Clinical Pharmacology Review

NDA Number	022,087/S-009 (SDN 362)
Link to EDR	*\\CDSESUB1\evsprod\NDA022087\022087.enx (eCTD 0035)*
Submission Date	September 17, 2019
Submission Type	Efficacy/Labeling supplements
Brand Name	VECTICAL®
Generic Name	Calcitriol ointment 3 mcg/g
Related Indication	For the topical treatment of mild to moderate plaque psoriasis in patients aged 2 years and older
Applicant	Galderma Labs, LP.
Primary Reviewer	Cindy (Liping) Pan, Ph.D.
Secondary Reviewer	Chinmay Shukla, Ph.D.
OCP Division	Division of Inflammation and Immune Pharmacology (DIIP)
OND Division	CDER/ODEIII/DDDP

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1. EXECUTIVE SUMMARY

VECTICAL® (calcitriol) ointment 3 mcg/g, a vitamin D analog, was approved in 2009 for the topical treatment of mild to moderate plaque psoriasis in patients 18 years of age and older.

At the time of original approval, there were four Pediatric Research Equity Act (PREA) Post-marketing requirements (PMRs) as shown below:

#1 Conduct PK/PD study of vectical ointment under maximum use conditions in 25 evaluable pediatric subjects with psoriasis aged 12 to 17 years.

#2 Conduct a PK/PD study of vectical ointment under maximum use conditions in pediatric subjects with psoriasis aged 2 to 12 years; the number of subjects enrolled should be sufficient to detect a 10% change in serum ionized calcium from baseline with 90% confidence or minimum of 25 evaluable subjects, whichever is larger.

#3 Conduct a vehicle-controlled study of the safety and efficacy of vectical ointment in pediatric subjects with psoriasis 2 to 12 years of age with a minimum of 100 evaluable subjects exposed to active.

#4 Conduct a long-term safety study of vectical ointment in 100 evaluable pediatric patients 2 to 17 years of age.

PMR#1 reviewed earlier by Dr. Abimbola Adebowale was considered fulfilled without labeling revisions during the review cycle (*see Clinical Pharmacology Review dated 03/03/2011 in DARRTS, Reference ID: 29131668)*. On November 20, 2015, the Agency released the applicant from PMRs # 2 - 4 and generated a new PMR #5 *below (see communication in DARRTS).*

#5 Conduct a long-term safety trial, including assessment of calcium metabolism, of Vectical® (calcitriol) Ointment in 100 evaluable pediatric subjects with plaque psoriasis aged 2 to 16 years and 11 months. Pharmacokinetic/Pharmacodynamic (calcium metabolism) assessment should be performed in at least 9 subjects with plaque psoriasis under maximum use conditions aged 2 to 6 years and 11 months old.

In the current supplemental New Drug Application (sNDA), the Applicant submitted the final study reports to fulfill the aforementioned PMRs #2 - 5. In this review cycle, labeling revisions to reflect PK results from PMR#1 and PMR#2 have been submitted in this application.

1.1 Recommendation

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) has concluded that the Applicant has fulfilled the PMR #2 and PMR #5 from a Clinical Pharmacology's perspective.

2. SUMMARY OF A MAXIMAL USE STUDY 18104 (PMR # 2)

Title: Pharmacokinetics and pharmacodynamics of calcitriol 3 mcg/g ointment applied twice daily for 14 days under conditions of maximal use in pediatric subjects (2 to 12 years of age) with plaque psoriasis

2.1 Study Objective

The primary objective of the study was to assess calcitriol plasma level under conditions of maximal use of calcitriol 3 mcg/g ointment twice daily (BID) in pediatric subjects aged 2 to 12 with plaque psoriasis affecting 3% through 35% of body surface area (BSA) (excluding face and scalp).

2.2 Study Design

This was an open-label, multicenter, pharmacokinetic (PK) and pharmacodynamic (PD) study under conditions of maximal use in pediatric subjects aged 2 to 12 with plaque psoriasis affecting 3% to 35% BSA, excluding the face and scalp. Eighteen subjects were enrolled, and 17 subjects complete the study.
The duration of the study was approximately 28 days, including an up to 2-week screen period and a 14-day treatment period. The first and last applications were performed on site by trained study personnel, others were applied at home. The quantity applied during the first visit was recorded and the parents were instructed to apply the same quantity for each application (BID throughout the study), regardless of any changes to involved BSA during the study treatment period.

