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/001

Marketing Authorisation Holder: Galderma International

Rapporteur:	The Netherlands
Finalisation procedure (day 120):	8 August 2018

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Silkis ointment
INN (or common name) of the active substance(s):	Calcitriol
MAH:	Galderma International
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 sections 4.2 4.4, 5.1 and 5.3, and PL section 2.

II. RECOMMENDATION

Overall calcitriol seems to be well tolerated in the paediatric population. The three studies provided by the MAH showed that the calcium homeostasis remained within the reference range after maximal exposure to calcitriol. The adverse events that occurred were mild and transient in nature. The efficacy outcomes have shown a numerical reduction in global severity after calcitriol treatment, though the results are inconclusive due to the small sample sizes. Based on the paediatric data submitted, the Member States have agreed that the SmPC and PL should be adapted.

III. INTRODUCTION

Following the US approval of Calcitriol 3 mcg/g ointment (Vectical ointment) on 23 January 2009, a paediatric clinical program was designed to address three post-marketing requirements.

On 17 May 2017, the MAH submitted three completed paediatric studies for Silkis ointment in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Silkis ointment and that there is a consequential regulatory action.

The MAH proposed the following changes to be made to the SmPC based on the study results:

Section 4.2 Posology and Method of Administration:
Paediatric population
There is limited data on ~~no experience~~ of the use of Silkis in children (see 4.4. Special Warnings and Precautions for Use).

Section 4.4 Special warnings and precautions for use:
Paediatric population
There is limited amount of data supporting the use of Silkis in the paediatric population.
No safety alert has been raised from the paediatric population evaluated in clinical studies.
In view of the particular sensitivity of neonates versus adult rodents to the toxic effects of calcitriol, exposure of children to calcitriol ointment should be avoided (see also 4.2. Posology and Method of administration).

The PL is updated accordingly. The following change is proposed:

Section 2 What you need to know before you use Silkis:
Children
There is limited data on ~~no experience~~ with the use of Silkis in children. Therefore, use in children should be avoided.

IV. SCIENTIFIC DISCUSSION

IV.1 Clinical aspects

IV.1.1 Introduction

The MAH submitted the final reports for the following three studies:

1. **RD.06.SPR.18102:** Pharmacokinetics and Pharmacodynamics of Calcitriol Following Twice-Daily Application of Calcitriol 3 µg/g Ointment Under Conditions of Maximal Use in Adolescents (12 to 17 years of age) with plaque psoriasis;
2. **RD.06.SPR.18104:** Pharmacokinetics and pharmacodynamics of Calcitriol 3 mcg/g ointment applied twice daily for 14 days under conditions of maximal use in paediatric subjects (2 to 12 years of age) with plaque psoriasis;
3. **RD.06.SPR.18132:** A multicentre, randomized, double blind, parallel group, vehicle controlled study of the safety and efficacy of Calcitriol 3 µg/g ointment applied twice daily for 8 weeks in paediatric subjects (2 to 12 years of age) with mild to moderate plaque psoriasis.

IV.1.2 Clinical studies

1. RD.06.SPR.18102

Description
This was an open-label, multicentre study to assess the systemic exposure to Calcitriol 3 µg/g ointment in adolescents with plaque psoriasis under conditions of maximal use (2 mg/cm² per application, up to 30 g daily) applied twice daily to 10% to 35% Body to Surface Area (BSA) involved skin (excluding face, scalp and intertriginous areas) for 8 weeks (56 days). Full pharmacokinetic (PK) and pharmacodynamic (PD) data were to be collected during the first three weeks of the study; safety and efficacy data were to be assessed for the entire study period of eight weeks.

Methods
Objectives

- Primary objective: to asses systemic exposure to Calcitriol 3 µg/g in adolescents with plaque psoriasis under conditions of maximal use of Calcitriol 3 µg/g twice daily (2 mg/cm² per application, up to 30 g daily) applied to 10% to 35% BSA-involved skin (excluding face, scalp and intertriginous areas).
- Secondary objective: to assess the effect of Calcitriol 3 µg/g ointment on calcium and phosphorus homeostasis and to evaluate the safety of Calcitriol 3 µg/g ointment twice daily in adolescents with plaque psoriasis.

Study design
The study was set up as an open-label, multicentre study. It involved six study visits: the screening period visit (Day -7), the treatment period visits (Day 0, Day 14, Day 21, Day 42 and Day 56) and the final visit (Day 56 or early termination (ET) visit, if applicable).

Study population /Sample size
The study involved adolescent subjects (aged 12 to 17 years) with a confirmation of plaque psoriasis involving 10-35% of their BSA, excluding face, scalp and intertriginous areas.

Treatments
Calcitriol 3 µg/g ointment was to be applied twice daily at 12-hour intervals ± 2 hours for 8 weeks (56 days).

Daily treatment was to be applied by the subject under supervision for the first 3 weeks and thereafter without mandatory supervision. Approximately 2 mg/cm^2 were to be applied to involved skin; consistent dosing throughout the study was to be ensured using the "Silkidose spatula".

Outcomes/endpoints
Pharmacokinetic endpoints: system exposure under maximal use as measured on Day 0 and Day 21.
Pharmacodynamic endpoints: effects of calcitriol 3 µg/g ointment on calcium and phosphorus homeostasis (serum calcium, albumin, albumin-adjusted calcium, phosphorus; urinary calcium, creatine, calcium/creatine ratio).
Efficacy endpoints: global severity and % BSA involved as evaluated by the investigator at screening, baseline and day 56/ET visit.

- Global severity of psoriasis was to be evaluated by the Investigator on all treated areas using a 6- point scale ranging from 0 (clear) to 5 (very severe).

Safety variables: adverse event reports, local tolerability (physical exam, vital signs routine haematology/biochemistry and urinalysis results and evaluation of local sensitization reactions.

Statistical Methods
PK/PD parameters and safety data were summarized for the safety population defined as all subjects in the intent-to-treat (ITT) population who applied the study medication at least once.

$AUC_{(0\text{-}9h)}$, $AUC_{(0\text{-}12h)}$, C_{max}, and T_{max} of plasma levels of Calcitriol were determined and summarized on Days 0 and 21. The 90% Confidence Interval (CI) for the mean difference at Day 0 versus Day 21 were calculated using the student's paired-t distribution. Prior to the analysis, the $AUC_{(0\text{-}12h)}$ and C_{max}, were transformed into their natural logarithms. The trough plasma levels (C_{trough}) of calcitriol were summarized using descriptive statistics. The limits of the CI, as well as the mean difference, were back transformed into exponential. Descriptive statistics were applied to the PD parameters. Moreover, the PK/PD relationship was assessed by calculating the Spearman correlation coefficients and displayed graphically when appropriate.

