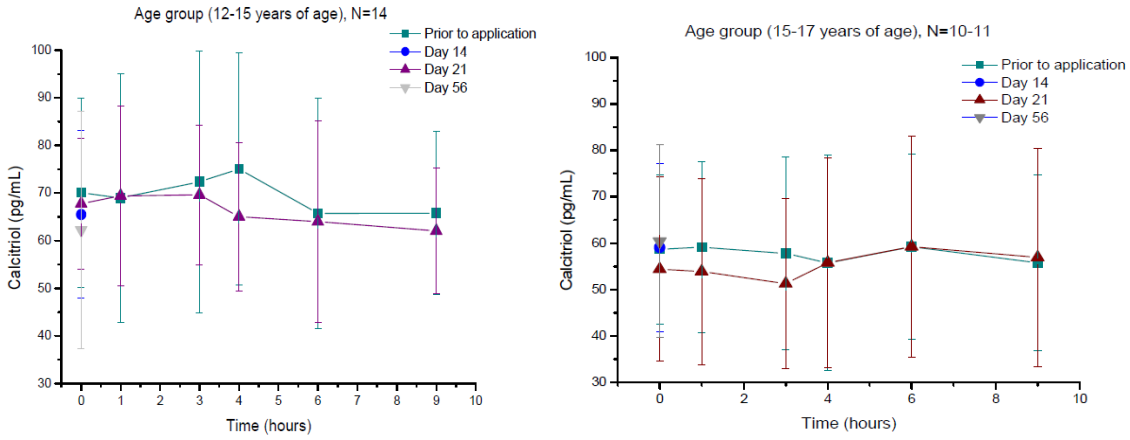
a) Subjects with at least 1 application of study drug

Note: The percentage of subjects was calculated based on the number of subjects with study drug at least once.

Most of the protocol violations were missing doses or missing a visit. In four patients a (topical) medication was used that was not allowed according to the protocol. This was classified as minor protocol violation.

Only one subject consented for the pharmacokinetic assessments. Therefore, pharmacokinetic data was not further discussed.

Figure 1 Mean Calcitriol plasma concentrations per age group (± SD)



Endogenous plasma calcitriol levels at baseline appeared to be higher (C_{max} increased by 26%; $AUC_{0\text{-}9h}$, and $AUC_{0\text{-}12h}$ increased by 19%) in the 12 to-<15-year age group than in the older adolescents (see figure 1). Similar to calcitriol levels at baseline, the age effect in adolescents was also observed for calcitriol levels after an application period of 21 days (C_{max} increased by 21 calcitriol $AUC_{0\text{-}9h}$ and $AUC_{0\text{-}12h}$ increased by 17%) in younger adolescents (12 to <15 years of age) compared to older adolescents (15 to 17 years of age).

Efficacy results

The main efficacy outcome was IGA 0 or 1 at week 26, which was reached by 19/41 (46%) or by 20/54 (37%) if LOCF was used. The majority of subjects improved from baseline to week 26, with most of them having a 1- or 2-grade improvement in IGA score (CSR Table 14.2.1.1), analysed in available cases (not shown) and when using LOCF (Table 2).

Most subjects had a 1- or 2-grade improvement in pruritis score (CSR Table 14.2.2.1), analysed in available cases (not shown) and when using LOCF (Table 3). At the week 26/End of Study visit, 17 (41.5%) subjects had a pruritus score of 0 (none).
The median (range) percent involved BSA at baseline was 6.0 (1.0-30), which improved to 2.5 (0-15) at week 26 with a mean (SD) change of -3.6 (4.4).

Table 2 Change from baseline in IGA score at week 26 (LOCF)

	Change from Baseline at week 26 N=54
Week 26 (LOCF): Change from baseline	
-3 (3-grade improvement)	3 (5.5%)
-2	10 (18.5%)
-1	18 (33.3%)
0 (no change)	20 (37%)
1 (1-grade worsening)	3 (5.6%)
2	0
3	0
Total	54 (100%)
N	54
Mean (SD)	-0.8 (0.99)
Median	-1.0
Min, Max	-3, 1

Table 3 Change from baseline in Pruritis score at week 26 (LOCF)

	Change from Baseline at week 26 N=54
Week 26 (LOCF): Change from baseline	
-4 (4-grade improvement)	0
-3	1 (1.9%)
-2	10 (18.5%)
-1	25 (46.3%)
0 (no change)	15 (27.8%)
1 (1-grade worsening)	2 (3.7%)
2	1 (1.9%)
3	0
4	0
Total	54 (100%)
N	54
Mean (SD)	-0.8 (0.91)
Median	-1.0
Min, Max	-3, 2
Table redrawn from CSR Table 14.2.2.1	

Safety

At study closure there were 54 patients included of whom 41 (76%) had completed the 26 weeks of study, equivalent to 182 days (Table 4). The actual drug exposure was median (range) 180 (1-209) days. The majority had been compliant to study drug, counted as study days or as drug dose

Table 4 Summary of treatment duration (Safety population).