Reviewer's comments: *Study 18104 did not achieve the planned protocol or PMR#2 due to slow enrollment. In the original protocol, 25 subjects were planned to be dosed with 12 of them affecting ≥10% BSA. At the time of granting the new PMR#5, Study 18104 under PMR#2 had 16 completers including 5 subjects in the 2 to 6 year-old range and 11 subjects in the 7 to 12 year-old range. Therefore, Clinical Pharmacology requested PK assessment in additional 9 subjects in the lowest age range of 2 to 6 year-old (see review in DARRTS dated 10/15/2015 by Dr Chinmay Shukla). In this submission, the sponsor submitted the PK data from Study 18104 (**PMR # 2**) which included 5 subjects aged 2-6 and 13 subjects aged 7-12 (see Table 3).*

*Additional PK data from Study RD.06.SRE.18131 (18131) (**PMR # 5**) was obtained from only one subject aged 4 years. In this subject, the baseline calcitriol level was 59.2 pg/mL and post treatment, calcitriol concentrations were 67 pg/mL (Week 4), 80.8 pg/mL (Week 12), and 44.8 pg/mL (Week 26). There were no systemic safety signals and issues with calcium metabolism observed in this subject. This reviewer notes that there is wide variability in the endogenous levels of calcitriol as observed in PMR#2. Specifically, the baseline endogenous calcitriol levels ranged from 61.3 pg/mL to 172 pg/mL (Table 1). Based on this information, the post-dose increase in calcitriol concentration in the single 4 year old subject in PMR# 5 appears to be within the range of baseline variability and there is no clear evidence of any increase in systemic absorption of calcitriol post-treatment. This reviewer recommends not*

adding PK data from this single subject to the label as it will not provide any additional information.

Although the applicant did not meet the requirement of assessing PK in 9 subjects under PMR#5; the lack of any systemic safety signals and furthermore lack of any increase in systemic concentrations of calcitriol from baseline in pediatric subjects aged 2 years to 12 years under maximal use conditions suggests that the currently available PK data in 18 subjects (17 subjects from PMR # 2 and 1 subject from PMR # 5) aged 2 years to 12 years is considered adequate to release the sponsor from PMR #2 and PMR# 5.

Dosing regimen
Calcitriol 3 mcg/g BID for 14 days with ≤ 0.25 g/kg of body weight or 14 g daily.

Reviewer's comments: *The approved maximum weekly dose for adults is 200 g. Based on data in Table 3, in the maximal use study, the observed maximum weekly dose studied in the pediatric patients aged 2 to 6 years was 103.6 g (14.8 g x 7 days) and in subjects 7 to 12 years was 199.5 g (28.5 g x 7 days). Based on this information, the proposed maximum weekly dosing will be limited to not more than 100 g in subjects 2 to 6 years old and not more than 200 g in subjects 7 years of age and older. This information is proposed to be added in the label.*

2.3 Pharmacokinetic and Pharmacodynamic Sampling

- Blood samples were collected on Day 1 and Day 14 for PK analysis of calcitriol as:
  - Body weight ≥15 kg: 0 (prior to dosing), 1, 3, 6 hours post dose
  - Body weight < 15 kg: 0 (prior to dosing), 3, 6 hours post dose

Primary PK analysis

C_{max}: the observed peak plasma concentration of calcitriol
C_{min}: the minimal plasma concentration of calcitriol
T_{max}: the time at which C_{max} occurs
AUC: area under the curve from time 0 to the last sampling point in the dose interval, e.g. $AUC_{0\text{-}6h}$, $AUC_{0\text{-}9h}$, $AUC_{0\text{-}12h}$.

- 24-hour urine samples were collected on Day 1 and Day 14 to evaluate the effect of calcitriol on the ratio of urine calcium/creatinine.

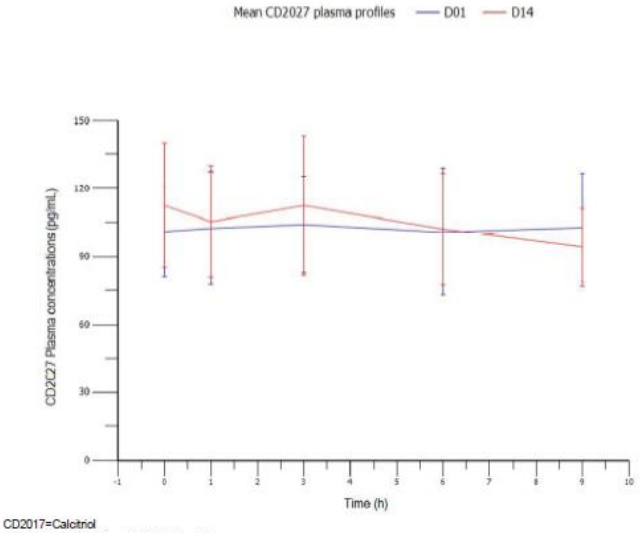
- Blood samples were collected on Day 1 and Day 14 to evaluate the effect of calcitriol on calcium and phosphorus homeostasis.