Results
Recruitment/ Number analysed
Of the 25 male and female adolescents planned for recruitment, 13 subjects were to be between the ages of 12 and <15 years and 12 subjects between the ages of 15 and 17 years.

Pharmacokinetic results

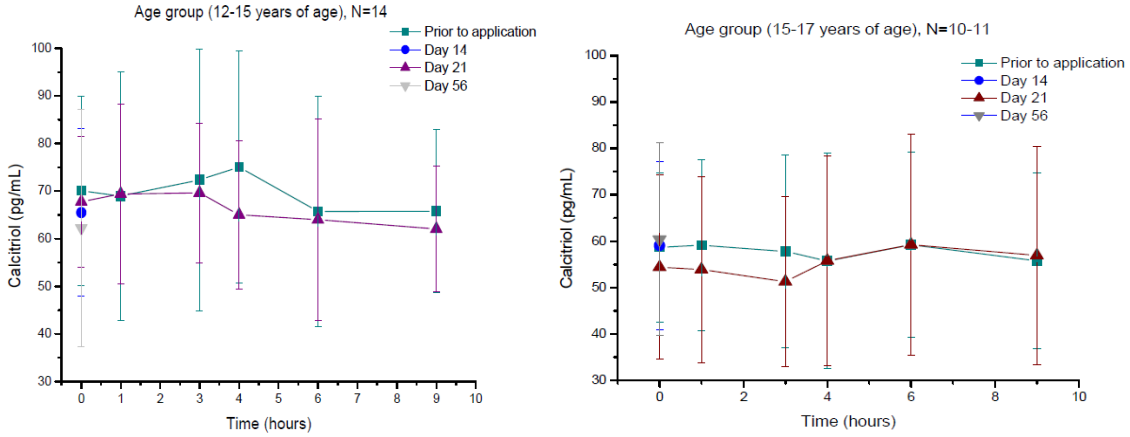
Table 1 Summary of Calcitriol PK parameters

Parameters	Baseline	Day 14	Day 21	Day 56	Day 21/Baseline p value [a] [90% CI] [b]
C_{trough} (pg/mL)					
Mean (SD)	65 (19)	63 (18)	62 (18)	61 (23)	
Percent CV	29%	28%	29%	37%	
C_{max} (pg/mL)					
Mean (SD)	76 (24)		73 (22)		0.457
Percent CV	32%		29%		[0.89-1.04]
AUC_{0-9h} (pg*h/mL)					
Mean (SD)	575 (182)		549 (155)		0.290
CV	32%		28%		[0.87-1.03]
AUC_{0-12h} (pg*h/mL)					
Mean (SD)	765 (230)		738 (204)		0.319
Percent CV	30%		28%		[0.88-1.03]

[a] P-value for the mean difference in natural logarithmic transformed data on Day 21 against Day 0/Baseline was based on the Student paired t-test.
[b] The 90% confidence interval (CI) for the mean difference in natural logarithmic transformed data on Day 21 against Baseline (Day 0) was expressed by the antilog.
CV = coefficient of variation
Data Source: Section 14.3, Table 14.3.1.1, Table 14.3.1.2, Table 14.3.1.3, and Table 14.3.1.4

Plasma levels of calcitriol were not increased upon twice daily application of a maximized dose of Calcitriol 3 µg/g ointment for 56 days (i.e. eight weeks) in adolescents with stable chronic plaque psoriasis. Overall, the mean values for C_{max} and AUC_{0-9h} measured at day 21 were not statistically different from the baseline values. Inter-subject variability was moderate, as supported by coefficients of variation ranging from 28% to 32% at each period for C_{max} and AUC_{0-9h} (see table 1). No correlation was found between BSA treated and systemic exposure to calcitriol. Systemic exposure to Calcitriol was not increasing with treatment of large body surface areas.

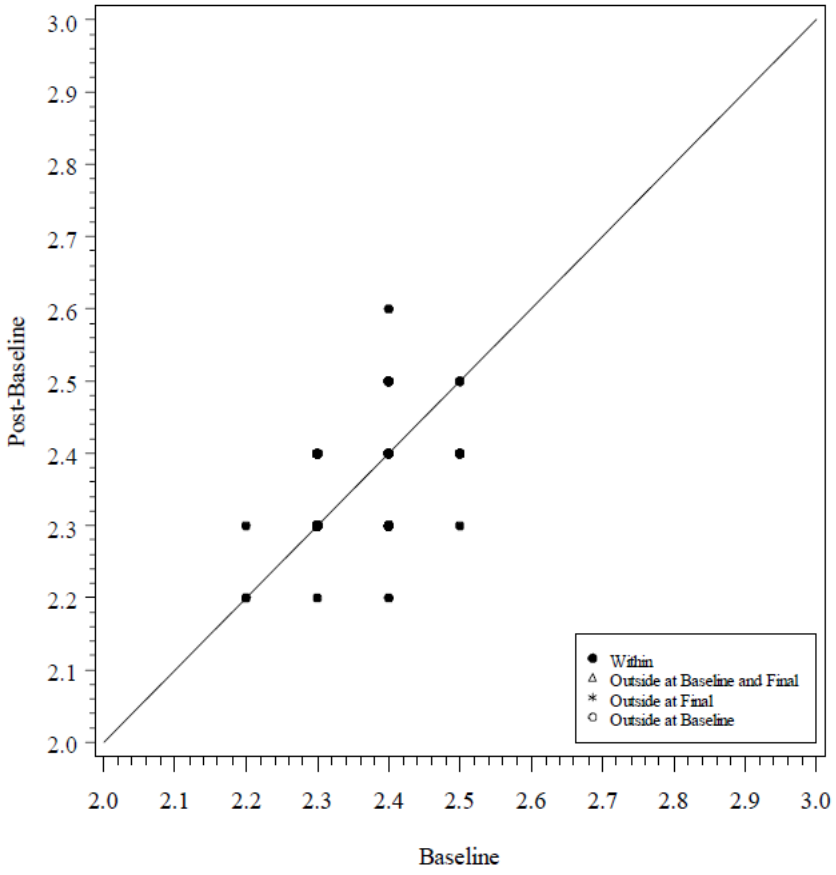
Figure 1 Mean Calcitriol plasma concentrations per age group (± SD)



Endogenous plasma calcitriol levels at baseline appeared to be higher (C_{max} increased by 26%; AUC_{0-9h}, and AUC_{0-12h} 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_{0-9h} and AUC_{0-12h} increased by 17%) in younger adolescents (12 to <15 years of age) compared to older adolescents (15 to 17 years of age).