Treatment Duration (days)	**Calcitriol 3 µg/g (N=54)**
N	54
Mean (SD)	159.1 (53.17)
Median	181.0
Min, Max	1, 209
≤42 days	4 (7.4)
43 - 70 days	2 (3.7)
71 - 112 days	4 (7.4)
113 - 161 days	0
162 - 196 days	41 (75.9)
>196 days	3 (5.6)

Max=maximum; Min=minimum; SD=standard deviation

Of the 54 included subjects, 20 subjects (37.0%) reported 49 treatment emergent adverse events (TEAEs) (Table 5). Of these, 5 subjects had an AE that was related to the study drug/study procedure, all of which occurred in the first 90 days of treatment. All AEs were mild or moderate in severity.

Table 5 Overview of treatment-emergent adverse events (Safety population)

	Calcitriol 3 mg/µL N=54		Period[a]			
			Day 1 - 90 N[a] = 15		Day 91 – EOT N[a] = 10	
	Event n	Subjects n (%)	Event n	Subjects n (%)[b]	Event n	Subjects n (%)[b]
Total TEAEs	49	20 (37.0)	30	15 (100.0)	19	10 (100.0)
Related TEAEs to study drug	5	4 (7.4)	5	4 (26.7)	0	0
Related TEAEs to protocol procedure	1	1 (1.9)	1	1 (6.7)	0	0
TEAEs by severity						
Severe	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Moderate	18	9 (16.7)	10	7 (46.7)	8	4 (40.0)
Mild	31	17 (31.5)	20	12 (80.0)	11	9 (90.0)
SAEs	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
AESIs	2	1 (1.9)	2	1 (6.7)	0	0
Related AESIs	2	1 (1.9)	2	1 (6.7)	0	0
TEAEs possibly related to calcium metabolism[c]	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
TEAEs leading to discontinuation	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Deaths	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)

AE=adverse event; AESIs=adverse events of special interest; EOT=End-of-treatment; HLGT=high-level group term; SAE-serious adverse event; SOC=System Organ Class; TEAEs=treatment-emergent adverse events

a) Includes subjects with any AE that started during each period.

b) The percentage of subjects was calculated based on the number of subjects with any AE started during the period

c) AEs possibly related to calcium metabolism were defined as AEs with Hypercalciuria (PT), Renal and urinary disorders (SOC), Urinary tract signs and symptoms (HLGT) or AEs with Urine calcium/creatinine ratio increased (PT), Investigations (SOC), Metabolic, Nutritional and blood gas investigations (HLGT).

Adverse events of special interest (AESIs) were predefined (signs and symptoms consistent with Vitamin D toxicity, clinically significant out-of-range laboratory result deemed related to the study drug, skin manifestations such as severe skin irritation and severe local and/or generalized pruritus, skin sensitization, cutaneous AEs related to calcitriol leading to its discontinuation).
Two AESIs of moderate skin irritation of the treated area were experienced by 1 subject during the first 90 days of the study. In both instances, irritation resolved after 1 day after which treatment was resumed. No subjects experienced TEAEs that were possibly related to calcium metabolism or TEAEs that led to discontinuation from the study.

No subjects experienced a severe TEAE or a serious AE during the study and no deaths were reported during the study.

AEs (Table 6) were most often reported in the Infections and infestations SOC (12 subjects; 22.2%), followed by the Skin and Subcutaneous tissue disorders SOC (7 subjects; 13.0%). With the exception of nasopharyngitis (6 subjects), skin burning sensation (3 subjects), and abdominal pain upper, vitamin D deficiency, skin papilloma, and nasal congestion (2 subjects each), all other AEs were reported by no more than 1 subject each in either study period. The skin and subcutaneous tissue disorders were: skin burning sensation (n=3), erythema (n=1), pityriasis alba (n=1), rash (n=2), skin irritation (n=2).

In the age group 6-12 years 17/27 (26%) of subjects had an AE, in the age group 13-17 this was 9/21 (48%).

