Clinical Study Protocol

A Multi-Center, Phase 1 Dose-Escalation Study, to Evaluate the Safety, Tolerability and Pharmacokinetics of a Topical Compound 31543 (Calcitriol, USP) in Adult Cancer Patients Receiving Taxane-based Chemotherapy Regimens for the Treatment of Advanced or Recurrent Disease

Protocol Number:	CTL0211
Amendment Number:	9
Study Drug:	Compound 31543
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1 PROTOCOL SUMMARY AND/OR SCHEMA

1.1 Berg Protocol CTL0211

Study Title: A multi-center, Phase 1, dose-escalation study to evaluate the safety, tolerability and pharmacokinetics of a topical compound31543 (Calcitriol, USP) in adult cancer patients receiving taxane-based chemotherapy regimens for the treatment of advanced or recurrent disease.

This will be a dose escalation study to determine the maximum tolerated dose (MTD) and the overall safety and tolerability of a topical compound 31543 (Calcitriol) in patients with a diagnosis of early stage or locally advanced, unresectable and/or metastatic cancer, or patients with operable cancer, who are scheduled to receive follow up treatment with a taxane-based chemotherapy regimen (either pre-operatively or post-operatively), as per physician's discretion.A standard 3+3 dose escalation design will be employed with 3-6 patients at each dose level. Eligible patients ≥18 years of age and scheduled to receive a taxane-based regimen with treatment breaks as per physician's discretion, will start applying the topical solution twice a day at each cohort dose level two weeks or 7 days ± 2 days prior to initiation of chemotherapy and then continue twice daily for 3 months or until termination of chemotherapy treatment. If topical calcitriol is found to be effective in preventing and/or diminishing taxane chemotherapy-induced alopecia as determined by the photographic assessments and patient self-assessments, patients will be allowed to continue topical application for the duration of their chemotherapy treatment, assuming no dose limiting toxicities (DLTs) related to the topical agent or intolerable side effects are observed. Toxicity to the topical compound 31543 (calcitriol) will be assessed on a weekly basis during the first 28 days of topical treatment and subsequently every four weeks by a study clinician, either a physician or a nurse. For the purpose of pharmacokinetic studies (PKs), blood samples will be collected on Day 1 of topical treatment at the following time points: pre-dose, at 2 hrs (±30 minutes), 4 hrs (±30 minutes), and 8 hrs (±1 hr post dose) after a single application on the morning of Day 1. The second application of drug product will be applied 10-14 hrs after the initial application and after the 8 hr PK sample. Thereafter, topical application frequency will be twice daily, morning and night. Subsequently, a PK sample will be taken 12 hrs (±2 hrs) after the last dose of each 28-day treatment, before the first application of Day 1 of the next 28-day treatment cycle. This schedule will continue for three consecutive 28-day topical treatment cycles. (PKs will be drawn at Weeks 1, 5, 9, and 13. In addition, if patients are still on study, a PK will also be drawn at Week 54.)

As a secondary objective, potential efficacy of the topical calcitriol will be evaluated by photographic assessment. Photographic assessment will be performed using a Canon digital camera system to ensure standardization and uniformity among all enrolled patients. The following five views will be obtained at each photographic assessment: bilateral sides of head/scalp view, front of head/face view, back of head/scalp view, and top of head/scalp view**.**Additionally, close-up photographs will be taken at the same time points. They will include the mid-pattern of the scalp from a superior view and a vertex view with hair parted in the center and combed away from the center part. Photographs will be standardized for lighting, camera angle, and position to the participant's head.These assessments will be performed at the following time points: at baseline, Weeks 7, 15, 27, and 54. Photographs for patients in each cohort representing baseline, and treatment Weeks 7 and 15 will be presented blind to the study PI and dermatologist, Mario Lacouture, after at least 3 patients have completed 15 weeks of treatment. Photographs will also be taken at Week 27 and Week 54 of the study but will be

included in the final photographic assessment as secondary information. In addition, all patients will be asked to maintain an application log throughout treatment to ensure compliance.

Additionally patients will maintain a medication application diary and a self-assessment diary. The medication application diary will collect daily application details of the medication. This will include application dates and times, chemotherapy cycle, and whether the medication was applied (or reason if the medication was not applied). The self-assessment diary will require assessment of hair thickness, hair fullness, hair breakage, and hair cosmetic qualities (ease of styling, etc.) on an analog 10 point scale to assess patient-reported efficacy. The PI clinical assessment of baseline, Weeks 7 and 15 photographs will be used, together with the patient diary information, for the primary assessment of alopecia. The study is expected to take place over a period of approximately 12 months, including the screening period.

2 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective

- To determine the maximum tolerated dose (MTD) and the overall safety and tolerabilityof topical Compound 31543(Calcitriol, USP)in adult cancer patients receiving taxane-based chemotherapy regimens.

2.2 Secondary Objectives

- To determine the single and multiple dose pharmacokinetics of Compound 31543 at different dose levels.
- To evaluate preliminary efficacy of Compound 31543 Topical Solution for preventing chemotherapy-induced alopecia.

3 BACKGROUND AND RATIONALE

3.1 Chemotherapy-Induced Alopecia

Chemotherapy-Induced Alopecia or CIA is a non-cicatricial alopecia and represents one of the most common and distressing dermatological adverse events associated with the use of many different chemotherapeutic agents. Taxanes (paclitaxel/ docetaxel), doxorubicin, cyclophosphamide, and 5-fluorouracil can cause alopecia in >80%, 60%-100%, >60%, and 10%-50% of patients, respectively.[1] Among women undergoing therapy with paclitaxel monotherapy, alopecia can be observed in up to 82% of patients.[2,3] CIA is believed to occur when hair follicles are in anagen phase and results in anagen effluvium due to toxicity of chemotherapy and its metabolites on the hair follicle.[1] CIA typically begins at 1-3 weeks and is complete at 1-2 months after the initiation of chemotherapy. This type of hair loss is usually reversible after the completion of therapy, with regrowth that occurs after a delay of 3-6 months. Nevertheless, the new hair often demonstrates changes in its color, structure, and texture with growth rate that may be significantly reduced.[1] This particular toxicity has significant psychosocial and quality-of-life consequences. It negatively affects patients' perception of physical appearance, body image, sexuality, and self-esteem.[5-7] More importantly, among women, 58% consider it the most disturbing reaction and 8% are at risk of avoiding therapy due to this toxicity.[8] Despite such profound effects on patients, to date no effective preventative or treatment options are available. One approach, scalp-cooling, has been investigated since 1970s and has shown to diminish CIA. However, there is a lack of adequate clinical data with only 7 out of 53 conducted trials that were randomized, and further clinical and biochemical research is needed.[9] Scalp cooling has been used to treat CIA.[10] Topical minoxidil 2% topical solution has also been investigated in prevention of CIA and has been shown to diminish its duration but failed to prevent it.[11] While multiple other experimental approaches are being investigated, no pharmacologic agent has been approved for prevention or treatment of CIA.[1]

3.2 Calcitriol, 1,25-dihydroxyvitamin D3

Vitamin D plays a critical role in calcium and phosphate homeostasis through its actions in the intestine, kidney, and parathyroid glands. These actions are mediated by the activated, hormonal form, 1,25-dihydroxyvitamin D3 (calcitriol).[12] Calcitriol is made by hydroxylation of calcidiol and represents the active form of Vitamin D and is the most potent steroid hormone derived from cholecalciferol. In addition to these critical functions, calcitriol also plays a role at other sites, including control of cell proliferation, differentiation, the synthesis and secretion of cytokines and other hormones. Calcipotriol is a Vitamin D analogue that has a similar activity in regard to Vitamin D receptor binding when compared with the active form of Vitamin D3, calcitriol. It inhibits epidermal proliferation, modulates keratinization and inflammation but is much less potent in regulating calcium metabolism. Because of these properties, numerous investigations have been conducted with Vitamin D and its analogs in their potential therapeutic application in cancer, immune modulation, and regulation of endocrine system.[14] Interest in Vitamin D3 derivatives for prevention of CIA has emerged based on the novel work by Joaquin Jimenez, MD at the University of Miami. A serendipitous experiment showed a topical solution of calcitriol to reduce alopecia that was attributed to its ability to arrest the cell cycle and reduce the sensitivity of the epithelium to chemotherapy. Unlike androgenetic alopecia, CIA occurs due to massive anagen effluvium attributed to toxicity of chemotherapy and their metabolites on the hair follicle cells. The rapid cell proliferation in hair follicles during anagen renders hair follicles susceptible

to the toxicity of chemotherapy. Therefore, one approach to prevent CIA is to inhibit cell proliferation in order to diminish the sensitivity of hair follicles to chemotherapy.

3.3 Pre-clinical Studies

3.3.1 Animal Studies

Both CIA and alopecia areata (AA) have been extensively studied due to the availability of animal models which closely mimic the diseases in the human. In this regard, it was previously demonstrated that alopecic chemotherapies (cytarabine, cyclophosphamide, doxorubicin, doxorubicin/cyclophosphamide, etoposide) induce alopecia in the neonatal rat model (Sprague Dawley rats). In this model, rats of 8 to 11 days of age are injected intraperitoneally with chemotherapy. Alopecia ensues 5-7 days later, and is graded depending on the hair loss observed. The protective compounds are given on Day 5 after birth for 6 days. This model is useful to study CIA because the hair follicles at this stage are in 100% anagen, which renders them susceptible to chemotherapy toxicity and is comparable to the human setting.[17-19] This is a very effective and a reproducible model and can be used to study protective formulations against CIA. Some of the drawbacks of this model is that the hair follicles are in the first hair growth cycle after birth and that the rats have white fur and lack pigmentation.[1] In contrast, the use of neonatal Long Evans rats allows studying pigmented hairs. Another model that is widely used to study the effect of chemotherapy is an adult C57BL/6 mouse model. The hair follicles in this model have gone through several postnatal growth cycles and the hair shafts are pigmented, similar to the human scalp.[1] The anagen cycle in this particular model is induced by depilation and is observed 8 to 9 days after the procedure. Using this model and cyclophosphamide, it has been demonstrated that as a response to cytotoxicity of chemotherapy, the hair follicle utilizes two pathways: dystrophic anagen or dystrophic catagen, which determines the onset of chemotherapy-induced alopecia and the pattern of hair re-growth.[1] A new model that has been used to investigate CIA is an adult Long Evans rat model, which allows studying hair follicles that have gone through several cycles and rats possess both pigmented and non-pigmented hairs. Additionally, the induction of anagen phase is performed by shaving fur with clippers, the method that may avoid the trauma to the hair follicles that is induced by depilation. Another excellent model to study alopecia, more specifically, AA, has been the C3H/HeJ mouse model.[20] In this model, 20% of the animals spontaneously develop alopecia in clusters or throughout the entire body (alopecia universalis) by 18 months of age. Alopecia patterns and histopathological analysis has shown that the pathology in this animal is almost identical to that of the human.