Pharmacodynamics results

Figure 2 Baseline Data vs. Post-Baseline Data - Albumin-adjusted Calcium (mmol/l), Safety Population



Mean changes in all pharmacodynamic parameters were very minimal. No subjects had serum calcium or adjusted serum calcium levels shift from within the reference range at baseline to above this range during the study.

Serum phosphorus levels for eight subjects shifted from within the normal reference range (i.e. 2.5 to 4.5 mg/dl) at Baseline to above the reference range during the treatment period. Of the eight subjects, four subjects were back to normal at the end of the study. The highest phosphorus level recorded in these eight subjects was 5.7 mg/dl.

Serum calcium and adjusted serum calcium values remained within the respective reference ranges throughout the study for all subjects (see figure 2).

Hence, there is no correlation between any of the other PD parameters and the elevation of phosphorus. The reference range for phosphorus used in this study in adolescents was

relatively narrow, in comparison to the much broader ranges reported for this age group in the literature. There is a well documented physiological elevation of phosphorus levels during the rapid growth spurt in early puberty (Aksnes and Aarskog, 1982).

Efficacy results

Efficacy was assessed as change in percent BSA of involved skin and change in Global Severity Score. Overall, 18 subjects (72.0%) exhibited decreases of one or two grades of the Global Severity Score at the end of the study. After the 8-week treatment period, seven subjects (28%) achieved a two-grade improvement in Global Severity Score and 11 (44%) achieved a one-grade improvement (see table 2).

Overall, the mean (± SD) change in percent BSA was -6.5% (± 8.51) at the end of the study. After the 8-week treatment period, the mean (± SD) percent BSA affected by psoriasis changed from a baseline level of 17.8% ± 8.08 to 11.3% ± 11.47 at day 56/ET visit. The decrease in mean involved BSA over the treatment period was more marked in the 15 to-17-year age group (i.e. a decrease of 10.5% or approximately half of the involved area at Baseline).

Table 2 Summary of Global Severity of Psoriasis, ITT Population

Global Severity of Psoriasis	Age (12 to <15 years)	Age (15 to 17 years)	Total
Baseline			
0 = Clear	0	0	0
1 = Minimal	0	0	0
2 = Mild	0	1 (9.1%)	1 (4.0%)
3 = Moderate	13 (92.9%)	9 (81.8%)	22 (88.0%)
4 = Severe	1 (7.1%)	1 (9.1%)	2 (8.0%)
5 = Very Severe	0	0	0
Total	14 (100.0%)	11 (100.0%)	25 (100.0%)
Day 56			
0 = Clear	0	0	0
1 = Minimal	4 (28.6%)	2 (18.2%)	6 (24.0%)
2 = Mild	4 (28.6%)	8 (72.7%)	12 (48.0%)
3 = Moderate	6 (42.9%)	1 (9.1%)	7 (28.0%)
4 = Severe	0	0	0
5 = Very Severe	0	0	0
Total	14 (100.0%)	11 (100.0%)	25 (100.0%)
Change from Baseline in Global Severity			
2-Grade Improvement (-2 Grade)	4 (28.6%)	3 (27.3%)	7 (28.0%)
1–Grade Improvement (-1 Grade)	5 (35.7%)	6 (54.5%)	11 (44.0%)
No Change	5 (35.7%)	2 (18.2%)	7 (28.0%)
Worse (+1 Grade)	0	0	0
Total	14 (100.0%)	11 (100.0%)	25 (100.0%)

Description of severity grades can be found in Table 4.

Safety results

Overall, 13 subjects (52%) reported at least one adverse event during the study (see table 3 for an overview of AEs regardless of causality). There were no SAEs or adverse events leading to discontinuation.

Two subjects (age 12 to <15 years) experienced AEs related to study drug that were mild in intensity, required no concomitant therapy, and resolved with no residual effects. The degree of relationship to study drug was considered to be “possible” by the Investigator for both subjects.

Calcitriol 3 µg/g ointment appeared to be well tolerated locally. Overall, at the final observation, 14 subjects (56.0%) experienced no local irritation; the remainder experienced mild (six subjects, 24.0%) or moderate (five subjects, 20.0%) symptoms.

Table 3 Summary of Adverse Events by System Organ Class and Preferred

System Organ Class/Preferred Term[a]	Age (12 to <15 years) N=14	Age (15 to 17 years) N=11	Total N=25
Total Number of Adverse Events	20	8	28
Total Number (%) of Subjects with Adverse events[b]	9 (64.3%)	4 (36.4%)	13 (52.0%)
Skin and subcutaneous tissue disorders	5 (35.7%)	2 (18.2%)	7 (28.0%)
Psoriasis	2 (14.3%)	0	2 (8.0%)
Acne	1 (7.1%)	0	1 (4.0%)
Erythema	1 (7.1%)	0	1 (4.0%)
Skin Burning sensation	1 (7.1%)	0	1 (4.0%)
Ecchymosis	1 (7.1%)	0	1 (4.0%)
Pruritus	0	1 (9.1%)	1 (4.0%)
Post-inflammatory pigmentation change	0	1 (9.1%)	1 (4.0%)
Infections and infestations	3 (21.4%)	2 (18.2%)	5 (20.0%)
Nasopharyngitis	2 (14.3%)	0	2 (8.0%)
Pharyngitis	1 (7.1%)	0	1 (4.0%)
Upper respiratory infection	0	1 (9.1%)	1 (4.0%)
Tinea versicolor	0	1 (9.1%)	1 (4.0%)
Injury, poisoning and procedural complications	2 (14.3%)	3 (27.3%)	5 (20.0%)
Excoriations	2 (14.3%)	0	2 (8.0%)
Joint injury	0	1 (9.1%)	1 (4.0%)
Procedural site reaction	0	1 (9.1%)	1 (4.0%)
Mouth injury	0	1 (9.1%)	1 (4.0%)
Investigations	2 (14.3%)	0	2 (8.0%)
Cardiac murmur	1 (7.1%)	0	1 (4.0%)
Blood triglycerides increased	1 (7.1%)	0	1 (4.0%)
Blood cholesterol increased	1 (7.1%)	0	1 (4.0%)
Respiratory, thoracic and mediastinal disorders	2 (14.3%)	0	2 (8.0%)
Pharyngolaryngeal pain	2 (14.3%)	0	2 (8.0%)

