PROTOCOL CTL0211

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

STATISTICAL ANALYSIS PLAN
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CONFIDENTIAL

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE(s)	Adverse event(s)
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CFB	Change From Baseline
CIA	Chemotherapy-Induced Alopecia
CRC	Cohort Review Committee
CRF	Case Report Form
DLT	Dose-limiting toxicity
FAS	Full Analysis Set
MTD	Maximum tolerated dose
PK	Pharmacokinetic(s)
SAE	Serious Adverse Event
SD	Standard Deviation

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1 INTRODUCTION

This analysis plan, Version 4.0, is to be used in conjunction with the protocol (Version 9, dated 15 November 2015) and the corresponding e-CRFs.

1.1 Background

Chemotherapy-Induced Alopecia (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. Despite profound effects on patients, no effective preventative or treatment options are available.

2 TRIAL DESIGN

This will be a single-arm, dose-escalation study to determine the maximum tolerated dose (MTD) and the overall safety and tolerability of Compound 31543 in patients with metastatic breast cancer undergoing chemotherapy with paclitaxel. A standard 3+3 dose escalation design will be employed with 3-6 patients at each dose level.

2.1 Study Objectives

The primary objective of this study is to:

1. Determine the maximum tolerated dose (MTD) and the overall safety and tolerability of topical calcitriol in patients with metastatic breast cancer receiving chemotherapy with paclitaxel.

The secondary objectives of this study are to:

1. Determine the single and multiple dose pharmacokinetics (PK) of calcitriol at different dose levels; and
2. Evaluate preliminary efficacy of calcitriol for preventing chemotherapy induced alopecia.

2.2 Study 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).

2.3 Study Drug Dosage and Administration

Eligible patients will be instructed to apply 0.25mL of topical Compound 31543 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 two 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.

Patients will be treated in cohorts of size three to six starting at dose level 1 (5μg/m1). The dosage will be escalated if the clinical toxicity is declared acceptable (below). Subsequent escalation cohorts will be treated with 10, 20, 40, 60, and 80 μg/ml.

Determination of a DLT will be made during the first 28 days of topical treatment. No intra-patient dose escalation will be performed. DLT will need to be possibly, probably or definitely related to topical Compound 31543 and not paclitaxel as best determined by participating investigators. The dose escalation scheme 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 experiences a 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 only one of the six patients experiences DLT.
- If two or more patients in a cohort experience DLT, then the 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.

The original protocol had 3 dose levels: 5, 10, and 20 μg/ml. Since the MTD was not established after completing three cohorts of escalating doses, the Sponsor amended the study protocol to add additional dose escalating cohorts: 40, 60, and 80 μg/ml.

3 SAMPLE SIZE, RANDOMIZATION AND BLINDING

3.1 Sample Size

A standard 3+3 dose escalation design will be employed with 3-6 patients at each of three dose levels. Thus, the maximum number of subjects is 18 (6 per dose level).

3.2 Randomization and Blinding

This study is a non-randomized unblinded single-arm, dose-escalation study.

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; otherwise not applicable.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients must meet the following 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 with historically confirmed solid tumor that have relapsed to previous therapy and are scheduled to receive a taxane-based regimen at treating physician's discretion.
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 v.4.0. 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 hours prior to registration
7. Has serum calcium < 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 hours prior to registration

4.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Receiving calcium-lowering therapy or drugs that may affect calcium levels (e.g., calcitonin, mithramycin, phosphate, denosumab) within 4 weeks of initiation of topical calcitriol. Patients who have been managed with bisphosphonates or calcium-lowering therapy for 6 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, e.g. Atopic Dermatitis, etc.
5. Has participated in any investigational trial within 30 days or six half-lives of its biologic activity whichever is longer, before the start of study.
6. 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 day prior to the start of the study and that the dose of the Vitamin D supplement remains the same throughout the study.
10. 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. Hypercalcemia or kidney stones
12. 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. Any visible signs of androgenic alopecia or alopecia areata or significant hair loss, hair thinning, or hair breakage.
14. Prior radiation to the cranium
15. Pregnant or breastfeeding

4.3 Premature Discontinuation from Dosing

Safety follow-up visits will be performed for patients who discontinue dosing prematurely. Patients who discontinue dosing due to AEs will be monitored until resolution of all AEs. If a patient discontinues dosing prematurely at any time, either at his or her request or at the Investigator's discretion, the reason(s) for discontinuation will be recorded.