1,25-Dihydroxyvitamin D3 protects by modulating the differentiation of hair follicle keratinocytes, rendering them resistant to the toxic metabolites of chemotherapy. During the course of screening therapeutic compounds to treatAA, 1,25-Dihydroxyvitamin D3 was tested. The following study was conducted to characterize the effect of 1,25-Dihydroxyvitamin D3 indifferent types of alopecia, namely, CIA, Post-Chemotherapy Alopecia (PCA) andAA. The overall goal of this project was to determine if 1,25-Dihydroxyvitamin D3could be used to treat alopecia in general.

The results of pre-clinical studies strongly suggest that 1,25(OH)2D3 exerts a protectiveeffect against chemotherapy-induced alopecia, but it does not treat alopecia itself. The rationale behind the preventive effect of 1,25(OH)2D3 in CIA is that healthy hair follicles can be arrested and thereby rendered resistant to the chemotherapy. However, in hair follicles that are already apoptotic, treatment with 1,25(OH)2D3 does not offer any benefit.

Findings in another animal study demonstrated a potential mechanism by which application of topical calcitriol may diminish the incidence of CIA. Topical treatment with calcitriol was demonstrated to significantly diminish the degree of follicular apoptosis induced by cyclophosphamide in C57BL/6 mice.[21] Another experiment conducted with BALB/c mice, the animal model which allows investigating the hair follicles in the first adult anagen phase and evaluate gender differences, demonstrated that topical application of calcitriol for 5 days prior to intraperitoneal administration of cyclophosphamide significantly reduced the degree of CIA in a dose-dependent manner in male mice.[22] The protective effect of topical calcitriol was diminished in tumor-bearing male mice that were injected with EMT-6 murine breast tumor cells.[22] In contrast, pre-treatment with topical calcitriol in tumor-bearing female mice injected with EMT-6 murine breast tumor cells had a more efficient protective effect against cyclophosphamide induced alopecia as compared to female mice without tumor and their tumor-bearing male counterparts.[22] Histopathologic examination of post-mortem skin demonstrated marked reduction in morphological alterations induced by cyclophosphamide in hair follicles and a protective effect from cyclophosphamide-induced follicular damage.[22] However, in this model, no significant differences in apoptosis staining pattern were noted between mice treated with topical calcitriol and those without exposure to the solution.

On the other hand, another animal study using the female C57BL/6 adolescent mice instead of a neonatal rat model, failed to demonstrate efficacy of topical calcitriol in prevention of cyclophosphamide-induced alopecia. Interestingly, however, the regrowth of pigmented hair shafts was significantly accelerated, enhanced, and quantitatively improved. Histopathologic investigations suggested that this may have been due to hair follicles favoring the “dystrophic catagen pathway” of response to chemical injury: follicular repair strategy allowing for the unusually fast reconstruction of a new, undamaged anagen hair bulb.[23]

Multiple in vivo animal investigations failed to demonstrate the potential protective effect of calcitriol from cytotoxicity of chemotherapy on cancer cells. No statistically significant difference in the survival rate was seen between Sprague Dawley rats transplanted with chloroleukemia C51 cells pretreated with 0.2μg of 1,25(OH)2D3 and those pretreated with an ethanol vehicle prior to cyclophosphamide treatment.[16] More importantly, pretreatment with topical calcitriol of EMT-6 murine breast tumor-bearing male mice prior to intraperitoneal administration of cyclophosphamide resulted in the greater reduction in the rate of tumor growth as compared to mice treated with either agent alone, suggesting potential anti-tumor effects of calcitriol. Similarly, pretreatment with 2.5 μg of calcitriol 3 doses daily for 3 days, followed by administration of varying doses of paclitaxel of squamous cell carcinoma and human prostate cell carcinoma bearing mice resulted in significant tumor regression.[15]

3.3.2 Summary of Pre-clinical Skin Penetration Studies

Prototype formulations of Berg Compound 31543 (calcitriol) Topical Solution containing either 1 µg/mLor 3 µg/mL of active calcitriol and excipient control were tested and evaluated utilizing human cadaver skin in Franz cell percutaneous measurement chambers. Data from 3 donors with 3 replicates/donor/formulation (1 replicate/blank) at a 48-hr dose exposure period were conducted (Figure 1).The purpose of this study was to determine the penetrability of both formulations in a human skin model.

Figure 1. Total Absorption and Mass Balance Results across Skin Donors

Distribution of Calcitriol from Intact Human Cadaver Skin over 48 hrs from a Single Application. (Mean ± SE as Total Mass [ng/cm]).

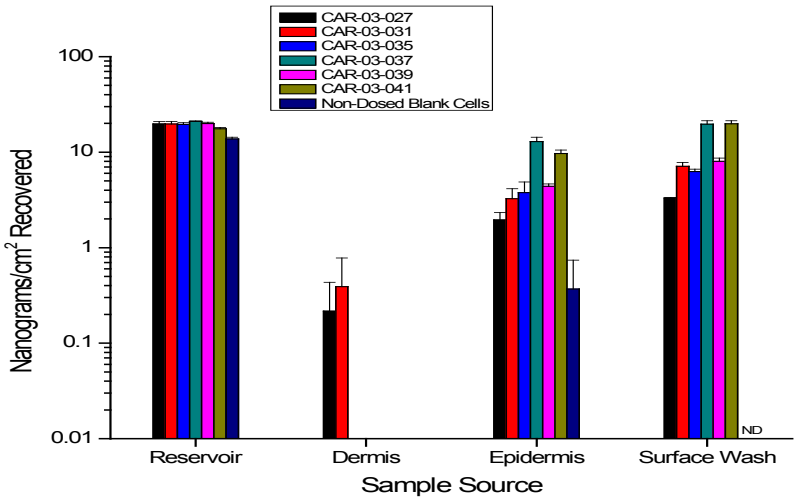

Table 1: Average Results across Donors for Calcitriol Content in Epidermis, Dermis, and Total Absorption

Percutaneous Absorption of Calcitriol using Human Cadaver Skin over 48 hrsfrom a Single Application. (Mean ± SE as Total Mass [ng]).

Test Article	Epidermis (ng/cm^2)	Dermis (ng/cm^2)	Total Absorption (ng/cm^2)
Calcitriol 1µg/mL Lot CAR-03-027	1.95 ± 0.37	0.22 ± 0.22	19.71 ± 1.24
Rogn 1 µg/mL Lot CAR-03-031	3.26 ± 0.89	0.39 ± 0.39	19.69 ± 1.33
Trans 1 µg/mL Lot CAR-03-035	3.78 ± 1.09	0.00 ± 0.00*	19.49 ± 0.86
Trans 3 µg/mL Lot CAR-03-037	12.88 ± 1.48	0.00 ± 0.00	21.02 ± 0.20
Phospho 1 µg/mL Lot CAR-03-039	4.38 ± 0.27	0.00 ± 0.00	19.92 ± 0.63
Phospho 3 µg/mL Lot CAR-03-041	9.66 ± 0.84	0.00 ± 0.00	17.60 ± 0.50
Non-Dosed Blank Cells	0.37 ± 0.37	0.00 ± 0.00	13.75 ± 0.59**

* Zero values indicate results below the lower limit of detection.
** Presumed to be endogenous calcitriol being released from the skin.

The data suggests that the amount measured in the reservoir solution is slightly greater than the amount of endogenous calcitriol that may be present (which is being released from the skin into the reservoir solution) and does not differentiate the topical formulations. However, no endogenous calcitriol was measured in non-dosed chambers for the epidermis, dermis and surface wash samples, indicating that the amount that is measured in those compartments from the dosed skin sections is from the applied dose. This is further supported by the two formulations that contain 3 µg/mL calcitriol versus those with 1 µg/mL concentration. The formulations showed a range of approximately 10-20% of drug penetration into the epidermis, based on the applied dose, but little to no penetration into the dermis (1% or less of applied dose).

Prototype formulation CAR-03-031 containing API # 31543 (calcitriol) in a vehicle of propylene glycol and dehydrated alcohol, 200 proof in a 40/60 ratio (W/W), has been identified as the prototype formulation for further development.