System Organ Class/Preferred Term[a]	Age (12 to <15 years) N=14	Age (15 to 17 years) N=11	Total N=25
Blood and lymphatic system disorders	1 (7.1%)	0	1 (4.0%)
Lymphadenopathy	1 (7.1%)	0	1 (4.0%)
Musculoskeletal and connective tissue disorders	1 (7.1%)	0	1 (4.0%)
Rotator cuff syndrome	1 (7.1%)	0	1 (4.0%)
Nervous system disorders	1 (7.1%)	0	1 (4.0%)
Headache	1 (7.1%)	0	1 (4.0%)

[a] Multiple occurrences within a System Organ Class by a subject were counted once per System Organ Class.
[a] Multiple occurrences of a Preferred Term by a subject were counted once per Preferred Term.
[b] A subject was counted once even if the subject experienced more than one adverse event during the study.
MedDRA dictionary version 9.0.

2. RD.06.SPR.18104

Description
This was a PK and PD study under conditions of maximal use in paediatric subjects 2 to 12 years of age, with plaque psoriasis affecting 3% to 35% of BSA, excluding the face and scalp (i.e., area of involvement representative of the upper level of disease severity). Calcitriol 3 µg/g ointment was applied twice a day for 14 days.

Methods
Objectives

- Primary objective: To assess system exposure of Calcitriol 3 µg/g ointment twice a day. The Calcitriol PK profile was assessed at Day 1 before treatment (endogenous Calcitriol levels) and after the last application on Day 14.
- Secondary objective: To assess the effect of Calcitriol 3 µg/g ointment on calcium homeostasis (at screening, day 1 and day 14) and to evaluate safety of Calcitriol 3 µg/g ointment applied twice daily.

Study design
This was an open-label, uncontrolled, multicentre PK and PD study under conditions of maximal use in paediatric subjects (2 to 12 years of age) with plaque psoriasis affecting 3% to 35% of BSA (excluding face and scalp).
Each subject participated in the study for approximately 28 days, which included a screening period of up to two weeks and 14 days (two weeks) of treatment.

Study population /Sample size
It was planned to enrol approximately 30 paediatric subjects with plaque psoriasis to allow for 25 subjects to complete the study. In agreement with the FDA, the study was closed in December 2015 due to slow enrolment. At the time of closure, 18 subjects were enrolled and 17 subjects had completed the study.

Treatment
Calcitriol 3 µg/g ointment was applied twice a day for 14 days. The first application was performed on site by trained study personnel. The quantity to be applied was determined by the Investigator/designee and was based on the percentage of affected BSA, with a maximum dose of 0.25 g of ointment/kg of body weight or 14 g (whichever was lower), and was to cover at least 5% BSA. The quantity applied was not to exceed the maximal dose per application.

Outcomes/endpoints
Pharmacokinetic endpoints: Calcitriol plasma level (maximum plasma concentration [C_{max}], minimum plasma concentration [C_{min}], time drug is present at maximum concentration [T_{max}], and area under the curve [AUC]) under conditions of maximal use (i.e., area of involvement that is representative of the upper level of disease severity and at least 5% BSA [body surface area] treated).
Pharmacodynamic endpoints: effects of calcitriol 3 µg/g ointment on calcium and phosphorus homeostasis. (serum calcium, albumin, albumin-adjusted calcium, phosphorus; urinary calcium, creatine, calcium/creatine ratio).
Safety endpoints: adverse events , physical examination, vital signs, and laboratory parameters. Height and 25-hydroxy Vitamin D (25(OH)D) were evaluated at screening only.

Statistical Methods
AUC, C_{max}, C_{min}, and T_{max} of plasma levels of Calcitriol were determined and summarized on day 1 and day 14. The 90% confidence interval (CI) for the mean difference at day 1 versus day 14

was calculated using the Student's paired-t distribution. Prior to the analyses, the AUC_{0-6h}, AUC_{0-9h}, AUC_{0-12h}, and C_{max} were transformed into their natural logarithms.

Descriptive statistics were applied to the PD variables. The PK/PD relationship on AUC_{0-9h} was assessed by calculating the Spearman correlation coefficients.
The relationship between AUC_{0-9h} and the PD variables was assessed by calculating the Spearman correlation coefficients (PK/PD analysis).

Results

Recruitment/ Number analysed

A total of 32 subjects were screened; 14 subjects were considered screening failures based on eligibility criteria. At the time of closing, 18 subjects had been enrolled into the study. Of the 18 subjects enrolled, 17 subjects completed the study.

Total (n= 18)	
Group I (2 – 6 years)	**Group II** (7 – 12 years)
5 subjects	13 subjects

Pharmacokinetic results

Baseline endogenous intra-individual calcitriol plasma levels measured prior to application of Calcitriol 3 µg/g ointment did not display marked fluctuations.

After two weeks of BID treatment, the maximum Calcitriol plasma levels (C_{max}) varied from 75 to 208 pg/mL (see table 4). The mean C_{max} was 121 ±31 pg/mL and AUC_{0-12h} was 1269 ±307 pg.h/mL (n=17). The inter-subject variability remained low and the CV% of systemic exposure parameters (C_{max}, C_{min} and AUC) ranged from 24% to 26%.