Table 6 Adverse events in at least 2 subjects by SOC and PT (Safety population)

System Organ Class Preferred term	Calcitriol 3 mg/µL N=54		Period[a]			
			Day 1 - 90 N[a] = 15		Day 91 – EOT N[a] = 10	
	Event n	Subjects N (%)	Event n	Subjects N (%)[b]	Event n	Subjects N (%)[b]
Total AEs	**49**	**20 (37.0)**	**30**	**15 (100.0)**	**19**	**10 (100.0)**
Gastrointestinal disorders	5	4 (7.4)	3	3 (20.0)	2	1 (10.0)
Abdominal pain upper	3	2 (3.7)	1	1 (6.7)	2	1 (10.0)
Infections and infestations	16	12 (22.2)	10	8 (53.3)	6	4 (40.0)
Nasopharyngitis	7	6 (11.1)	5	4 (26.7)	2	2 (20.0)
Metabolism and nutrition disorders	2	2 (3.7)	2	2 (13.3)	0	0
Vitamin D deficiency	2	2 (3.7)	2	2 (13.3)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2 (3.7)	1	1 (6.7)	1	1 (10.0)
Skin papilloma	2	2 (3.7)	1	1 (6.7)	1	1 (10.0)
Respiratory, thoracic and mediastinal disorders	5	3 (5.6)	2	1 (6.7)	3	2 (20.0)
Nasal congestion	3	2 (3.7)	0	0	3	2 (20.0)
Skin and subcutaneous tissue disorders	9	7 (13.0)	8	6 (40.0)	1	1 (10.0)
Skin burning sensation	3	3 (5.6)	3	3 (20.0)	0	0

AEs=adverse events

Note: A subject was counted only once for multiple occurrences within a System Organ Class or Preferred Term.

a) Includes subjects with any AE that started during each period.

b) The percentage of subjects was calculated based on the number of subjects with any AE started during the period.

On average, there were no changes in parameters of calcium homeostasis in serum (Table 7) or plasma (not shown) and there were no individual subjects with clinically relevant changes. No individual clinically significant haematology, chemistry, or urinalysis laboratory abnormalities occurred during the study.

Table 7 Pharmacodynamic parameters in serum (Safety population)

Laboratory Parameter	Screening[a] N=53 Mean (SD)	Week 26 N= 40 Mean (SD)	Change from Screening at Week 26 N= 40 Mean (SD)
Calcium (mmol/L)	2.516 (0.0843)	2.520 (0.1014)	0.014 (0.0787)
Phosphate (mmol/L)	1.4798 (0.17004)	1.4879 (0.25231)	0.0091 (0.21262)
Albumin (g/L)	47.0 (2.78)	46.2 (2.59)	-0.8 (2.09)
Calcium corrected (mmol/L)	2.377 (0.0683)	2.395 (0.0844)	0.028 (0.0679)
Intact PTH (pmol/L)	3.44 (1.307)	3.43 (1.744)	-0.07 (1.744)

PTH=parathyroid hormone; SD=standard deviation

a) Screening is defined as the last test prior to study medication use

Mean values for 1,25(OH)2D and 25(OH)D decreased from baseline through week 12 and week 26. One subject had a clinically significant decrease in 25(OH)D below the reference range (Table 8).

Table 8 Shift table laboratory data for 1,25(OH)2D and 25(OH)D (Safety population)

		CD2027 (N = 54)				
		Week 26 (Final)				
Laboratory Parameter (unit)	Screening	Low	Normal	High	Missing	Total
1, 25-Dihydroxyvitamin D (pmol/L)	Low	0	0	0	0	0
	Normal	1 (2.0)	23 (45.1)	6 (11.8)	0	30 (58.8)
	High	0	10 (19.6)	11 (21.6)	0	21 (41.2)
	Missing	0	0	0	0	0
	Total	1 (2.0)	33 (64.7)	17 (33.3)	0	51 (100.0)
25-Hydroxyvitamin D (nmol/L)	Low	18 (35.3)	6 (11.8)	0	0	24 (47.1)
	Normal	10 (19.6)	17 (33.3)	0	0	27 (52.9)
	High	0	0	0	0	0
	Missing	0	0	0	0	0
	Total	28 (54.9)	23 (45.1)	0	0	51 (100.0)

Source: Listing 16.2.8.6
- Screening: the last test prior to study medication use.
- Week 26 (Final) = the scheduled test at Week 26 or last post-baseline available test for early termination during the treatment period.
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IV.2.3 Discussion on clinical aspects

Study 18131 was of 26-weeks duration, open-label and observational. It was primarily aiming at safety and secondarily had efficacy and pharmacokinetics objectives. It was aimed to include 100 patients, but due to slow enrolment the study was closed prematurely, with 54 patients included and 41 having completed the 26 weeks study.

Efficacy

The MAH was requested to use the same standard IGA outcome that also was used previously for study 18132: IGA 0 or 1 AND at least 2-point improvement in IGA. This replaces the presentation of the separate outcomes on IGA 0 and 1 and change in IGA.