3.4 Clinical Studies

One Phase 1 trial of topical topitriol (calcitriol) has been conducted. In this study, patients with stage II-IV breast cancer were scheduled to receive cyclophosphamide $500mg/m^2$, doxorubicin $50mg/m^2$, and 5-fluorouracil $500mg/m^2$ on Day 1 every 21 days. Topical calcitriol was applied to the scalp twice a day. The drug was applied by a nurse during the first 5 days of treatment and by the patient or a family member thereafter. The cream was rubbed around the entire scalp and was maintained without washing for 8 hrs. Three different doses were evaluated: 500 µg per day for 7

days prior to chemotherapy, 1000µg per day for 7 days prior to chemotherapy, and 2000µg per Day 5 days prior and post-chemotherapy. Treatment was continued until the appearance of grade 2 alopecia, as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events NCI-CTCE. Patients' serum and urine calcium excretion were monitored. Overall, there were 14 patients evaluated in this trial. All of the patients developed grade 2 alopecia 20-30 days after the first course of chemotherapy. Plasma and urinary calcium levels remained within normal limits during the study period. All patients treated with the first dose level, 4 out of 6 treated with 1000µg per day, and 2 out of 4 patients treated with 2000µg per day developed mild pruritic maculopapular dermatitis on the scalp and surrounding skin exposed to topical topitriol.[24]

One of the drawbacks of this pilot Phase 1 trial may be the inadequate dosing schedule, because topical application of the cream was only performed 1 week prior to chemotherapy administration. It is possible that the treatment duration was not sufficient to induce catagen stage in scalp hair follicles that subsequently made them more susceptible to cytotoxicity of chemotherapy. To compensate for this potential deficiency, in our trial topical calcitriol will be applied starting 2 weeks prior to the initiation of chemotherapy in an attempt to induce catagen stage that is anticipated to render protection against CIA. Patients unable or unwilling to wait the 2 week pre-treatment period may elect to pre-treat for 7 days ± 2 days. Continued application on the daily basis will ensure the maintenance of catagen stage and extended protection throughout administration of multiple doses of a taxane-containing regimen.

Additionally, the previously conducted Phase 1 trial used a water-based formula that was originally intended for use in psoriasis. The drug delivery mechanisms are likely to vary significantly between the scalp epidermis and hyperproliferative psoriasis plaques, which may explain higher penetration and increased incidence of maculopapular dermatitis. Secondly, higher doses utilized in the previous Phase 1 trial may have been also responsible for the high incidence of contact dermatitis in the majority of treated patients. The formulation of topical compound31543 (calcitriol) that will be employed in this proposed trial is an anhydrous alcohol and glycol based formulation with penetration characteristics that favors epidermal exposure of the active ingredient.

Another trial investigated the potential of a topical Vitamin D analogue, calcipotriol, in preventing chemotherapy-induced alopecia. Patients with breast cancer undergoing therapy with cyclophosphamide 600mg/m^2, methotrexate 40mg/m^2, and 5-fluorouracil 600mg/m^2 given on Days 1 and 8 in a 4-weekly cycle were randomized to receive either topical calcipotriol scalp solution 50 µg/mL or a vehicle. The solution was applied twice daily from 4 days prior to chemotherapy and continued for 14 days in each treatment cycle. However, there was no detectable effect of topical calcipotriol on the proportion of patients that experienced hair loss, hair shedding rates, and hair regrowth of hair density.[25]

The lack of interference of calcitriol with the efficacy of chemotherapy and the ability to potentiate its cytotoxic effects, previously demonstrated in in vitro and in vivo animal models, has also been demonstrated by several clinical trials. This was demonstrated by a Phase 2 randomized controlled trial of patients with advanced androgen-independent prostate cancer who received weekly docetaxel with DN-101(high-dose calcitriol, 45 µg) versus placebo. The primary objective of this study was to evaluate the proportion of patients achieving PSA response (≥ 50% PSA reduction, confirmed at least 4weeks later) in the two treatment arms. DN-101 (45µg) or placebo was administered orally on Day 1 followed by docetaxel 36mg/m^{2}intravenously on Day2

along with dexamethasone (4mgorally 12 hrs before, 1 hr before, and 12 hrs after docetaxel administration).This regimen was administered weekly for 3 consecutive weeks of a 4-week cycle. For each patient, the first dose of docetaxel (Week 1, Cycle 1 only) was attenuated (27 mg/m^2) to collect additional safety data for the combination of DN-101 with docetaxel. Two hundred-fifty patients were randomly assigned (125 patients in each arm). PSA decline (≥50%confirmed 4weeks later) within 6 months of enrollment was reached in 49% of placebo treated patients and 58%of DN-101-treated patients (P=0.16). At anytime while on study, this end point was achieved in 52% of placebo treated patients and 63% of DN-101-treated patients (P=0.07). Measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0)was present in 59 of placebo-treated patients (47%) and 48 of DN-101 treated patients (38%). Tumor response was seen in 14 (24%) and 14 (29%) of placebo and DN-101-treated patients, respectively (P=0.51). Overall survival showed a promising improvement in the DN-101 group over the placebogroup withaHRof 0.67 (95%CI, 0.45 to 0.97;P=0.04).The addition of calcitriol was associated with a reduction in the risk of death by approximately one third.[26] Overall, no increase in toxicity was seen with the addition of DN-101 to docetaxel. Toxicities that might be expected with administration of supraphysiologic doses of calcitriol were uncommon with weekly administration ofDN-101 except for mild hypercalcemia. Six percent of placebo-treated patients and 7% of DN-101-treated patients had grade 1 to 2 creatinine elevation, 8% of placebo-treated patients and 33%of DN-101-treated patients had transient hypercalcemia. All the hypercalcemia episodes observed in theDN-101 arm were grade 1 and required no intervention, and did not result in dose reduction or delay in therapy. No patients on placebo and one patient on DN-101 experienced symptomatic renal calculi. Interestingly, the incidence of any grade 3 or 4 adverse events was 70% in placebo treated patients and 58% in DN-101 treated patients (P=0.065). Adverse effects leading to discontinuation of therapy were seen in 28% of placebo-treated patients and 22% of DN-101-treatedpatients. Serious adverse events, generally those requiring hospitalization, were observed in 41% of placebo-treated patients and 27% of DN-101-treated patients (P=0.023).[26] The incidence of docetaxel-induced alopecia was comparable between the two arms. The incidence of all-grade alopecia was 41% and 45% in the docetaxel plus placebo arm and DN-101 plus docetaxel arm, respectively.[26]

In contrast, the follow-up randomized Phase 3 trial of high-dose calcitriol in combination with weekly docetaxel as compared with placebo in combination with docetaxel administered every three weeks, showed that treatment with calcitriol was associated with significantly shorter survival.953 men with castration resistant prostate cancer were randomized to 45 µg DN-101, 36 mg/m^2docetaxel, and 24 mg dexamethasoneweekly (ASCENT arm, 477 patients) for 3 out of every 4 weeks or control arm (476 patients, 5 mg prednisone twice a day, and 75 mg/m^2docetaxel and 24 mg dexamethasone every 3 weeks). The primary endpoint was overall survival. At an interim analysis, more deaths were observed in the ASCENT arm, and the trial was halted early. Median overall survival was 16.8 months (95% CI, 15.8-19.3) for ASCENT subjects and 19.9 months (95% CI, 18.6-22.7) for controls. In multivariate analysis adjusting for baseline variables, ASCENT was associated with shorter survival (HR=1.33; p=0.019). The proportions of patients with adverse events (AEs) were similar, and consistent with the known side effects of docetaxel. Dose modification for docetaxel toxicity was more frequent in the ASCENT arm (229 ASCENT vs. 160 control subjects).The shorter survival in the ASCENT arm was potentially attributed to inferior efficacy of weekly docetaxel administration as compared to docetaxel administered every three weeks.[27]

14 patients have been enrolled in this current study, CTL0211 (2 patients were enrolled but did not receive study drug, therefore 12 patients have been treated with study drug.) No DLT have been observed. Amendment 8 will add additional patients to be enrolled at increasing dose levels to determine the MTD.

4 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a multi-center, single arm, dose-escalation Phase 1 study. Eligible patients will begin applying the topical formulation of Compound 31543 to the scalp twice daily 2 weeks prior to the first dose of chemotherapy and continue the application twice daily until termination of chemotherapy treatment. Patients unable or unwilling to wait the 2 week pre-treatment period may elect to pre-treat for 7 days ± 2 days. Dose escalation will occur in stepwise increments of the immediate prior dose group, in the absence of grade 3 or greater toxicities attributed to the topical calcitriol, in order to determine the MTD for this agent. Dose-limiting toxicity (DLT) will need to possibly, probably or definitely (defined in Section 8.4) be related to topical calcitriol and not taxane-based regimen as best determined by participating investigators. Similarly, appropriate dose modifications or treatment interruption of the chemotherapeutic regimen will be instituted according to the current standard of care. Determination of DLTs of the topical calcitriol formulation will be made during the first 28 days of topical agent application. Subjects will be managed with adequate safety monitoring and pharmacokinetic (PK) analysis in order to determine levels of exposure. PK analysis will be done before each new cohort moves forward. For the purpose of PK studies, blood samples will be collected on Day 1 of topical treatment at the following time points: pre-dose, at 2 hrs (± 30 minutes), 4 hrs (± 30 minutes), and 8 hrs (±1 hr post-dose) after a single application on the morning of Day 1. The second application of drug product will be applied 10-14 hrs after the initial application and after the 8 hr PK sample. Thereafter, topical application frequency will be twice daily, morning and night. Subsequently, a PK sample will be taken 12 hrs (±2 hrs) after the last dose of each 28-day treatment, before the first application of Day 1 of the next 28-day treatment cycle. This schedule will continue for three consecutive 28-day topical treatment cycles (PKs will be drawn at Weeks 1, 5, 9, 13. In addition, if patients are still on study, a PK will also be drawn at Week 54).