2.4 Pharmacokinetic results

PK results from PMR# 2: All PK data of calcitriol were summarized in Figure 1 and Table 1. Overall, the mean calcitriol plasma concentrations were relative flat at baseline (Day 1) and after 2-week treatment application (Day 14) (Figure 1). At baseline, endogenous plasma calcitriol levels over the time in all subjects ranged from 61.3 pg/mL to 172 pg/mL (Table 1). After 2-week BID treatment, the plasma calcitriol levels over the time ranged from 59.3 pg/mL to 208 pg/mL (Table 1). The range, mean, or median of AUCs after the treatment appear to be numerically higher that those obtained at baseline or prior to the treatment (Table 1).

PK results from PMR# 5: In the long-term safety and efficacy study (Study 18131), PK samples were collected from one subject aged 4 who received the topical treatment of calcitriol 3 mcg/g BID for 26 weeks. The endogenous calcitriol levels in this subject were 59.2 pg/mL, 67 pg/mL, 80.8 pg/mL, 44.8 pg/mL, and 59.2 pg/mL at baseline and Weeks 4, 12, 26, and after treatment at Week 30, respectively, which were comparable or slightly lower to those observed in the PK Study 18104. This reviewer notes that there is wide variability in the endogenous levels of calcitriol as observed in PMR#2. Specifically, the baseline endogenous calcitriol levels ranged from 61.3 pg/mL to 172 pg/mL (Table 1). Based on this information, the post-dose increase in calcitriol concentration in the single 4 year old subject in PMR# 5 appears to be within the range of baseline variability and there is no clear evidence of any increase in systemic absorption of calcitriol post-treatment.

Figure 1 Plasma Concentrations of Calcitriol



(Source of data: Figure 1, Clinical Study Report 18104)

Table 1 Pharmacokinetics of Calcitriol

		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_{0-8h}= 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 (b) (6) was discontinued from the study

Source: Appendix 16.1.12, Pharmacokinetic Report, Table 2

(Source of data: Table 6, Clinical Trial Report 18104)

Reviewer's comments: *Plasma concentrations of calcitriol in Study 18104 were determined by a new validated bioanalytical assay using a solid phase extraction with liquid chromatography – tandem mass spectrometry (LC-MS/MS). The standard curve of calcitriol was linear in the range of 20 pg/mL to 200 pg/mL with the lower limit of quantification (LLOQ) of 20 pg/mL.*

In the original NDA and PMR #1 study, a validated RadioImmuno Assay (RIA) method, based on a commercially available (b) (4) *for 1,25-dihydroxyvitam D (1,25-$(OH)_2$-D), was used to determine plasma concentrations of calcitriol in adult and adolescent subjects with psoriasis.* (b) (4) *A brief summary of the method is as follows: the standard curve of 1,25-$(OH)_2$-D was linear in the range of 5 pg/mL to 200 pg/mL with the LLOQ of 5 pg/mL.*

Of note, no cross-validation study for determination of calcitriol was performed.

2.4 Labeling recommendations

Labeling recommendations on Section 12 of the label of (b) (4) are summarized in Table 2. The text in red is proposed by the Applicant. The ~~strikethrough in red text~~ indicates recommended deletion by the reviewer. The texts in blue are recommended addition to the labeling by the reviewer.

