A Phase 1 Open-Label Multicenter Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of Calcipotriene Foam, 0.005%, Applied Under Maximal-Use Conditions in Adolescent Subjects with Plaque Psoriasis

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SYNOPSIS

Psoriasis is a chronic immune-mediated inflammatory skin disorder with significant physical and psychosocial ramifications which begins in childhood in almost one-third of cases.[2,3] The etiology of plaque psoriasis in children and adults is thought to be the same, as evidenced by similar response rates to therapies.[2] However, pediatric treatment guidelines are limited and most therapies are not approved in this patient population.[4] Additionally, the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs and certain factors that are unique to children such as metabolism, physical development and cutaneous absorption make safe and effective treatment of psoriasis in this patient population a challenge.[5]

Phase III clinical trials established the efficacy and safety of calcipotriene foam, 0.005%, in adults. While subjects under the age of 18 were included in these trials, there were not sufficient numbers to fully evaluate the safety and efficacy in this age group. For this reason, two subsequent studies were initiated in patients 4 to 11 years and 12 to 16 years. The data presented here highlight the results of the Phase I clinical study in the adolescent group.

OBJECTIVE

To evaluate the safety and tolerability of calcipotriene foam, 0.005%, in subjects 12 to 16 years of age with plaque psoriasis via analysis of calcium metabolism and to evaluate whether these changes were related to the average dose administered, age, body surface area (BSA), BSA treated, and/or %BSA treated.

Primary endpoints:

- The relative change from Day 1 to Day 15 (Day 15/Day 1 ratio) of albumin adjusted serum calcium, intact parathyroid hormone (iPTH), alkaline phosphatase, magnesium, and phosphorus
- Change in Urine calcium/creatinine from Day 1 to Day 15

Secondary endpoints:

- Safety: Adverse events, clinical laboratory test results, vital signs, concomitant medications
- Tolerability: Investigator assessment of erythema, subject assessment of pain
- Pharmacokinetics: Plasma concentrations of calcipotriene

METHODS

- Phase 1 multicenter, open-label, repeat-dose safety, tolerability, and PKPD study in adolescent subjects with moderate plaque psoriasis (defined as a score of 3 on the Investigator's Static Global Assessment [ISGA]) involving a minimum of 10% body surface area (BSA) excluding face and scalp, and a minimum of 20% scalp involvement
- Subjects were instructed to apply calcipotriene foam as a thin layer twice a day for 14 days and once on Day 15 on all treatment areas (excluding the face).
- Average daily dose was 5.04g
- Blood samples for albumin adjusted calcium, intact parathyroid hormone (iPTH), alkaline phosphatase, magnesium, and phosphorus were scheduled to be collected at Screening, on Day 1 (before the first dose), on Day 15 (3 to 9 hours after dosing), and on Day 22 if the results from Day 15 showed any abnormalities
- Serum 25-OH vitamin D concentrations were evaluated on Day 1 (before the first dose)
- Safety and tolerability were evaluated throughout the treatment period and a 7-day follow-up period
- Urine samples for evaluation of calcium/creatinine ratio were collected before dosing on Days 1 and 15

DEMOGRAPHICS	n (%)	DEMOGRAPHICS	n (%)
Age (years)		Weight (kg)	
Mean	14.4	Mean	74.1
12-13	5 (26%)	Minimum	47.0
14-16	14 (74%)	Maximum	129.3
Race		Baseline ISGA	
Caucasian	12 (63%)	Mean Body	3.0
African American	4 (21%)	Mean Scalp	2.8
Asian	2 (11%)		
Other	1 (5%)		
Gender		Total BSA (%)	
Male	9 (47%)	Mean	1.3
Female	10 (53%)	Minimum	1
		Maximum	1.8
Ethnicity		Time since diagnosis (yrs)	
Hispanic/Latino	6 (32%)	Mean	4.3
Not Hispanic/Latino	13 (68%)		

RESULTS

There were no quantifiable changes in serum labs. While urine Ca/Cr and serum iPTH were highly variable there were no significant trends apparent. No relationships between covariates and markers of calcium metabolism were seen. No relationship was seen between PD markers for calcium metabolism and the covariates average dose, age, BSA, BSA treated and/or %BSA treated. There were 5 adverse events considered related to treatment and no serious adverse events, deaths or adverse events leading to permanent discontinuation of study drug or withdrawal from study. Compliance with treatment regimen was high in study subjects at approximately 92%.