The MAH did plan that no missing data handling would be performed and that all data would be summarised as observed. However, seen the number of discontinuations and the reasons for those, this did not seem tenable. It was asked that to reflect IGA and pruritis outcomes, non-responder imputation is used for nearly all discontinuations, LOCF may be used for subjects who discontinued due to study closure only.
On November 8, 2017, a meeting was held with the US Food and Drug Administration (FDA) to discuss the issue of low enrolment in the ongoing long-term study (RD.06.SPR.18131). During this meeting the FDA agreed that enrolment of new subjects in the study could be closed at that date but that those subjects already enrolled in the study would be allowed to complete the study according to the clinical protocol. The last subject completed the study in June 2018, therefore, there were no subjects discontinued due to study closure only. Since no subjects discontinued due to study closure, the non-responder imputation is considered for missing IGA and pruritus outcomes. The IGA success outcome (IGA 0 or 1 AND at least 2-point improvement) is summarised using non-responder imputation at each visit. For ordinary IGA and pruritus scores, the baseline observation carried forward (BOCF) and the worst observation carried forward (WOCF) are used at Week 26.

Safety
The open-label and non-comparative nature together with the low number of patients limits the usefulness of the data, it is difficult to attribute causality to the occurrence of AEs. However, the sample size may be considered sufficient to establish a common side effect.

There were 9 AEs classified as ‘skin and subcutaneous disorders’, most them can be associated with a skin reaction such as ‘skin burning sensation’ or ‘rash/erythema’, or ‘skin irritation’. This is a known ADR in adults [SmPC Calcitriol]. All these only occurred in the first 90 days of

application and were mild or moderate in severity. There were no new safety concerns regarding calcium homeostasis or other laboratory abnormalities reported. Due to the low numbers of events, non-comparative design and absence of a safety signal, it was not proposed to add information to section 4.8. of the SmPC.

IV.2.4 Conclusion on clinical aspects

No conclusions can be made on the efficacy of Calcitriol in plaque psoriasis the paediatric population. Due to the small sample size and non-comparative nature of the study, results are inconclusive. Calcitriol seems to be well tolerated in the paediatric population. Addition of description of this study to section 5.1 of the SmPC is agreed, but changes to the text have been proposed.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Overall calcitriol seems to be well tolerated in the paediatric population. The MAH submitted a final clinical study report for study RD.06.SRE.18131 'A multicentre open-label uncontrolled study of the long-term safety and efficacy of calcitriol 3 mcg/g ointment applied twice daily for 26 weeks in paediatric subjects (2 to 16 years and 11 months of age) with mild to moderate plaque psoriasis.' No conclusions can be made on the efficacy of Calcitriol in plaque psoriasis the paediatric population. Due to the small sample size and non-comparative nature of the study, results are inconclusive. The MAH proposed to add a description of design and data of study 18131 to section 5.1 of the SmPC

Based on the paediatric data published, the Member States have agreed that the SmPC should be adapted.

- **Recommendation**

The following changes should be made to the SmPC:

SmPC section 5.1:
Paediatric population
Very limited efficacy data of Calcitriol in the paediatric population are available from a 8-week randomized, vehicle-controlled study (18132) in children aged 2 to 12 years with plaque psoriasis (n= 19; 8 on active, 11 on vehicle), and a 26-weeks open-label, uncontrolled, multicentre long-term safety and efficacy study (18131) in children aged 2 to 17 years (n=54). Calcitriol 3µg/g was applied twice daily excluding the face and scalp. However, due to slow enrolment, both studies were closed prematurely. The safety and efficacy of Calcitriol ointment in children less than 18 years have not been established (see section 4.2).

In Study 18132 ~~The~~ the primary endpoint was the success rate, defined as the percentage of subjects with an Investigator Global Assessment score of 0 (clear) or 1 (almost clear) and at least a 2-grade improvement from baseline. The success rate was not statistically significantly different (p=0.370) for the Calcitriol 3 µg/g ointment group compared with the Vehicle group, with 3 subjects (37.5%) of the Calcitriol 3 µg/g ointment group achieving success and 7 subjects (63.6%) of the Vehicle group. Due to the very small sample size, any observed numerical difference in treatment groups is most likely due to chance. Local irritations were the most reported adverse events.

~~*Due to slow enrolment this study was closed prematurely.*~~

In Study 18131 the primary endpoint was the percentage of subjects with an IGA score of 0 (clear) or 1 (almost clear); and the secondary endpoint change from baseline in pruritus. The study was completed by 76% of the subjects. The majority of subjects improved the IGA score from baseline to week 26, with 24.1% having at least a 2-grade improvement. At the end of the study, 37% of the subjects had an IGA of clear/almost clear. For the secondary endpoint, 37% of subjects had no pruritus at Week 26 and 20.4% of subjects achieved at least 2-grade improvement from baseline. Due to the uncontrolled study design, no conclusion can be drawn regarding efficacy in paediatric patients. Most common AE's were infections and skin reactions, there were no changes in parameters of calcium homeostasis. However, the safety data are considered limited. See also section 5.3.

The MAH is requested - in line with the guidance on Art. 46 Paediatric worksharing - to submit a type IB variation application to update the product information in line with the PdWS conclusion.