Table 2 Reviewer's recommendations on labeling

Proposed labeling by the Applicant	Reviewer's labeling recommendations
2 DOSAGE AND ADMINISTRATION Apply VECTICAL Ointment to affected areas twice daily, morning and evening. The maximum weekly dose should not exceed 200 grams. (b) (4) **8.3 Pediatric Use** (b) (4)	**2 DOSAGE AND ADMINISTRATION** ***Adults:*** Apply VECTICAL Ointment to affected areas twice daily, morning and evening. The maximum weekly dose should not exceed 200 grams. ***Pediatrics:*** Apply VECTICAL Ointment to affected areas twice daily, morning and evening. • 2 to 6 years of age: the maximum weekly dose should not exceed 100 grams • 7 years of age and older: the maximum weekly dose should not exceed 200 grams **8.3 Pediatric Use** (b) (4)

(b) (4)

(b) (4)

12 CLINICAL PHARMACOLOGY

Specific populations

Pediatric Patients

The systemic exposure of calcitriol was assessed in pediatric subjects aged 2 to 17 years old with plaque psoriasis in two studies. In one study, 25 subjects aged 12 to 17 years applied (b) (4) calcitriol ointment 3 mcg/g for 8 weeks to a body surface area of 10% to 35%. The mean daily dose was 10.43 g/day. In the second study, 17 subjects aged 2 to 12 years applied (b) (4) calcitriol ointment 3 mcg/g for 14 days to a body surface area of 3% to 18%. The mean daily dose was 17.09 g/day. In both the studies, the systemic concentrations of calcitriol post treatment were relatively flat and were generally comparable to the

	endogenous levels observed at baseline. The PK parameters could not be reliably estimated. There was no correlation between the elevated calcitriol levels and the pharmacodynamic parameters of serum albumin adjusted calcium, serum phosphorus, urinary calcium and urinary phosphorus.

3. QUESTION-BASED CLINICAL PHARMACOLOGY REVIEW

Refer to the *Clinical Pharmacology Review by Dr. Abimbola Adebowale (Reference ID 2913168; dated 03/03/2011)* for detailed information of study design and results of the maximal use PK Study in pediatric subjects aged 12 to 17 with psoriasis (Study 18102) which fulfilled the PMR #1. The current clinical pharmacology review focuses on the PK/PD of calcitriol in pediatric subjects aged 2 to 12 with psoriasis based on the full Clinical Study Report of 18104 (PMR #2).

3.1 What are the study population and drug usage information in Study 18104?

Demographic characteristics are summarized by age in Table 3. More than twice as many subjects aged 7 to 12 (n=13) were enrolled compared with those aged 2 to 6 (n=5). There were more females than males in the 2- to 6-year-old group and more males than females in the 7- to 12- year-old group. The majority of subjects was white in both groups (>76%). At Baseline or prior to the treatment, the mean BSA affected was 7.8 ± 1.9% (ranging from 5% to 10%) in the 2- to 6-year-old group and 8.8 ± 4.7% (ranging from 3% to 18%) in the 7- to 12-year-old group. Of note, for two subjects who had <5% of affected BSA, the investigational product was applied on all involved areas and surrounding uninvolved skin to reach a total of 5% BSA. The mean maximal daily doses used in the 7- to 12-year-old group (~20 g) is 2-fold greater than those used in the 2- to 6-year-old group (~10 g) (Table 3).

Table 3 Demographic Data

		Age 2-6 years N=5	Age 7-12 years N=13	Total N=18
Age	N	5	13	18
	Mean ± SD	4.2 ± 1.5	10.0 ± 1.5	8.4 ± 3.0
	Median	4.0	10.0	9.5
	Min, Max	2, 6	7, 12	2, 12
Age group	Children (2-11 years)	5 (100.0%)	11 (84.6%)	16 (88.9%)
	Adolescents (12 years)	NA	2 (15.4%)	2 (11.1%)
	Total	5	13	18
Sex	Male	1 (20.0%)	9 (69.2%)	10 (55.6%)
	Female	4 (80.0%)	4 (30.8%)	8 (44.4%)
Race	White	5 (100.0%)	10 (76.9%)	15 (83.3%)
	Black/African American	0	2 (15.4%)	2 (11.1%)
	Other	0	1 (7.7%)	1 (5.6%)
Ethnicity	Hispanic or Latino	0	3 (23.1%)	3 (16.7%)
	Not Hispanic or Latino	5 (100.0%)	10 (76.9%)	15 (83.3%)
Skin phototype	I	1 (20.0%)	1 (7.7%)	2 (11.1%)
	II	2 (40.0%)	3 (23.1%)	5 (27.8%)
	III	2 (40.0%)	4 (30.8%)	6 (33.3%)
	IV	0	4 (30.8%)	4 (22.2%)
	VI	0	1 (7.7%)	1 (5.6%)
BSA involved at Baseline	Mean ± SD	7.8 ± 1.9	8.8 ± 4.7	8.6 ± 4.1
	Median	8.0	8.0	8.0
	Min, Max	5, 10	3, 18	3, 18
Maximal daily dose (g)	Mean ± SD	9.66 ± 3.06	19.94 ± 5.55	17.09 ± 6.81
	Median	8.70	19.50	16.70
	Min, Max	6.7, 14.8	12.2, 28.5	6.7, 28.5
BMI (kg/m2) at Screening	Mean ± SD	15.94 ± 1.22	20.14 ± 4.33	18.97 ± 4.16
	Median	15.80	18.70	17.80
	Min, Max	14.5, 17.8	15.6, 30.4	14.5, 30.4