Table 4 Summary of pharmacokinetic parameters at Day 1 and Day 14

		T_{max} (h)	C_{max} (pg/mL)	C_{min} (pg/mL)	AUC_{0-6h} (pg.h/mL)	AUC_{0-9h} (pg.h/mL)	AUC_{0-12h} (pg.h/mL)
Day 1 (Baseline)	N	18	18	18	18	18	18
	Mean ± SD	3.73 ± 3.06	115.9 ± 26.5	89.3 ± 18.1	619.6 ± 128.8	925.4 ± 196.2	1230.3 ± 251.2
	CV (%)	82%	23%	20%	21%	21%	20%
	Min - Max	0.00 - 9.12	72.3 - 172.0	61.3 - 131.0	416.7 - 843.5	617.1 - 1356.5	814.0 - 1766.4
	Median	3	113	85.95	580.04	874.29	1183.28
Day 14	N [a]	17	17	17	17	17	17
	Mean ± SD	1.46 ± 2.36	120.7 ± 31.5	92.6 ± 24.2	650.3 ± 166.8	952.6 ± 235.9	1268.9 ± 307.3
	CV (%)	162%	26%	26%	26%	25%	24%
	Min - Max	0.00 - 9.43	75.1 - 208.0	59.3 - 167.0	415.7 - 1143.4	628.7 - 1651.4	852.8 - 2174.6
	Median	1	113	90.6	633.45	928.13	1218.82

AUC=area under the curve; AUC_{0-6h}= AUC from time 0 to 6 hours; AUC_{0-9h}= AUC from time 0 to 9 hours; AUC_{0-12h}=AUC from time 0 to 12 hours; C_{max}=maximum plasma concentration; C_{min}=minimum plasma concentration; CV=coefficient of variation; Max=maximum; Min=minimum; N=number of subjects; SD=standard deviation; T_{max}=time drug is present at maximum concentration

a) Subject 8299-005 was discontinued from the study

Source: Appendix 16.1.12, Pharmacokinetic Report, Table 2

After 2 weeks of BID treatment, the mean and median values of C_{max} and AUC (AUC_{0-6h}, AUC_{0-9h}, and AUC_{0-12h}) calculated at day 14 were similar to baseline values. For all PK parameters, the difference between day 14 and Baseline expressed as ratio was 1 (range 1.01 to 1.03). These differences were not statistically significant among the 17 subjects who completed the study (see table 4).

No trend could be established between the systemic exposure and (1) the treated BSA (from 5% to 18%), (2) the actual applied daily dose (from 1.9 to 16.7 g), or (3) the age of the paediatric subjects.

Table 5 Statistical analysis of intra-individual Day 14 to Baseline ratio for pharmacokinetic parameters

Ratio Day14/Baseline	C_{max}	AUC_{0-6h}	AUC_{0-9h}	AUC_{0-12h}
N	17	17	17	17
Mean ± SD	1.03 ± 0.20	1.03 ± 0.18	1.01 ± 0.17	1.01 ± 0.16
CV (%)	19.23%	17.43%	16.45%	15.60%
90% CI	[0.93; 1.09]	[0.95; 1.10]	[0.93; 1.07]	[0.94; 1.07]
p-value	0.833	0.656	0.972	0.943

AUC=area under the curve; AUC_{0-6h}= AUC from time 0 to 6 hours; AUC_{0-9h}= AUC from time 0 to 9 hours; AUC_{0-12h}=AUC from time 0 to 12 hours; CI=confidence interval; C_{max}= maximum plasma concentration; CV=correlation coefficient; SD=standard deviation
Source: Table 14.2.1

Pharmacodynamic results

There were few shifts among PD serum parameters during the study. The majority (>83%) of subjects had normal serum values at Baseline that remained normal at the day 14 assessment (see table 6). Most values that were outside the normal range at screening (low or high) remained that way at day 14.

Table 6 Pharmacodynamic parameters in serum (Safety population)

Parameter (Mean ± SD)	2-6 years n=5			7-12 years n=13			Total n=18		
	Screening	Baseline	Day 14/ET	Screening	Baseline	Day 14/ET	Screening	Baseline	Day 14/ET
Calcium (mmol/L)	2.48 ± 0.13	2.44 ± 0.11	2.43 ± 0.05	2.46 ± 0.08	2.41 ± 0.08	2.37 ± 0.09	2.47 ± 0.09	2.42 ± 0.09	2.38 ± 0.08
Albumin (g/L)	45.8 ± 2.8	45.6 ± 1.7	43.8 ± 3.2	45.6 ± 3.0	44.7 ± 2.4	43.5 ± 1.9	45.7 ± 2.9	44.9 ± 2.2	43.5 ± 2.1
Albumin-adjusted calcium (mg/dL)	9.36 ± 0.45	9.26 ± 0.37	9.35 ± 0.19	9.35 ± 0.24	9.27 ± 0.23	9.22 ± 0.22	9.35 ± 0.30	9.27 ± 0.26	9.25 ± 0.22
Phosphorus (mmol/L)	1.58 ± 0.08	1.58 ± 0.22	1.60 ± 0.08	1.48 ± 0.17	1.52 ± 0.15	1.53 ± 0.18	1.51 ± 0.15	1.53 ± 0.17	1.55 ± 0.16
Intact PTH (pg/mL)	20.8 ± 5.5	28.4 ± 17.5	24.4 ± 9.8	31.7 ± 14.2	31.2 ± 14.1	31.2 ± 17.8	28.7 ±13.2	30.4 ± 14.6	29.3 ± 16.0

ET=early termination; Hr-hour; PTH=parathyroid hormone; SD=standard deviation
Source: Tables 14.2.2.1.1, 14.2.2.1.2, 14.2.2.1.3, 14.2.2.1.4, and 14.2.2.1.5

For those subjects with calculated calcium/creatinine ratio, all subjects had normal values at Baseline that remained normal at day 14.

Safety results

Of the 18 subjects who received Calcitriol 3 µg/g, half of the subjects (9 [50.0%]) reported 11 AEs (see table 7). Of these, all five subjects in the 2 to 6 year-old group, and four subjects (30.8%) in the 7 to 12 year-old group experienced at least one AE. All AEs were mild or moderate in severity. Three (60.0%) subjects 2 to 6 years of age reported one cutaneous AE each and two (15.4%) subjects 7 to 12 years of age reported one cutaneous AE each. All except one cutaneous event experienced by a subject in the 2 to 6 year-old group were considered to be related to the investigational product.