4.2 Intervention

Patients with a diagnosis of early stage or locally advanced, unresectable and/or metastatic cancer, or patients with operable cancer, who are scheduled to receive follow up treatment with a taxane-based chemotherapy regimen (either pre-operatively or post-operatively), as per physician's discretion will be screened for eligibility to participate. All eligible patients will start applying 0.25mL of Compound 31543 (Calcitriol, USP) to each of the four quadrants of the scalp(front right, front left, back right, andback left) with the metered pump spray unit twice a day 2 weeks prior to chemotherapy and subsequently continue twice-daily until termination of chemotherapy. Patients unable or unwilling to wait the 2-week pre-treatment period may elect to pre-treat for 7 days ± 2 days. If topical calcitriol is found to be effective in preventing and/or diminishing the taxane-based chemotherapy-induced alopecia, as determined by photographic assessments and patient self-report, patients will be allowed to continue twice-daily topical application for the duration of their chemotherapy treatment, assuming no DLTs related to the topical agent are observed. Patients who elect to shave their hair prior to or during chemotherapy treatment will be excluded from the trial. The topical solution will be applied to the scalp. Hair and scalp should be dry or, if application is immediately after shampooing, the hair and scalp should be damp, not wet, to the touch by first towel drying the hair and scalp before application of the topical solution. The hair and scalp will not be washed or shampooed for at least 8 hrs after each application. Patients will be advised that that they may apply no more than two consecutive doses of Compound 31543 (calcitriol USP) before washing or shampooing.

Treatment induces catagen phase of hair cycling which will last 2-3 weeks after last application. Application of the drug will ensure this catagen phase protection through multiple chemotherapeutic treatments.

5 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Investigational Product

Berg C31543 (Calcitriol, USP) Topical Solution

Chemical Name:(5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol

IUPAC Name: (1α,3β,5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol

Alternate Names: Calcitriol is also known as: 1α,25-dihydroxycholecalciferol, 1α,25-dihydroxyvitamin D3, 1(S),25-dihydroxyvitamin D3, 1,25-DHCC, 1,25-(OH)2D3

Route of Administration: Topical

Availability: C31543 (Calcitriol, USP) Topical Solution is an investigational agent supplied by Berg.

Clinical Trial Formulation: The clinical trial formulation for Berg C31543 (Calcitriol) Topical Solution contains calcitriol, USP in a vehicle of Propylene Glycol, USP and Anhydrous 200 proof, UndenaturedAlcohol, USP at a ratio of 40:60 by weight propylene glycol/alcohol. The concentration ofCalcitriol in the topical solution vehicle for human studies has been determined based on the completion of the nonclinical toxicology. The Phase 1 study will utilize C31543, withCalcitriol at concentrations of 5, 10 and 20 µg/mL (dose levels complete without DLT), 40, 60 and 80 µg/mL (additional dosing levels to be evaluated in this amendment).

Packaging: The Phase 1 clinical drug product is packaged in a 33 mL Type III amber glass bottle fitted with a black phenolic screw cap. The drug product will also include a separately packaged metered dose dispensing applicator system capable of uniformly dispensing 0.25 mL per applicator compression. The total dosage of drug product is intended to be 1.0 mL, or four repeat metered unit applications. The application of a total of 1.0mL of drug product will be twice daily, morning and night, 10-14 hours between applications.

Prior to dispensing the drug product to the subjects, the screw cap should be removed and the metered dose dispensing applicator will be inserted into the bottle and secured. The bottle and the attached applicator should be weighed at this time. The site should document this initial weight in the drug accountability records.

Patients will be supplied with 1-2 amber glass bottles of C31543 Topical Solution containing approximately 31.5 mL of drug product of topical solution sufficient to dispense 28 mL of drug product (0.25 mL x 4 applications x 2 times/day x 14 days=28 mL). The glass bottle unit will be properly labeled with use instructions, use warnings, and a place for patient ID which will be assigned by the clinical site. Patients will be provided an application log with instructions on how to apply C31543 and record the date and time of each application. Research staff will monitor compliance by requesting patients bring their used glass bottle, application log, medication application diary, and self-assessment diary at each visit. Research staff will review the bottles and application log to ensure compliance of topical treatment administration and document oversight by recording their comments, initials and date of each review. The used bottles will also be weighed upon return to the pharmacy. The return weight should be documented in the drug accountability records. The initial and final weights will be used as a tool to assess compliance. Any evidence suggesting non-compliance should be submitted to Berg immediately and confirmed with the patient.

Patients will be instructed to dispense drug product by depressing the pump three times to prime the pump and then spraying 0.25mL of drug product four separate times to each quadrant of the scalp followed by massaging the scalp to ensure even distribution of the product. This dosing regimen will be repeated twice daily, morning and night, for 14 consecutive days (or 7 days ± 2 days) prior to initiation of chemotherapy and subsequently twice on a daily basis.

Clinical drug product supplies will be stored upright at controlled room temperature (20-25 ºC) and protected from light and heat.

Storage:Described inTable 2.

Table 2: Stability Storage Conditions for Clinical Phase 1

Storage Conditions:	20 -25 ºC, protect from heat and light
Storage Position:	Upright
Strengths:	5 µg/mL*, 10 µg/mL*, 20 µg/mL*, 40 µg/mL, 60 µg/mL 80 µg/mL
Intended Dose	5 µg/mL* – 1.25 µg per actuation 10 µg /mL* – 2.5 µg per actuation 20 µg /mL* – 5 µg per actuation 40 µg /mL – 10µg per actuation 60 µg/mL – 15 µg per actuation 80 µg /mL – 20µg per actuation

*Dose level complete without DLT

Phase 1 Dosing Rationale: The NOAEL (no--observed --adverse --effect --level) in the non---clinical animal studies was 10.31 µg/mL. To compare the animal and human doses of C31543, a margin of safety (MOS) was calculated using the NOAEL dose in the 4--week minipig study and the initial dose in the Phase 1 clinical trial. In minipigs, the NOAEL, 10.31 µg/mL is equivalent to a dose of 3.33 µg/kg (10.31 µg/mL x 2.1 mL (dose volume) x 2X/day ÷ 13 kg [average weight of minipigs in Week 4]). In humans, the starting dose was 5 µg/mL x 1 mL 2X/day ÷ 60kg=0.166). Based on these doses, the MOS was 20 which was an adequate margin over the initial clinical dose (5µg/ml). The daily dose for 40 µg/ml x 1mL BID is 1.33 µg/kg, at 60 µg/ml x 1ml BID the daily dose is 2.00 µg/kg, and at 80 µg/ml x 1mL BID 2.67 µg/kg, all below the calculated NOAEL of 3.33 µg/kg.

6 CRITERIA FOR SUBJECT ELIGIBILITY

The study will be conducted in patients with a diagnosis of early stage or locally advanced, unresectable and/or metastatic cancer, or patients with operable cancer, who are scheduled to receive follow up treatment with a taxane-based chemotherapy regimen (either pre-operatively or post-operatively),, as per physician's discretion.

6.1 Subject Inclusion Criteria

1. Adult patients at least 18 years of age
2. Able to fully understand and participate in the informed consent process
3. Patients who are scheduled to receive a taxane-based regimen for a histologically confirmed solid tumor that is:
    a. Early stage and/or treatment naïve, or
    b. Relapsed or is refractory to previous therapy, or
    c. Operable and necessitates adjuvant or neo-adjuvant treatment
4. Have no evidence of alopecia or mild alopecia (NCI CTCAE Grade 1 alopecia defined as *hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage.*)Female/male-pattern baldness or age-related hair loss are allowed if not greater than Grade 1, per NCI-CTCAE v4.0. Subjects that have previously lost their hair may enroll if they currently have Grade 0 or 1 alopecia
5. ECOG Performance Score of 0 or 1 within 14 days prior to registration
6. Has baseline neutrophil counts of > 1500 cells/mm^3 within 72 hrs prior to registration
7. Has serum calcium $\leq$ ULN (for patients with an albumin lower than 3.0, a corrected calcium serum calcium = serum calcium +[0.8][3.5- serum albumin]) within 72 hrs prior to registration.

6.2 Subject Exclusion Criteria

1. Patients receiving calcium-lowering therapy or drugs that may affect calcium levels (eg, calcitonin, mithramycin, phosphate, denosumab) within 4 weeks of initiation of topical calcitriol. Patients who have been managed with bisphosphonates or calcium-lowering therapy for 3 months or greater prior to the start of the trial and have demonstrated evidence for stability of calcium metabolism would be considered eligible for participation in the trial.
2. Has a history of drug or alcohol abuse within 1 year of study enrollment as determined by the investigator.
3. Patients who elect to shave the scalp hair prior to the initiation of chemotherapy or who plan to do so during the chemotherapy treatment.
4. Any dermatological condition that in the opinion of the investigator will affect the absorption of the study medication, eg, Atopic Dermatitis, etc.
5. Has been treated **with an investigational agent** within 30 days or six half-lives of its biologic activity whichever is shorter, before the start of study drug. (Patients may not be concurrently treated with another investigational agent).

6. Patients with a history of hypercalcemia or Vitamin D toxicity, or hospitalization for treatment of angina, myocardial infarction, or congestive heart failure or psychiatric illness currently or within 30 days of study entry as determined by the investigator.
7. Has a history of significant allergy to calcitriol as determined by the investigator.
8. Has any condition that interferes with the ability of the subject to understand or comply with the requirements of the study.
9. Patients taking Vitamin D supplements during the study, unless they have been taking Vitamin D supplements for 30 days or more prior to the start of the study and that the dose of the Vitamin D supplement remain the same throughout the study.
10. Patients treated with medications that are known to affect calcium levels within 4 weeks of initiation of topical therapy (>500 IU Vitamin A, calcium supplements, fluoride, antiepileptics), With the exception of subjects on stable therapy for more than six months.
11. Patients with hypercalcemia or kidney stones
12. Patients that indicate they have significant hair breakage or hair damage and associated hair loss from hair over processing within the last 30 days due to peroxide applications, permanent hair coloring, bleaches, streaking, perms, relaxers and/or hair oxidative dyes.
13. Current alopecia Grade 2 or greater as per NCI-CTCAE v4.0, or significant hair loss or hair breakage.
14. Prior radiation to the cranium.
15. Pregnant or breastfeeding.

7 PRETREATMENT EVALUATION

The following are required within2 weeks prior the start of calcitriol:

- Complete medical history and physical exam, including concomitant medication
- CBC with differential, comprehensive chemistry panel, serum phosphorus level, and urinalysis
- Serum 1, 25 dihydroxy Vit D
- Pregnancy test
    - Pregnancy tests outlined here are for women of childbearing potential (WCBP) only. Please exclude all women that do not meet the criteria for WCBP and meet the criteria for women not of childbearing potential.