BSA=body surface area; BMI=body mass index; NA=not applicable; SD = standard deviation.
Data source: Section 14.1, Table 14.1.4
(Source of data: Table 5, Clinical Study Report 18104)

3.2 How does the systemic exposure of calcitriol in pediatric subjects compare with adults?

A comparison PK data among adults, adolescents, and pediatrics aged 6 to 12 following calcitriol 3mcg/g topical treatment under maximal use conditions is summarized in Table 4. The adult PK data is obtained from the *original NDA review* dated 08/29/2008 and the adolescent PK data is obtained from *Clinical Pharmacology Review by Dr. Abimbola Adebowale dated 03/03/2011.*

The PK results suggest endogenous plasma calcitriol levels in the pediatric patients aged 6 to 12 were higher than those in adolescents and adults (Table 4). At baseline, the C_{max} and AUC_{0-12} values of calcitriol decreased with increasing age (Table 4). Compared to the baseline, the mean C_{max} and AUC_{0-12} values of calcitriol after 2- or 3-week repeat treatment, increased by 32% to 44% in adult subjects with psoriasis (Table 3). Whereas, the mean C_{max} and AUC_{0-12} values of calcitriol after 2- or 3-week treatment were similar to the values observed at baseline in adolescents and pediatrics aged 6 to 12 (Table 4).

Table 4 Comparison Calcitriol Concentrations Among Adults, Adolescents, and Pediatrics Aged 6 to 12 Following Calcitriol 3 mcg/g Application Under Maximal Use Conditions

	Mean C_{max} (pg/mL)						Mean AUC_{0-12} (pg*hr/mL)				
	Baseline	Day 14	Day 14/ Baseline	Day 21	Day 21/ Baseline		Baseline	Day 14	Day 14/ Baseline	Day 21	Day 21/ Baseline
Adults[a] (n=23)	51.59	67.96	1.32	70.23	1.36		471.65	635.99	1.35	677.21	1.44
Adolescents[b] (n=25)	75.74	NA	NA	75.3	0.99		737.74	NA	NA	725.6	0.98
Pediatrics aged 6-12 (n=17)	115.9	120.7	1.04	NA	NA		1230.3	1268.9	1.03	NA	NA

NA=not available
a: a maximal use PK study (RD.03.SRE.40005). Each subject aged ≥18 had at least 25% affecting BSA and received 15 g BID calcitriol 3 mcg/g for 3 weeks.
b: a maximal use PK study (RD.06.SRE.18102). Each subject aged 12 to 17 had 10% to 25% affecting BSA and received 2 mg/cm^2 calcitriol 3 mcg/g BID (maximum of 30 g daily) for 3 weeks.
c: a maximal use PK study (RD.06.SRE.18104). Each subject had 3% to 35% affecting BSA and received calcitriol 3 mcg/g BID (maximum of 0.25 g/kg of body weight or 14 g daily) for 2 weeks.
LLOQ: 5 pg/mL for calcitriol in Studies RD.03.SRE.4005 and RD.06.SRE.18102, and 50 pg/mL for calcitriol in Study RD.06.SRE.18104.

(Source of data: Reviewer's summary based on the data from Clinical Study Report 18104 and Clinical Pharmacology Review by Dr. Tapash K. Ghosh dated 8/29/2008, and Clinical Pharmacology Review by Dr. Abimbola Adebowale dated 03/03/2011 in DARRTS

3.3 What are the effects of calcitriol 3 mcg/g ointment on calcium homeostasis in pediatric subjects aged 6 to 12 with psoriasis in Study 18104?