PD Marker at Screening, Day 1, Day 15 and Day 22

PD Marker	Visit (n)	Mean	Min	Max
Corrected Calcium (mmol/l)	Screening (19)	2.31	2.2	2.42
	Day 1 (19)	2.30	2.16	2.42
	Day 15 (19)	2.29	2.18	2.4
	Day 22 (7)*	2.30	2.14	2.42
iPTH (pmol/l)	Screening (19)	3.93	1.1	8.3
	Day 1 (19)	4.14	1.6	8.8
	Day 15 (19)	3.74	1.2	7.9
	Day 22 (7)*	3.73	2.1	6.3
Alkaline Phosphatase (µ/l)	Screening (19)	172.8	66	553
	Day 1 (19)	172.6	79	600
	Day 15 (19)	173.0	62	621
	Day 22 (7)*	146.9	63	282
Magnesium (mmol/l)	Screening (19)	0.83	0.76	0.9
	Day 1 (19)	0.83	0.76	0.96
	Day 15 (19)	0.81	0.7	0.9
	Day 22 (7)*	0.84	0.8	0.9
Phosphorus (mmol/l)	Screening (19)	1.38	1.1	1.95
	Day 1 (19)	1.38	0.85	1.85
	Day 15 (19)	1.31	0.7	2.05
	Day 22 (7)*	1.25	0.85	1.55

***Serum labs were repeated at Day 22 if the results from Day 15 showed any abnormality**

Relative Change from Day 1 to Day 15 and Day 22 for PD Markers

PD Marker	Visit Ratios	n	Geometric Mean	95% CI	90% CI
Corrected Calcium (mmol/l)	Day 15/Day 1 Ratio	19	0.9970	0.9861 - 1.0079	0.9880 - 1.0060
	Day 22/Day 1 Ratio	7	0.9849	0.9533 - 1.0176	0.9597 - 1.0108
	Day 15/Day 22 Ratio	7	1.0091	0.9776 - 1.0417	0.9840 - 1.0349
iPTH (pmol/l)	Day 15/Day 1 Ratio	17	0.8546	0.6375 - 1.1455	0.6714 - 1.0878
	Day 22/Day 1 Ratio	7	1.0491	0.6436 - 1.7101	0.7117 - 1.5465
	Day 15/Day 22 Ratio	6	0.8257	0.4017 - 1.6969	0.4694 - 1.4523
Alkaline Phosphatase (u/l)	Day 15/Day 1 Ratio	19	0.9793	0.9282 - 1.0332	0.9369 - 1.0235
	Day 22/Day 1 Ratio	7	0.9585	0.8480 - 1.0835	0.8696 - 1.0565
	Day 15/Day 22 Ratio	7	1.0038	0.9361 - 1.0763	0.9497 - 1.0609
Magnesium (mmol/l)	Day 15/Day 1 Ratio	19	0.9770	0.9383 - 1.0173	0.9450 - 1.0101
	Day 22/Day 1 Ratio	7	1.0085	0.9684 - 1.0502	0.9765 - 1.0415
	Day 15/Day 22 Ratio	7	1.0000	0.9554 - 1.0467	0.9644 - 1.0369
Phosphorus (mmol/l)	Day 15/Day 1 Ratio	19	0.9372	0.8389 - 1.0469	0.8553 - 1.0269
	Day 22/Day 1 Ratio	7	0.9440	0.8680 - 1.0266	0.8831 – 1.0090
	Day 15/Day 22 Ratio	7	0.9812	0.7350 - 1.3099	0.7800 - 1.2343

Relative Change from Day 1 to Day 15 for Urine Calcium/Creatinine Ratio

PD Marker	Visit Ratio (n)	Geometric Mean
Calcium : Creatinine (mmol/mol cr)	Day 15 : Day 1	1.2731

Relative Change from Day 1 to Day 15 and Day 22 for PD Markers

AE Type	n (%)	# of Events
OVERALL	3 (16%)	5
General disorders and administration site conditions	2 (11%)	4
Application site pain	1 (5.3%)	2
Application site pruritus	2 (11%)	2
Skin and subcutaneous tissue disorders	1 (5.3%)	1
Pruritus	1 (5.3%)	1

***No serious AEs or deaths**

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CONCLUSIONS

Topical application of calciptrione foam, 0.005%, on up to 56% BSA with a median of 22% BSA (including 100% scalp) in adolescent subjects with plaque psoriasis, showed no adverse effect on calcium metabolism. The lack of effect on PD markers of calcium metabolism is consistent with non-quantifiable concentrations in all subjects and confirms that there is no clinically relevant systemic exposure under maximal use conditions. The data presented here demonstrates that this therapy is safe, without evidence of systemic exposure or systemic effects on calcium metabolism, when utilized in adolescent patients with moderate plaque psoriasis. The low incidence of adverse events, lack of discontinuation, and high compliance rates demonstrate that calcipotriene foam, 0.005%, was also well tolerated in this adolescent group. This may lead to additional options in this patient population, which currently has limited treatment alternatives.

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