  Women of Child-Bearing Potential Defined:
    - Any female who has experienced menarche and does not meet the criteria for "Women Not of Childbearing Potential"

  Women Not of Childbearing Potential Defined:
    - Women who are permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
    - Women who are >45 years of age, not using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40pg/mL (140 pmol/L)
    - Women who are >45 years of age, using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone replacement therapy)
- Photographic record of hair and scalp prior to chemotherapy (will serve as the baseline assessment for the study)
- Patient self-assessment of hair condition

8 TREATMENT/INTERVENTION PLAN

Eligible patients will be instructed to apply 0.25mL of topical calcitriol to each of the four quadrants of the scalp - front right, front left, back right, back left with the provided metered pump spray unit twice a day 2 weeks prior to the start of chemotherapy treatment. Patients unable or unwilling to wait the 2-week pre-treatment period may elect to pre-treat for 7 days ± 2 days. Subsequently, application will continue twice daily for three months or until termination of chemotherapy. The topical solution will be applied to the scalp. Hair and scalp should be dry or, if application is immediately after shampooing, the hair and scalp should be damp, not wet, to the touch by first towel drying the hair and scalp before application of the topical solution. The scalp will not be washed or shampooed for at least 8 hrs after each application. Patients will be advised that that they may apply no more than two consecutive of Compound 31543 (Calcitriol, USP) before washing or shampooing. Meaning, they must wash their hair after every other application of Compound 31543.Patients will self-administer the topical solution throughout the study; except for first dose, in which case application of topical calcitriol will be done by the study personnel. On days when pharmacokinetic studies will be performed, patients will self-administer the topical solution after the pharmacokinetics have been drawn.

8.1 Taxane-Based Chemotherapy Administration

All patients should be pre-medicated prior to administration of the chemotherapeutic agents in order to prevent severe hypersensitivity reactions, per institutional guidelines. The taxane regimen chosen is at the treating physician's discretion and should be standard for the patient's cancer type. The taxane regimen chosen should not change significantly while on study and receiving C31543 although dose reductions are allowed for toxicities related to chemotherapy.

8.2 Dose Escalation

Patients will be treated with the topical Compound 31543 (Calcitriol, USP) in cohorts of size three to six starting at dose level 1 (5 µg/mL). The dosage will be escalated if the clinical toxicity is declared acceptable (see below). Two dose levels were considered for escalation (10 and 20 µg/mL). These dose levels were completed without DLT. Amendment 8 will add additional dosing levels until MTD is achieved (40, 60, 80, µg/mL.)Determination of dose limiting toxicity (DLT, defined in Section 8.4) will be made during the first 28 days of topical treatment. No intra-patient dose escalation will be performed. DLT will need to possibly, probably or definitely (defined in Section 8.4) be related to topical calcitriol and not the chemotherapeutic regimen as best determined by participating investigators. The dose escalation scheme (Table 3) will occur as follows:

One 28-day cycle of treatment will be performed and evaluation of PK Data will occur before escalation to the next dose level.

If none of the initial three patients in a cohort experience dose limiting toxicity (DLT), then a new cohort of three patients will be treated at the next higher dose level.

If one of the three patients in a cohort experiences DLT, then up to three additional patients will be treated at the same dose level. Escalation will continue if a maximum of one of the six patients experiences DLT.

If two or more patients in a cohort experience DLT, then the maximum tolerated dose (MTD) will have been exceeded, and no further dose escalation will occur. The previous dose level will be considered as the MTD.

If only three patients were treated at a dose level under consideration as the MTD, then up to three additional patients will be accrued to that dose level. If no more than one of six patients at that dose level experience a DLT, then that dose level will be confirmed as the MTD.If two or more patients in that cohort experience DLT, then the previous dose level will be studied in the same fashion.

The MTD is defined as the dose level at which 0/3 or 1/6 subjects experiences DLT during the first 28-days treatment cycle below the dose at which 2/3 or 2/6 subjects experienced DLT. Thus, the MTD will have been exceeded when >30% (2/3 or 2/6) of subjects at any dose level develop DLT. If the MTD is not established after completing three cohorts of escalating doses, the study Sponsor will review the study findings with FDA Division of Dermatology to seek guidance as to amending the study protocol to add additional dose-escalating cohorts.

The Cohort Review Committee (CRC), comprised of the Berg medical monitor, Berg CMO and SVP of Regulatory Affairs or designee, and the principal investigator(s), will be fully aware of clinical and laboratory data, and must agree if dose escalation to the next cohort is appropriate. Pharmacokinetic data from each treatment cohort will also be reviewed by the CRC and considered in any decision to dose-escalate. Adverse event data from the treatment extension period will be presented, when available (at least monthly), to the CRC. These data will be considered for dose escalation decisions. In the event that MTD has not been reached after three cohorts have been treated, any further dose escalations will require a protocol amendment.

The CRC will review all available data from previous cohorts to assure that the actual dose escalation determined in this fashion does not expose subjects to unreasonable risk. The CRC may reduce or halt dose escalations for any reason (eg, observation of non-linear PK, AEs in subjects who receive more than one dose of C31543 Topical Solution). The decision to proceed with the next cohort will require unanimous agreement of the members of the CRC.

The nonclinical toxicology has been reviewed and the Cohort 1 drug concentration established by Berg, LLC and the FDA is approximately 1/20 or less of the expected MTD based on the nonclinical studies. As there is no presupposed risk of dose limiting toxicities at the Cohort 1 dosing detailed in the Phase 1 protocol, it has been determined that there will be no minus 1 dosing cohort. If two or more of the initial patients experience unacceptable toxicities at the initial Calcitriol dose, the CRC will review all available data and may elect to discontinue the study.

Table 3: Dose Escalation

Number of Subjects per Cohort with DLT during Treatment Period	Dose Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level
1 out of 3	Enter at least 3 more subjects at this dose level. If none of the 3 additional subjects has DLT, proceed to the next dose level. If 1 or more of the 3 additional subjects has DLT, then dose escalation is stopped, and this dose is declared the maximum administered dose (MAD). Three additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
2 out of 6	Dose escalation will be stopped. This dose level will be declared the MAD (highest dose administered). Three additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended Phase 2 dose.

8.3 Pharmacokinetics (All Patients)

For the purpose of pharmacokinetic (PK) studies, blood samples will be collected on Day 1 of topical treatment at the following time points: pre-dose, at 2 hrs (± 30 minutes), 4 hrs (± 30 minutes), and 8 hrs (± 1 hr post dose) after a single application on the morning of Day 1. The second application of drug product will be applied 10-14 hrs after the initial application and after the 8 hr PK sample. Thereafter, topical application frequency will be twice daily, morning and night. Subsequently, a PK sample will be taken 12 hrs (±2 hrs) after the last dose of each 28-day treatment, before the first application of Day 1 of the next 28-day treatment cycle. This schedule will continue for three consecutive 28-day topical treatment cycles. (PKs will be drawn at Weeks 1, 5, 9, 13. In addition if patients are still on study, a PK will also be drawn at Week 54.) Vital signs will be obtained approximately 5 minutes before each blood collection, and the actual collection times will be recorded.

At each collection, collect blood by venipuncture in a serum separator tube(s). Centrifuge at 1200 RCF for 10 ± 5 minutes, and aliquot 1.5 mL of serum each into 2 labeled externally threaded cryogenic vials and immediately freeze. Ship frozen samples to Berg Diagnostics. Samples collected from each cohort will be shipped frozen on dry ice to Berg Diagnostics for analytical determination ofC31543 concentrations in serum. Serum samples will be transported with a sufficient amount of dry ice to keep the samples frozen for at least 2 days, and should not be shipped to arrive over weekends or holidays. World Courier will provide all shipping materials. Please contact World Courier 3 days in advance for pre-filled waybills and to schedule pick-up.

Samples will be shipped to:

Berg Diagnostics
500 Old Connecticut Path
Building B, 3rd Floor
Framingham, MA, 01701

Attention: Sample Accessioning

The serum PK of C31543 will be calculated from serum collected from all subjects who receive C31543.The following serum PK parameters will be calculated using non-compartmental analysis:

- UC_{0-t}: Area under the concentration — time curve up to the last measurable concentration calculated by the trapezoidal rule and expressed in units of concentration — time
- $AUC_{0-inf:}$ Area under the serum concentration-time curve from time of dosing to infinity calculated by dividing the last quantifiable concentration by Kel and adding the result to $_{AUC0-t,}$ expressed in units of concentration-time.
- C_{max}: The observed peak drug concentration obtained directly from the experimental data without interpolation, expressed in concentration units
- T_{max}: The observed time to reach peak drug concentration obtained directly from the experimental data without interpolation, expressed in time units (hr)
- Kel: The apparent elimination rate constant, determined by regression analysis of the log-linear segment of the serum concentration-time curve, expressed in time-1 units (1/hr)
- $t_{1/2}$: The terminal half-life, calculated as -ln 2/Kel, expressed in time units(hr)
- CL: Clearance calculated as the drug $_{dose/AUC0-inf,}$ expressed in units offlow (L/hr)
- Vd: Volume of distribution calculated as CL divided by $_{Kel}$ and expressed in units of volume (L)

Descriptive statistics (including number, mean, median, standard deviation, and range) for PK parameters will be tabulated by dose level. Estimated renal elimination will be tabulated by dose level.

8.4 Definition of Dose-Limiting Toxicity (DLT) and Treatment Modifications

Toxicities will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0).

8.4.1 Dose-Limiting Toxicity Related to Calcitriol

Dose-limiting toxicity is defined as a clinically significant grade 3 or 4 non-hematologic toxicity occurring during the first 28-day treatment cycle of the topical agent application, and needs to be possibly, probably, definitely related to calcitriol (and not the chemotherapeutic regimen) as best determined by investigators.