Effects of calcitriol treatment on calcium metabolism were evaluated in pediatric subjects with psoriasis following BID application of calcitriol 3 mcg/g ointment for 2 weeks. Serum (nonfasting) calcium, albumin phosphors, and intact parathyroid hormone (PTH), and urine calcium and creatinine were measured, and the results of PD parameters are summarized in Table 5 and Table 6.

Overall, the majority of subjects had normal serum and/or urine values at baseline that remained normal at the Day 14 assessment.

Table 5 Pharmacodynamic Parameters in Serum

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
(Source of data: Table 8, Clinical Study Report 18104)

Review's comments: *Shifts of serum phosphorous levels from normal to high were observed in 2 subjects (29%) on Day 14. Subjects (80%) who had high levels of serum phosphorous remained that way on Day 14. However, the observed serum phosphorous levels at baseline or after the treatment in this study are within the reported normal range of 1.2 to 1.74 mmol/L[1].*

Table 6 Pharmacodynamic Parameters in Urine

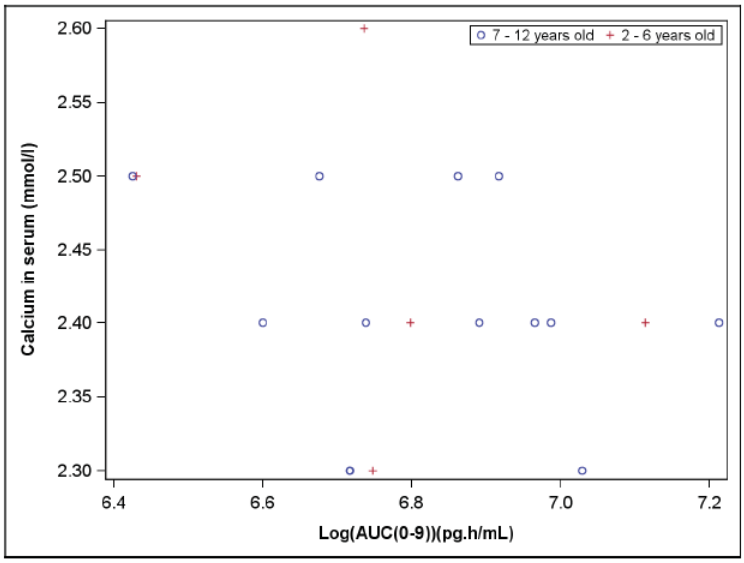
Parameter (Mean±SD)	2-6 years n=5			7-12 years n=13			Total n=18		
	Screening	Baseline (mg/24 hr)	Day 14/ET (mg/24 hr)	Screening	Baseline (mg/24 hr)	Day 14/ET (mg/24 hr)	Screening	Baseline	Day 14/ET
Calcium (mmol/L)[a]	16.2 ± 17.5	55.0 ± 62.1	46.8 ± 31.7	8.3 ± 8.1	56.1 ± 43.7	91.2 ± 54.8	10.6 ± 11.7	55.9 ± 45.4	80.7 ± 53.1
Creatinine (g/L)[b]	89.6 ± 28.6	370.3 ± 330.8	464.2 ± 311.0	102.8 ± 57.0	915.3 ± 373.6	922.3 ± 314.3	98.9 ± 49.8	798.5 ± 421.9	814.5 ± 363.8
Calcium/creatinine ratio	0.176 ± 0.144	0.127 ± 0.038	0.103 ± 0.039	0.091 ± 0.099	0.060 ± 0.036	0.098 ± 0.046	0.116 ± 0.116	0.074 ± 0.045	0.099 ± 0.043

a) Urine calcium measured in mg at Screening
b) Urine creatinine measure in mg/dL at Screening
ET=early termination; SD=standard deviation
Source: Tables 14.2.2.1.6, 14.2.2.1.7, and 14.2.2.1.8
(Source of data: Table 9, Clinical Study Report 18104)

3.4 What is the relationship between PK and PD in Study 18104 (PMR # 2)?

No significant correlation between PK and PD parameters were noted among the 17 subjects who completed the study. There were no correlations between AUC and PD variables evaluated. The lack of correlation between AUC_{0-9} and serum calcium is presented in Figure 2, as an example.

Figure 2 Relationship between AUC_{0-9} and Serum Calcium



Source: Section 14.4, Figure 14.4.1

(Source of data: Figure 2, Clinical Study Report 18104)

Reference:

1: Burritt MF, et al. Pediatric reference intervals for 19 biologic variables in healthy children, Mayo Clinical proceedings, 1990, 65(3), page 329-336

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