Table 7 Adverse events by system organ class and preferred term (Safety population)

		Age				Total N=18	
		2 - 6 years N=5		7 - 12 years N=13			
System Organ Class	Preferred Term	Event n	Subjects[a] N (%)	Event[b] n	Subjects[a] N (%)	Event n	Subjects[a] N (%)
Any adverse event		5	5 (100.0%)	6	4 (30.8%)	11	9 (50.0%)
Gastrointestinal disorders	All	2	2 (40.0%)	0	0 (0.0%)	2	2 (11.1%)
	Abdominal pain upper	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
	Vomiting	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
Infections and infestations	All	0	0 (0.0%)	2	2 (15.4%)	2	2 (11.1%)
	Rhinitis	0	0 (0.0%)	1	1 (7.7%)	1	1 (5.6%)
	Viral infection	0	0 (0.0%)	1	1 (7.7%)	1	1 (5.6%)
Injury, poisoning, and procedural complications	ALL	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
	Sunburn	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
Nervous system disorders	ALL	0	0 (0.0%)	2	2 (15.4%)	2	2 (11.1%)
	Headache	0	0 (0.0%)	2	2 (15.4%)	2	2 (11.1%)
Skin and subcutaneous tissue disorders	ALL	2	2 (40.0%)	2	2 (15.4%)	4	4 (22.2%)
	Pain of skin	0	0 (0.0%)	1	1 (7.7%)	1	1 (5.6%)
	Pruritus	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
	Skin burning sensation	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
	Skin exfoliation	0	0 (0.0%)	1	1 (7.7%)	1	1 (5.6%)

AE=adverse event; SOC=system organ class; PT=preferred term

Note: Multiple occurrences within an SOC by a subject were counted once per SOC. Multiple occurrences of a PT by a subject were counted once per PT.

a) Number of subjects with at least 1 event

b) Subject 8299-005 had 1 AE in the Skin and subcutaneous tissue disorders SOC and 1 AE in the Infections and infestations SOC. Subject 8434-002 had 1 AE in the Nervous system disorders SOC and 1 AE in the Skin and subcutaneous tissue disorders SOC.

Data source: Appendix 16.2.7, Table 14.3.2.2

Adverse events of special interest were predefined as typical clinical signs and symptoms consistent with vitamin D toxicity. No subjects experienced AESIs. No subjects experienced AEs that led to premature withdrawal from the study and no subjects experienced a serious adverse event (SAE) during the study.

3. RD.06.SPR.18132

Description

This study was designed to assess the efficacy and safety of the Calcitriol 3 µg/g ointment applied twice daily for eight weeks in paediatric subjects (2 to 12 years of age) with mild to moderate plaque psoriasis.

Methods

Objectives

- To compare the efficacy of up to eight weeks of treatment with Calcitriol 3 µg/g ointment versus its vehicle.
- To compare the safety of up to eight weeks of treatment with Calcitriol 3 µg/g ointment versus its vehicle.

- To evaluate the effect of twice daily applications of Calcitriol 3 µg/g ointment versus vehicle on calcium metabolism.

Study design
This was a multicentre, randomized, vehicle-controlled, double-blind, parallel group study comparing the efficacy and safety of up to eight weeks of topical treatment with Calcitriol 3 µg/g ointment versus its vehicle, when applied twice daily, without occlusion, in the treatment of children aged 2 to 12 years with plaque psoriasis (excluding the face and scalp).

Study population /Sample size
The original intent of the study was to screen approximately 400 paediatric subjects (aged 2 to 12 years) for study participation in order to achieve a minimum of 300 randomized subjects. This sample size of 300 randomized subjects would be the minimum required to detect a treatment difference of 12% in the success rate (i.e., 22% for Calcitriol and 10% for vehicle) at the 0.05 alpha level with 80% power. Due to slow study enrolment and in agreement with the FDA, the study was closed to enrolment in December 2015.

At the time of study closing, 19 subjects were randomized into the study; eight in the Calcitriol 3 µg/g ointment group and 11 in the Vehicle group.

Treatments
Calcitriol 3 µg/g ointment or vehicle (placebo) applied twice daily for eight weeks; maximum of 0.5 g/kg of body weight or 28 grams daily (whichever was the lower).

Outcomes/endpoints
Efficacy endpoints: primary endpoint was the success rate defined as the percentage of subjects with an IGA score of 0 (clear) or 1 (almost clear), and at least a 2 grade improvement from baseline. Secondary Efficacy Endpoint Variables were the changes from baseline in pruritus and percent body surface area (BSA) and the percent BSA involved.
Safety endpoints: Adverse Event recording at each study visit, vital signs, physical examination, and routine safety laboratory parameters.
Pharmacodynamic endpoints: effects of calcitriol 3 µg/g ointment on calcium and phosphorus homeostasis (serum calcium, albumin, albumin-adjusted calcium, phosphorus; urinary calcium, creatine, calcium/creatine ratio).

Statistical Methods
The planned statistical analyses were modified due to the small number of randomized subjects in the study. The primary efficacy analysis was the comparison of success rates between treatments at week eight for the ITT population defined as all subjects who were randomized and to whom investigational product was dispensed. Success rates were analysed using the Fisher Exact test. All other efficacy endpoints (Pruritus, %BSA and IGA values) were summarized descriptively.

All safety data are summarized for the Safety population defined as all ITT subjects who had applied the study medication at least once. Laboratory parameters at scheduled visits and change from Screening at post-baseline visit(s) are summarized descriptively by treatment and by visit. A shift table for lab parameters at Screening versus the week eight/Early Termination visit is provided by treatment when appropriate. Adverse events are summarized by frequency and percentage by System Organ Class (SOC) and Preferred Term (PT) based on the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Additional summary tables are provided for AEs, serious AEs (SAEs), AEs related to the investigational product, and AEs leading to discontinuation. Subgroup analyses of AEs based on gender, age group, and race were not performed due to the small numbers of subjects enrolled.

Results

Recruitment/ Number analysed

A total of 29 subjects were screened from 13 sites in the US, Canada, and Europe. Ten subjects were considered screening failures based on eligibility criteria (n=6), the subject's request (n=2), or "other" (n=2). The 19 randomized subjects received either Calcitriol 3 µg/g ointment (n=8) or vehicle (n=11).

Efficacy results

Table 8 Primary endpoint- Success rate at week 8

	Calcitriol (N=8)	Vehicle (N=11)	p-value[b]
ITT – LOCF	3 (37.5%)	7 (63.6%)	0.370
ITT – FAILURE[a]	2 (25%)	7 (63.6%)	0.170
PP	1 (20%)	6 (66.7%)	0.266

a) Subjects with missing success rate data were considered treatment failures.
b) P values based on Fisher-exact test.
Data Source: Section 14.2, Table 14.2.1

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 three subjects (37.5%) of the Calcitriol 3 µg/g ointment group achieving success and seven subjects (63.6%) of the Vehicle group (See table 8). Though there seems to be a numerical greater effect for vehicle, due to very small sample size, any observed numerical difference in treatment groups is most likely due to chance.