Excessive dosage of calcitriol induces hypercalcemia and in some instances hypercalciuria. If the patient presents with symptoms of hypercalcemia, serum calcium should be determined and treatment should be stopped immediately. Hypercalcemia defined using CTCAE version 4.0

grade 3 is serum calcium > 12.5-13.5 mg/dL; > 3.1-3.4 mmol/L or Ionized calcium > 1.6-1.8 mmol/L, hospitalization is indicated.

For patients with hypercalcemia determined by elevated serum calcium, if the ionized calcium level is in fact elevated, the study drug will be stopped and the patient removed from the study. If the ionized calcium level is normal, the patient will remain on the study and ionized calcium will be followed rather than serum calcium. If the patient is removed from the study for this reason, serum calcium and phosphate levels will be checked with daily blood draws at the testing center until they are normal for two consecutive days.

8.4.2 Dose-Limiting Toxicity

If patients develop toxicities related to their chemotherapeutic regimen, the dose reductions will be followed per institutional guidelines. During modifications in the chemotherapeutic regimen, calcitriol doses will remain stable unless modifications are deemed necessary by the investigator.

9 EVALUATION DURING TREATMENT/INTERVENTION

9.1 Clinical

History and physical examination will be performed as detailed in the table below. Following the start of application of topical calcitriol 2 weeks or 7 ± 2 days prior to initiation of chemotherapy, patients will be seen by an investigator for interim medical history, concomitant medication, physical exam including weight, vital signs (blood pressure, temperature, respiration rate, heart rate), and adverse events at Weeks 1, 2, 3, 5, 7, 11, 15, 27, and 54.

9.2 Laboratory

Laboratory evaluation will be performed as described in Table 4and Table 5below.

9.3 Dermatology Evaluation.

The subjects will be seen by a dermatologist during Weeks 2 and 7 as detailed in the tables below (Table 5 and Table 6). This review will include the following:

- A visual inspection of the scalp (oiliness/ dryness, erythema, inflammation, scaling, papules, pustules, erosions, pustules, excoriations, rash; including perifollicular changes)
- Palpation of the scalp
- Examination of hair (quantity/ length, density, color, texture, hair pull test, hair shaft, morphology, distribution) including eyelashes/eyebrows
- Interval dermatologic history: issues with use of agent (skin, hair etc.)

Any abnormalities will be documented in the medical record along with any problems reported by the patient with use of calcitriol (itchiness, stinging, irritation, burning, hair loss). All abnormalities and problems will be reviewed by the investigator to determine if they meet the criteria for adverse events.

9.4 Photographic Record of Hair and Scalp

Alopecia is defined as any hair loss. In this study centralized photographic review by a single dermatologist will be conducted using the Canfield Clinical Photography assessment images that will be acquired by the research staff to ensure standardization and uniformity among all enrolled patients. Please refer to the Canfield User Manual and Quick Reference Guide for instructions detailing the use of the Canfield equipment provided to photographically record the hair and scalp. These documents outline how to prepare the subjects, complete and use the ID card and ID card holders, photograph and upload the photos onto the Canfield portal.

The following five views will be obtained at each photographic assessment: bilateral sides of head/scalp view, front of head/face view, back of head/scalp view, and top of head/scalp view. Additionally, close-up photographs will be taken at the same times points. They will include the mid-pattern of the scalp from a superior view and a vertex view with hair parted in the center and combed away from the center part. Photographs will be standardized for lighting, camera angle, and position to the participants head.

Centralized photographic review will be conducted by one dermatologist reviewer and photographs will be evaluated using a 7-point evaluation scale for hair volume (Table 9-1).The reviewer will compare the photographs acquired at baseline, Week 7 and Week 15. Comparisons

may be made to Week 27 and Week 54, if applicable. The dermatologist reviewer scoring the photographs will be blinded to time sequence of the photographs aside from the baseline photographs to which all others will be compared.

Table 4: Evaluation Scale for Photographic Review of Hair Loss/Gain

7-point scale	Increase/decrease	% of Hair Gain/Loss
-3	Greatly decreased	> 75% hair loss
-2	Moderately decreased	50-75% hair loss
-1	Slightly decreased	25-49% hair loss
0	No change	0-24% hair loss/gain
1	Slightly increased	25-49% hair gain
2	Moderately increased	50-75% hair gain
3	Greatly increased	> 75% hair gain

9.5 Subjective Record of Hair and Scalp

Alopecia will also be subjectively recorded through the patient self-reported diaries. All patients are asked to complete this self-assessment diary weekly that will require assessment of hair thickness, hair fullness, hair breakage, and hair cosmetic qualities (ease of styling, etc.) on an analog 10 point scale throughout treatment to assess patient-reported efficacy of the study drug. These will be completed weekly and returned to the research staff at every visit during C31543 treatment. The study is expected to take place over a period of approximately 12 months, including the screening period.

Table 5: Study Evaluation Schedule Part A – The Basic Information

(All study assessments will be performed ± 72 hrs from the scheduled date unless otherwise noted.)

14-Day Pre-treatment Schedule:

Basic Information	*Chemo Week*	Sign Informed Consent	Demo-graphics	MedicalHistory	Concomitant Meds	Physical Examination	Urinalysis and Pregnancy Test	Weight	Vital Signs	Adverse Events Evaluation
Pre-study	–	*	*	*	*	*	*	*	*	*
Week 1 (topical application prior to chemo)	–			*	*	*		*	*	*
Week 2 †† (topical application prior to chemo)	–			*	*	*		*	*	*
Week 3 (start of chemo)	*1*			*	*	*		*	*	*
Week 4	*2*									
Week 5	*3*			*	*	*		*	*	*
Week 6††††	*4*									
Week 7 ††	*5*			*	*	*		*	*	*
Week 8	*6*									
Week 9	*7*									
Week 10††††	*8*									
Week 11	*9*			*	*	*		*	*	*
Week12	*10*									
Week 13	*11*									
Week 14††††	*12*									
Week 15	*13*			*	*	*		*	*	*
Week 27†††††††				*	*	*		*	*	*
Week 54†††††††				*	*	*		*	*	*

7-Day Pre-treatment Schedule:

Basic Information	*Chemo Week*	Sign Informed Consent	Demo-graphics	MedicalHistory	Concomitant Meds	Physical Examination	Urinalysis and Pregnancy Ttest	Weight	Vital Signs	Adverse Events Evaluation
Pre-study	–	*	*	*	*	*	*	*	*	*
Week 1 (topical application prior to chemo)	–			*	*	*		*	*	*
Week 2†† (start of chemo)	1			*	*	*		*	*	*
Week 3	2									
Week 4	3									
Week 5††††	4			*	*	*		*	*	*
Week 6	5									
Week 7††	6			*	*	*		*	*	*
Week 8	7									
Week 9††††	8									
Week 10	9									
Week 11	10			*	*	*		*	*	*
Week 12	11									
Week 13††††	12									
Week 14	13									
Week 15	14			*	*	*		*	*	*
Week 27†††††††				*	*	*		*	*	*
Week 54†††††††				*	*	*		*	*	*

† PK will be collected in the following manner: On Day 1 of topical treatment: PK will be collected pre-dose (before the first dose), and 2 hrs (± 30 minutes), 4 hrs (± 30 minutes) & 8 hrs (± 1 hr post-dose).

For study Weeks 5, 9, 13, and 54 of calcitriol, PK will be collected on Day 1 pre-dose. This should be 12 hrs (±2 hrs) after the last application of topical calcitriol.

†† For the Weeks 2 and 7 visits, patients will be seen by a study Dermatologist at their site.

††† All patients will be asked to maintain the self-assessment diary for up to approximately 7 months from initial application of study drug. The diary will be filled out weekly for the first 15 weeks after initiating calcitriol and at Weeks 19, 23, and 27.

†††† Note that some patients may be placed on a 3-week-on one-week-off regimen. The indicated weeks will be off-chemo weeks.

††††† Photographs for patients in each cohort representing baseline, and treatment Weeks 7 and 15 will be presented blind to the study PI after at least 3 patients have completed 15 weeks of treatment. Photographs will also be taken at Week 27 and Week 54 of the study but will be included in the final photographic assessment as secondary information. The PI clinical assessment of the baseline, and Weeks 7 and 15 photographs will be used, together with the patient self-assessment diary information, for the primary assessment of alopecia.

†††††† A patient self-assessment is required this week if treatment continues beyond Week 15.

††††††† Study assessments will be performed ± 7 days from the scheduled date.

Table 6: Study Evaluation Schedule Part B – The Tests and the Study Drug Application

14-Day Pre-treatment Schedule:

Tests and Study Drug Application	*Chemo Week*	PK blood samples†	Application of C31543 (Calcitriol)	CBC with diff	Comprehensive chemistry panel	Photographic record of hair and scalp	Serumphosphorus and Vitamin D	Patient self-assessment diary †††
Pre-study	–			*	*	*	*	*
Week 1 (topical application prior to chemo)	–	*	*	*	*		*	*
Week 2 †† (topical application prior to chemo)	–		*					*
Week 3 (start of chemo)	*1*		*	*	*		*	*
Week 4	*2*		*					*
Week 5	*3*	*	*	*	*		*	*
Week 6††††	*4*		*					*
Week 7††	*5*		*	*	*	*	*	*
Week 8	*6*		*					*
Week 9	*7*	*	*					*
Week 10††††	*8*		*					*
Week 11	*9*		*	*	*		*	*
Week12	*10*		*					*
Week 13	*11*	*	*					*
Week 14††††	*12*		*					*
Week 15†††††	*13*		*	*	*	*	*	*
Week 19††††††								*
Week 23††††††								*
Week 27†††††††			*	*	*	*	*	*
Week 54†††††††		*	*	*	*	*	*	

7-Day Pre-treatment Schedule:

Tests and Study Drug Application	***Chemo Week***	**PK blood samples†**	**Application of C31543 (Calcitriol)**	**CBC with diff**	**Comprehensive chemistry panel**	**Photographic record of hair and scalp**	**Serumphosphorus and Vitamin D**	**Patient self-assessment diary ††††**
Pre-study	–			*	*	*	*	*
Week 1 (topical application prior to chemo)	–	*	*	*	*		*	*
Week 2†† (start of chemo)	1		*	*	*		*	*
Week 3	2		*					*
Week 4	3		*					*
Week 5††††	4	*	*	*	*		*	*
Week 6	5		*					*
Week 7††	6		*	*	*	*	*	*
Week 8	7		*					*
Week 9††††	8	*	*					*
Week 10	9		*					*
Week 11	10		*	*	*		*	*
Week 12	11		*					*
Week 13††††	12	*	*					*
Week 14	13		*					*
Week 15	14		*	*	*	*	*	*
Week 19††††††								*
Week 23††††††								*
Week 27†††††††			*	*	*	*	*	*
Week 54†††††††		*	*	*	*	*	*	

† PK will be collected in the following manner: On Day 1 of topical treatment: PK will be collected pre-dose (before the first dose), and 2 hrs (±30 minutes), 4 hrs (± 30 minutes) a
hr post-dose).
For study Weeks 5, 9, 13, and 54 of calcitriol, PK will be collected on Day 1 pre-dose. This should be 12 hrs (± 2 hrs) after the last application of topical calcitriol.