Table 9 Secondary endpoint – Pruritus score (ITT-LOCF)

	Calcitriol (N=8)	Vehicle (N=11)
BASELINE PRURITUS N (%)		
None	2 (25)	1 (9.1)
Mild	2 (25)	6 (54.5)
Moderate	2 (25)	3 (27.3)
Severe	0	1 (9.1)
Very Severe	2 (25)	0
Baseline Mean pruritus score (SD)	1.8 (1.6)	1.4 (0.8)
Baseline Median pruritus score	1.5	1.0

	Calcitriol (N=8)	Vehicle (N=11)
WEEK 8 PRURITUS N (%)		
None	6 (75.0)	7 (63.6)
Mild	1 (12.5)	3 (27.3)
Moderate	1 (12.5)	0
Very Severe	0	1 (9.1)
Week 8 Mean pruritus score (SD)	0.4 (0.7)	0.6 (1.2)
Week 8 Median pruritus score	0	0
CHANGE FROM BASELINE		
Mean Week 8 change from baseline in pruritus score	-1.4 (1.1)	-0.7 (0.9)
Median Week 8 change from baseline in pruritus score	-1.5	-1.0

SD= standard deviation
Data Source: Section 14.2, Table 14.2.2.2

The majority of ITT population subjects in both groups had a score of 0 (none) by week eight, six (75%) and seven (63.6%) subjects for the Calcitriol 3 µg/g ointment group and Vehicle group, respectively (See table 9). The mean change from baseline at week eight was -1.4 for the Calcitriol 3 µg/g ointment group and -0.7 for the Vehicle group.

Another secondary efficacy endpoint was the evaluation of the change from baseline in the percentage BSA involved at week eight. Subjects randomized to the Calcitriol 3 µg/g ointment group showed a mean reduction in percentage BSA involvement of -1.5 at 8 weeks compared with -3.4 for the Vehicle group.

Evaluation of the change from baseline in the IGA score at week eight for the ITT Population, regardless of the success rate criteria, was also performed as a supportive secondary analysis. The Calcitriol 3 µg/g ointment group subjects showed a mean difference of -1.0 in the IGA score at week eight compared with a mean change of -1.8 for the Vehicle group subjects.

Safety results

Table 10 Adverse events by system organ class and preferred term (safety Population)

		Calcitriol (N=8)		Vehicle (N=11)		Total (N=19)	
		Event n	Subject[a] N (%)	Event n	Subject[a] N (%)	Event n	Subject[a] N (%)
ANY ADVERSE EVENTS		**10**	**6 (75.0)**	**18**	**8 (72.7)**	**28**	**14 (73.7)**
Gastrointestinal disorders	**ALL**	**3**	**2 (25.0)**	**0**	**0**	**3**	**2 (10.5)**
	Abdominal pain upper	1	1 (12.5)	0	0	1	1 (5.3)
	Diarrhoea	2	1 (12.5)	0	0	2	1 (5.3)
Infections and infestations	**ALL**	**4**	**2 (25.0)**	**8**	**6 (54.5)**	**12**	**8 (42.1)**
	Conjunctivitis bacterial	1	1 (12.5)	0	0	1	1 (5.3)
	Gastroenteritis	1	1 (12.5)	0	0	1	1 (5.3)
	Laryngitis	0	0	1	1 (9.1)	1	1 (5.3)
	Lice infestation	1	1 (12.5)	0	0	1	1 (5.3)
	Molluscum contagiosum	1	1 (12.5)	0	0	1	1 (5.3)
	Nasopharyngitis	0	0	4	2 (18.2)	4	2 (10.5)
	Upper respiratory tract infection	0	0	1	1 (9.1)	1	1 (5.3)
	Urinary tract infection	0	0	1	1 (9.1)	1	1 (5.3)
	Viral infection	0	0	1	1 (9.1)	1	1 (5.3)
Injury, poisoning and procedural complications	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Arthropod bite	0	0	1	1 (9.1)	1	1 (5.3)
Investigations	**ALL**	**0**	**0**	**3**	**2 (18.2)**	**3**	**2 (10.5)**
	Blood pressure increased	0	0	2	1 (9.1)	2	1 (5.3)
	Urine calcium/creatinine ratio increased	0	0	1	1 (9.1)	1	1 (5.3)
Musculoskeletal and connective tissue disorders	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Myalgia	0	0	1	1 (9.1)	1	1 (5.3)
Renal and urinary disorders	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Hypercalciuria	0	0	1	1 (9.1)	1	1 (5.3)
Respiratory, thoracic and mediastinal disorders	**ALL**	**1**	**1 (12.5)**	**2**	**2 (18.2)**	**3**	**3 (15.8)**
	Cough	0	0	2	2 (18.2)	2	2 (10.5)
	Oropharyngeal pain	1	1 (12.5)	0	0	1	1 (5.3)
Skin and subcutaneous tissue disorders	**ALL**	**2**	**2 (25.0)**	**2**	**2 (18.2)**	**4**	**4 (21.1)**
	Pruritus	0	0	1	1 (9.1)	1	1 (5.3)
	Psoriasis	0	0	1	1 (9.1)	1	1 (5.3)
	Skin irritation	2	2 (25.0)	0	0	2	2 (10.5)

Note: Adverse events are defined as events that occurred on the day of, or after, the first use of investigational product. Multiple occurrences within a System Organ Class by a subject were counted once per System Organ Class. Multiple occurrences of a Preferred Term by a subject were counted once per Preferred Term.
a) Number of subjects with at least one event
Data source: Section 14.3, Table 14.3.2.2

A similar proportion of subjects in both treatment groups experienced AEs (see table 10). No deaths, SAEs, or AEs leading to discontinuation were reported.

For the skin and subcutaneous tissue disorders SOC, 3 subjects experienced AEs related to local tolerability, one subject in the vehicle group had pruritus (worsening) and 2 subjects in the

Calcitriol 3 µg/g ointment group had AEs of skin irritation. All 3 local tolerability AEs were considered at least possibly related to investigational product.

In addition to these events, the subject in the Vehicle group with pruritus also had AEs of urine calcium/creatinine ratio increased and hypercalciuria that were considered related to investigational product (see table 11). An additional one subject in the vehicle group had the AE of urinary tract infection that was considered treatment-related.