†† For the Weeks 2 and 7 visits, patients will be seen by a study Dermatologist at their site.

††† All patients will be asked to maintain the self-assessment diary for up to approximately 7 months from initial application of study drug. The diary will be filled out weekly for the first 15 weeks after initiating calcitriol and at Weeks 19, 23, and 27.

†††† Note that some patients may be placed on a 3-week-on one-week-off regimen. The indicated weeks will be off-chemo weeks.

††††† Photographs for patients in each cohort representing baseline, and treatment Weeks 7 and 15 will be presented blind to the study PI after at least 3 patients have completed 15 weeks of treatment. Photographs will also be taken at Week 27 and Week 54 of the study but will be included in the final photographic assessment as secondary information. The PI clinical assessment of the baseline, and Weeks 7 and 15 photographs will be used, together with the patient self-assessment diary information, for the primary assessment of alopecia.

†††††† A patient self-assessment is required this week if treatment continues beyond Week 15.

††††††† Study assessments will be performed ± 7 days from the scheduled date.

10 POST-TREATMENT EVALUATION

Post-treatment physical examinations will be performed by an investigator and will take place within 30 days from the completion of the study treatment date. Exams will include:

- Weight measurement
- Vital signs
- Blood sample draws (complete blood count, comprehensive chemistry panel, serum phosphorus, and serum Vitamin D)
- Adverse Event evaluation

11 TOXICITIES/SIDE EFFECTS

NCI CTCAE v4.0 will be used to grade all toxicity. Below are some side effects that may be observed:

- **Common side effects (20-30%)**
  - Pruritus
  - Skin discomfort
  - Skin stinging or burning
  - Eye irritation or stinging
- **Less common side effects (<20%)**
  - Scalp xerosis and flaking
  - Erythema
  - Irritant dermatitis
- **Rare but serious side effects (1-5%)**
  - Hypercalcemia
  - Hypercalciuria
  - Renal stones
  - Increased thirst
  - Increased frequency of urination
  - Changes in pulse
  - Weakness
  - Drowsiness
  - Bone pain
  - Renal Insufficiency

12 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

This trial is a Phase 1 study and thus primarily a safety study of C31543 Topical Solution in patients with metastatic or recurrent cancer who are undergoing chemotherapy with a taxane-based regimen. This study will focus on determining an MTD.

Therapeutic response of C31543 Topical Solution will be assessed by photography and by patient self-assessment.

13 CRITERIA FOR REMOVAL FROM STUDY

All patients may continue therapy unless DLT is documented. In case of death, the cause of death should be documented.

The following events may be considered sufficient reason for discontinuing treatment with the study medication:

- Serious toxicity due to the study drug graded according to the NCI Common Terminology Criteria for Adverse Events v4.0
- Conditions requiring therapeutic intervention not permitted by the protocol
- Unacceptable toxicity in the opinion of the patient or investigator even if not specifically defined elsewhere
- Personal preference by the patient for any reason
- Subject non-compliance with the defined treatment plan
- Medical or psychiatric illness Any other situation where, in the opinion of the investigator, continued participation in the study would not be in the best interest of the patient or further therapy is not possible
- Pregnancy
- Loss of all of the patient's hair after the first three cycles of topical calcitriol application

Subjects may withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol. When possible, the tests and evaluations listed for the termination visit should be carried out. Berg should be notified of all subject withdrawals as soon as possible.

If a subject fails to return for the protocol defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, a registered letter, at the minimum, should be sent to the subject (or the subject's legal guardian) requesting contact with the clinic. This information should be recorded in the CRF.

The investigator will also withdraw a subject upon Berg's request or if Berg chooses to terminate the study. Upon occurrence of a serious or intolerable adverse effect, the principal investigator will confer with the Berg representative. If a subject is discontinued due to an adverse effect, the event will be followed until it is resolved, or if not resolved within a reasonable time (approximately 30 days), until its clinical relevance and etiology can be reasonably explained. A subject may withdraw his or her consent at any time during the study.

If a subject withdraws from the study at any time either at his or her request or at the principal investigator's discretion, the reason for withdrawal will be recorded in the CRF. All subjects who withdraw from the study prematurely will undergo all end-of-study assessments, if possible.

Every effort must be made to undertake protocol-specified safety follow-up procedures.

14 BIOSTATISTICS

This is a Phase 1 study designed to determine the maximum tolerated dose (MTD) of C31543 topical calcitriol in patients with CIA. Three doses of topical calcitriol (5 µg/mL, 10 µg/mL, and 20 µg/mL) have been tested to date without DLT. Amendment 8 adds additional dosing levels (40 µg/mL, 60 µg/mL 80 µg/mL)until MTD is achieved.

Patients will be treated in cohorts of size three to six and the dosage will be escalated if the clinical toxicity is acceptable. A patient is considered toxicity-free for the purpose of the trial if s/he completes the first month of topical agent application without experiencing dose limiting toxicity (DLT). If the topical agent is discontinued during the first month for reasons other than toxicity, an additional patient may be enrolled at that dose level to ensure adequate evaluation of toxicity. No intra-patient dose escalation will be performed. In all cases, including those when the topical treatment continues post 4 weeks, the MTD assessment will be based only on the DLT recorded during the first month. DLT is defined in Section 8.4and the design is constructed to minimize the chances of escalating the dose when the probability of DLT is high, and maximize the chance of escalating the dose when the probability of DLT is low. The dose escalation scheme is as follows:

1. If none of the initial three patients at a given dose level experience DLT, the next dose level will be studied.
2. If one of the initial three patients at a given dose level experiences DLT, three additional patients will be treated at the same dose level. Escalation will continue only if there has been no additional DLT observed.
3. If two or more patients experience DLT at a given dose, the previous dose will be declared the MTD.
4. If only three patients were treated at a dose under consideration as MTD, an additional three patients will be treated at that level to confirm previous results.

The probability that dose escalation will occur at any stage during MTD determination, is a function of the underlying DLT rate at the current dose level. This probability can be calculated as the sum of the binomial probabilities of the following two outcomes that would permit escalation to occur:

1. No DLT observed in the first three patients.
2. One DLT is observed in the first three patients followed by no DLT observed in three additional patients at the same dose level.

The true risk of toxicity is expected to be in the range of 10%-50%.The following table shows the corresponding probabilities of dose escalation:

True Risk of Toxicity	0.10	0.20	0.30	0.40	0.50
Probability of Escalation	0.91	0.71	0.49	0.31	0.17

These numbers show the probability of escalating to the next dose level is large when the underlying true toxicity rate is small and the probability of escalating decreases appropriately as the true toxicity rate increases.

14.1 Safety Analyses

Selected non-hematologic and hematologic toxicities, as measured by the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0), will be described by frequency and grade, by cycle and over all cycles, with the maximum grade over all cycles used as the summary measure per patient.

Adverse event terms recorded on the CRF will be mapped to preferred terms using the medical dictionary for regulatory activities (MedDRA) dictionary. All adverse events (AEs) will be listed or tabulated for overall incidence and for incidence for each dose cohort, worst reported severity, and relationship to study treatment according to system organ class and preferred term. Serious adverse events (SAEs) will be similarly summarized. Listings of deaths, SAEs, DLTs, and AEs leading to early termination of study treatment, or premature withdrawal from trial will also be provided.

Laboratory variables will be examined using mean change in value from baseline to various time points for each dose cohort. Laboratory values will also be categorized according to the CTCAE v4.0; listings or tables will be categorized by the worst on-study toxicity grade, dose cohort, and relationship. Shift tables will be presented to show the number and percent of subjects with high, normal, and low (or normal/abnormal) laboratory results at baseline and last assessment.

Concomitant medications will be summarized for all subjects, including summary by dose cohort.

14.2 Significance Level

Centralized Photographic review by a dermatologist and patient self-reported diaries will be used for preliminary statistical analyses. Analyses will look at the efficacy of Topical Compound C31543. This will be helpful for further studies looking more closely at the efficacy of C31543.

While no formal statistical testing is planned for this study, 95% confidence intervals may be calculated for selected safety variables. This Phase 1 trial will accrue only three patients per cohort, which is not a statistically significant number of patients, nor is the trial design adequate to provide objective statistical data sufficient for proof of efficacy.

14.3 Exploratory Analyses

Exploratory variables will be assessed for each subject, and descriptive statistics (including number, mean, median, standard deviation, and range) will be calculated for subjects by dose level**.**

14.4 Interim Analyses

No interim analysis is planned.

14.5 Sample Size/Accrual Rate

The Phase 1 portion of the study for 3-6 patients to be treated at each dose level. The original assumption was that 3 dose levels would be required resulting in a minimum of 2 and a maximum of 18 patients enrolled. Amendment 8 adds 3 additional dose levels resulting in a maximum of 18 additional patients enrolled. With 12 patients enrolled and treated to date, the maximum number of patients enrolled in the study would be 30. This clinical trial will be

conducted at two clinical sites. With the expected accrual rate of approximately 3-6 eligible patients per treatment cohort, it was expected that the Phase 1 portion of the trial would take less than 1 year. This would allow each 3-patient cohort to be observed for 28 days, the length of time for treatment with one cycle of therapy prior to additional patients being accrued. It is anticipated that the enrollment of the 3 additional dosing levels will take less than 1 year.

15 RESEARCH PARTICIPANT REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. Human protection committee approval of this protocol and consent form is required. Eligible patients who wish to participate will be enrolled into the trial.

Registration must occur prior to the initiation of protocol therapy. Patient registration and dose level assignment will be performed by Berg. The Berg registration desk will assign a patient identification number and dose level. The registration desk designee will document the patient identification number, dose level, and date of enrollment on the Registration Form and will send the completed form back to the site as soon as possible, and no later than 24 hrs following the registration request. Thesite coordinator will document the patient identification number, dose level, and date of enrollment in the EDC system.

The site coordinator must complete and submit an Eligibility Packet to the Berg Enrollment desk following the instructions outlined in the Enrollment Instructions.

All Eligibility Packets are to be or emailed to Berg Registration Desk:

Email: EnrollmentDesk@bergpharma.com

The enrollment packet will be reviewed by the Berg Medical Monitor for compliance with the study protocol screening and inclusion/exclusion criteria. All eligible patients will be authorized for participation in the study by Berg via an email confirmation, a copy of which will be maintained in the Berg Trial Master File.

16 ADVERSE EVENTS

16.1 Clinical Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that may or may not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. Pre-existing conditions that worsen during a study will be reported as AEs.

All AEs that occur after the informed consent is obtained will be reported on the AE page of the CRF**.**

16.2 Relationship Between the Adverse Event and the Study Drug

The investigator must also assess the relationship of any adverse event to the use of study drug, based on available information, using the following guidelines:

1. Not related
    a. The AE is not related if exposure to the investigational product has not occurred, or
    b. The AE is associated with an alternate cause.
2. Unlikely Related
    a. The occurrence of the AE is not reasonably related in time, or
    b. The AE is considered unlikely to be related to use of the investigational product (ie, there are no facts or arguments to suggest an alternate relationship).
3. Possibly Related
    a. The investigational product administration and the AE are considered reasonably related in time, and
    b. There are facts to suggest a reasonable causal relationship between the investigational product and the AE.
4. Probably Related
    a. The investigational product administration and the AE are reasonably related in time, and
    b. The AE is more likely explained by exposure to the investigational product than by other factors or causes, or is the most likely cause of the AE.
5. Definitely related

16.3 Treatment and Follow-Up of Adverse Events

All AEswill be monitored until resolution or, if the AE is determined to be chronic, a cause is identified. If an AE is considered potentially related to study treatment and remains unresolved at

the conclusion of the study, the event will be followed until resolution, stabilization, or initiation of treatment that confounds the ability to assess the event.

16.4 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the Case Report Form (CRF), or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable. Laboratory test value abnormalities as such should not be reported on the AE page of the CRF as AEs unless they result in a clinically relevant condition.

16.4.1 Follow-Up of Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the CRF.

17 SERIOUS ADVERSE EVENTS (SAE)

Any clinical AE or abnormal laboratory test value that is serious and that occurs during the course of the study, irrespective of the treatment received by the subject, must be reported to Berg (or designee) within 24 hrs of awareness of the event(expedited reporting).

The definition and reporting requirements of the International Conference of Harmonisation (ICH) Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A will be adhered to. An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening (ie, in the opinion of the investigator, the AE places the subject at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or prolongation of an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may not be immediately life-threatening, or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

17.1 SAE Reporting

Any SAE, whether or not considered to be related to treatment with topical calcitriol will be reported within 24 hrs from awareness of the event toBerg (or designee) and will be recorded on both the SAE initial report form and the CRF. The outcome of the SAE, and medications or other therapeutic measures used to treat the event, will be recorded on the appropriate CRF page. Forms for reporting SAEs and SAE Report Completion Guidelines will be provided to the study sites.

All SAEs that occur after the first dose of topical calcitriol and through study termination, will be reported in accordance with US regulations governing safety reporting (21 Code of Federal Regulations (CFR) 312.32 and 312.33).

Reporting of SAEs by the investigator to his or her internal review board (IRB) will be done in accordance with the standard operating procedures and policies of the IRB. Adequate documentation must be maintained showing that the IRB was properly notified.

For notification of an SAE, the following individual must be contacted:

Berg medical monitor: Brian Berman, MD, PhD

All SAE reports need to be faxed or emailed to Berg Safety:

FAX Number (615) 889-8880

Email (preferred method): Safety@bergpharma.com

17.2 Berg SAE Reporting Requirements

Berg must inform investigators and regulatory authorities of reportable events in compliance with applicable regulatory requirements on an expedited basis (ie, within specific timeframes). For this reason, it is imperative that investigational sites provide complete SAE information in the manner described above.

Berg is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations (21 CFR 312.32), and/or local regulatory requirements. Investigators are responsible for reporting to their IRBs per local requirements.

18 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

18.1 Informed Consent Procedures

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board. The consent form will include the following:

- The nature and objectives, potential risks and benefits of the intended study.
- The length of study and the likely follow-up required.
- Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
- The name of the investigator(s) responsible for the protocol.
- The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.2 IRB Approval

The trial protocol, ICF, IB, available safety information, patient documents (eg, trial diaries), patient recruitment procedures (eg, advertisements), information about payments (ie, PI payments) and compensation available to the patients and documentation evidencing the PI‘s qualifications should be submitted to the IRB for ethical review and approval prior to the trial start.

18.3 Confidentiality

18.3.1 Patient Confidentiality

Confidentiality of the patient‘s personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPPA) and national data protection laws, as applicable. HIPPA regulations require that, in order to participate in the trial, a patient must sign an authorization from the trial that he or she has been informed of the following:

- What protected health information (PHI) will be collected from patients in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;

- The information collected about the research trial will be kept separate from the patient‘s medical records, but the patient will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (ie, that the patient is alive) at the end of their scheduled trial period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of Berg, the regulatory authorities, and the IRB direct access to review the patient‘s original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include:

- Only a unique trial number and initials will identify patients on the CRF or other documents submitted to Berg.
- This information, together with the patient‘s date of birth, will be used in the database for patient identification.
- Patient‘s name and address will not be entered in the CRF or database.
- No material bearing a patient‘s name will be kept on file by Berg.
- Patients will be informed of their rights within the ICF.

18.3.2 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the Berg database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub-investigator, Berg shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

19 RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

19.1 Amendments to Protocol

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by Berg. The written amendment must be reviewed and approved by Berg, and submitted to the IRB at the investigator's facility for the Board's approval.

It should be further noted that, if an amendment to the protocol substantially alters the trial design or the potential risks to the patients, their consent to continue participation in the trial should be obtained.

19.2 Trial Documentation and Storage

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient‘s CRF data are obtained. The PI and research staff is responsible for maintaining trial-related (essential) documentation, suitable for inspection at any time by representatives from Berg and/or applicable regulatory authorities. This should contain at a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

The Investigator shall maintain adequate records of drug disposition, case histories and any other trial-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

If the investigator relocates, retires, or for any reason withdraws from the trial, both Berg and its representative should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another investigator, another institution, or Berg. The investigator must obtain the Sponsor‘s written permission before disposing of any records, even if retention requirements have been met. All trial files will be maintained by Berg or its representative throughout the trial, and will be transferred to Berg at the conclusion of the trial.

19.3 Data Collection

The trial eCRF is the primary data collection instrument for the trial. eCRFs will be completed using the English language and should be kept current to enable the monitor to review the patient‘s status throughout the course of the trial.

All data requested on the eCRF must be supported by and be consistent with the patient‘s source documentation. All missing data must be explained. For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided. The investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed.

19.4 Trial Monitoring, Auditing, and Inspecting

The investigator will permit trial-related monitoring, quality audits, and inspections of all trial-related documents (eg, source documents, regulatory documents, data collection instruments, case report forms) by Berg or its representative(s) and government regulatory authorities. The investigator will ensure the capability for inspections of applicable trial-related facilities. The investigator will ensure that the trial monitor or any other compliance or QA reviewer is given access to all trial-related documents and trial-related facilities.

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by qualified staff chosen by Berg to ensure the human subject protection, trial procedures, laboratory, trial intervention administration, and data collection processes are of high quality and meet Sponsor, GCP/ICH and, when appropriate, regulatory guidelines. The Site Monitoring Plan will outline the details of the monitoring process.

19.5 Disclosure and Publication Policy

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. Berg reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per Berg's publication strategy.

Berg will register the trial on www.clinicaltrials.gov. In addition, Berg will publish the results of the trial.

Inclusion of the investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the trial. The investigator acknowledges that the trial is part of a multicenter trial and agrees that any publication by the investigator of the results of the trial conducted at the research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within fifteen (15) months after the trial has been completed or terminated at all trial sites, and all data has been received, the investigator shall have the right to publish its results from the trial, subject to the notice requirements described herein and subject to acknowledgement of Berg as appropriate. Investigator shall provide Berg thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the trial for the purpose only of determining if any confidential or patentable information is disclosed thereby. If Berg requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit Berg to seek patent protection and to remove any Berg Confidential Information from all publications.

20 APPENDICES

A. Calcitriol Application Diary
B. Patient Self-Assessment Diary, Baseline
C. Patient Self-Assessment Diary, On-Treatment

21 REFERENCES

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