Table 11 Adverse events related to investigational product by system organ class and preferred term (Safety Population)

		Calcitriol (N=8)		Vehicle (N=11)		Total (N=19)	
		Event n	Subject[a] N (%)	Event n	Subject[a] N (%)	Event n	Subject[a] N (%)
ANY ADVERSE EVENTS		**2**	**2 (25.0)**	**4**	**2 (18.2)**	**6**	**4 (21.1)**
Infections and infestations	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Urinary tract infection			1	1 (9.1)	1	1 (5.3)
Investigations	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Urine calcium/creatinine ratio increased			1	1 (9.1)	1	1 (5.3)
Renal and urinary disorders	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Hypercalciuria			1	1 (9.1)	1	1 (5.3)
Skin and subcutaneous tissue disorders	**ALL**	**2**	**2 (25.0)**	**1**	**1 (9.1)**	**3**	**3 (15.8)**
	Pruritus			1	1 (9.1)	1	1 (5.3)
	Skin irritation	2	2 (25.0)			2	2 (10.5)

Note: Adverse events are defined as events that occurred on the day of, or after, the first use of investigational product. Multiple occurrences within a System Organ Class by a subject were counted once per System Organ Class. Multiple occurrences of a Preferred Term by a subject were counted once per Preferred Term.
a) Number of subjects with at least one event
Data source: Section 14.3, Table 14.3.2.10

One of the skin irritation AEs for the Calcitriol 3 µg/g ointment group subjects resulted in dose reduction, but the other related AEs did not require dose modification. The skin irritation AE leading to dosing changes and the related AEs of pruritus, urine calcium/creatinine ratio increased, hypercalciuria, and urinary tract infection also met the protocol-defined criteria for AEs of special interest.

Pharmacodynamic results
One subject in the Vehicle group had laboratory abnormalities and associated AEs of calcium/creatinine ratio increased and hypercalciuria that were considered associated to altered calcium metabolism but no subjects in the Calcitriol 3 µg/g ointment group had AEs of this class.

No trends in the pharmacodynamics profile, serum chemistry, hematology, or vital signs suggested any systemic toxic effect of investigational product. The Vehicle group had the only clinically significant post-treatment laboratory results. There were no study discontinuations due to abnormal laboratory parameters or vital sign measurements.

In this study, Calcitriol ointment 3 µg/g did not affect calcium homeostasis and demonstrated good systemic and topical safety comparable to the vehicle.

IV.1.3 Discussion on clinical aspects

As part of their paediatric clinical program the MAH has submitted three clinical studies evaluating the pharmacokinetic, pharmacodynamic, safety and efficacy effects of Calcitriol 3 µg/mg in children and adolescents. A long term safety study (RD.06.SPR.18131) in children aged 2 to 17 years is not included in this report, as it is currently recruiting participants.

All studies were performed in compliance with good clinical practice. The participants included in the studies are representative for the target population. The twice daily dose regime is the adult dose regime. A major drawback for the studies was the slow enrolment, leading to a premature closing of the studies contributing to the limited number of participants in the studies.

In the two studies that include efficacy outcomes it was shown that exposure to calcitriol lead to a numerical reduction in Global Severity Score. In the vehicle-controlled study vehicle had a numerical greater reduction in Global Severity than calcitriol, and the MAH argues that this is most likely due to the small sample size i.e. chance of the study which is a plausible explanation.

No serious adverse events occurred. The most frequent adverse events were local, such as pruritus or skin burning and were mild to moderate. There were no discontinuations due to adverse events.

Overall, all three studies have shown that the calcitriol plasma levels and calcium/phosphorus parameters were within the predefined reference ranges after maximal exposure of calcitriol.

Serum phosphorus levels shift during the treatment period from normal to above the reference range for eight subjects in Study RD.06.SPR.18102. Four subjects reverted back to normal at the end of the study. The MAH argued that the range used in the study was rather narrow as compared to the ranges reported for this age group in literature. This is accepted.

In the two PK/PD studies no trends were observed between systemic exposure of calcitriol and area of body surface involved (up to 35%).

No changes in calcium homeostasis were observed after systemic exposure to calcitriol, as measured by serum calcium, albumin, albumin-adjusted calcium, urinary calcium, creatine, and urinary calcium/creatine ratio.

Information regarding the calcium phosphate product is lacking. This is requested to exclude the potential of calcinosis.

Summarizing, no conclusions can be made on the efficacy of calcitriol in plaque psoriasis the paediatric population. Due to the small sample sizes results are inconclusive. Calcitriol seems to be well tolerated in the paediatric population.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Overall calcitriol seems to be well tolerated in the paediatric population. The three studies provided by the MAH showed that the calcium homeostasis remained within the reference range after maximal exposure to calcitriol. The adverse events that occurred were mild and transient in nature. The efficacy outcomes have shown a numerical reduction in global severity after calcitriol treatment, though the results are inconclusive due to the small sample sizes.

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

- **Recommendation**

The following changes should be made to the SmPC and PL:

SmPC section 4.2:
Paediatric population
*The safety and efficacy of Silkis in children ~~aged 2 to 17 years~~ **less than 18 years** have not ~~yet~~ been established.*
*Currently available data are described in section **4.4**, 5.1 **and 5.3** but no recommendation on a posology can be made.*

SmPC section 4.4:
Paediatric population
*There is limited amount of **clinical** data supporting the use of Silkis in the paediatric population (See section 5.1). In view of the particular sensitivity of neonates versus adult rodents to the toxic effects of calcitriol, exposure of children to calcitriol ointment should be avoided (see section 5.3).*

SmPC section 5.1:
Paediatric population
Very limited efficacy data of Calcitriol in the paediatric population are available from an 8-week randomized, vehicle-controlled study in children aged 2 to 12 years with plaque psoriasis (n= 19; 8 on active, 11 on vehicle). Calcitriol 3µg/g was applied twice daily excluding the face and scalp. 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 (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.

SmPC section 5.3:
In rats, intra muscular injections of Calcitriol for 2 weeks induced calcification in soft tissues. However, the neonatal rats seem to be more sensitive than the adults, as calcification occurred in all dose groups (0.13, 0.38 and 1.28 µg/kg/day) whereas it was observed only in the adult high dose group (0.03, 0.13 and 0.64 µg/kg/day).

PL section 2:
Children
There is limited data on the use of Silkis in children. Therefore, use in children should be avoided.

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.