All patients may continue therapy unless DLT is 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 or 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 Compound 31543 application
- Investigator decision. 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.
- Sponsor decision. 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.

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.

5 CLINICAL PROCEDURES AND ASSESSMENTS

The schedule of procedures is given in the following table. Further details are given in the protocol.

Study Evaluation Schedule
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†††††††		*	*	*	*	*	*	

† 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) and 8 h 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.

Study Evaluation Schedule
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) and 8 h 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.

6 STUDY ENDPOINTS

6.1 Maximum Tolerated Dose (MTD)

The primary objective of this study includes determination of the MTD. A 3+3 dose escalation design with 3-6 patients at each dose level is a standard design for this objective. The details are given in Section 2.3.

6.2 Safety and Tolerability

The primary objective of this study includes determination of the overall safety and tolerability of topical Compound 31543. Safety endpoints include treatment-emergent adverse events (AEs), toxicities, and Change from Baseline (CFB) in vital signs, physical examinations, and laboratory tests.

6.3 Pharmacokinetics (PK)

Blood samples for PK analysis will be collected at various times, as presented in Section 5. Details and results of the PK analyses will be presented in a separate document.

6.4 Efficacy

6.4.1 Subjective record of hair and scalp

Alopecia will be subjectively recorded through the patient self-reported diaries. All patients are asked to maintain this self-assessment diary 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. The diary will be filled out weekly for the first 15 weeks after initiating topical Compound 31543l and at Weeks 19, 23, and 27.

6.4.2 Photographic record of hair and scalp

Photographic record of hair and scalp will be performed pre-study and Weeks 7, 15, 27, and 54. 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 participants head.

7 STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

7.1 Analysis Populations

The analyses will be conducted using the populations described below:

The **Safety Population** consists of all patients who received at least one application of topical Compound 31543. Analyses of safety assessments will be performed for the Safety Population.

The **Full Analysis Set (FAS) Population** is defined as all patients who complete the treatment or discontinue due to a DLT. A patient who discontinues due to an AE that does not qualify as a DLT will be considered non-evaluable and replaced by another patient enrolled at the same dose level. Patients who discontinue for other reasons will be considered on a case-by-case basis. In this document, the FAS population will be referred to as FAS.

The **Evaluable Population** is defined as all patients in the Safety Population who complete at least one photographic assessment and diary completion through Week 7.

7.2 General Analysis

The following standards will be applied for analyses unless otherwise specified. Simple descriptive statistics for continuous data are: n (number of non-missing observations), mean, SD, maximum, median, and minimum. Categorical data will be summarized by the number and percentage of patients in each category. All data will be listed and sorted by investigator number, patient number and, where appropriate, by day. Calculation of CFB is discussed in Section 8.1.2. If the FAS is the same as the Safety Population, then the table or listing will be presented only once.

7.3 Patient disposition

The total number of patients will be presented with the number and percentage of patients in each analysis population by cohort and overall. The number and percentage of patients who were enrolled, eligible for the study, treated, treated and eligible, not eligible but treated, completed the study, discontinued, and primary reason for discontinuation will be summarized for all patients enrolled for each dose cohort and overall.

Protocol deviations will be listed.

7.4 Demographics, Baseline Characteristics and Medical History

7.4.1 Demographics

Demographic parameters, including age, sex, race, and ethnicity will be summarized for the Safety and FAS for each dose cohort and overall.

7.4.2 Medical History and Baseline Disease Characteristics

Previous therapy for breast cancer (chemotherapy, radiation therapy, surgery, hormone therapy, or immunotherapy) will be summarized using frequencies and percentages (“Yes” or “No”) for each dose cohort and overall. The above questions will be included in a listing, with Therapy Type, Therapy Details, Start Date, End Date, and Occurrence of Hair Loss. Detailed cancer history will include time since diagnosis, cancer type, planned taxane, and confirmation of ECOG status. General medical history will be coded by MedDRA preferred term and body system, and will be summarized.

7.4.3 Concomitant medications

Concomitant medications will be summarized by dose cohort and overall.

7.5 Safety and Tolerability

Safety endpoints include treatment-emergent adverse events (AEs) and CFB for vital signs, physical examinations, and laboratory tests. All safety data will be listed. Listings of deaths, SAEs, DLTs, and AEs leading to early termination of study treatment will also be provided.

7.5.1 Adverse events

The original reported (verbatim) terms used by the Investigator to identify adverse events will be entered into the database and coded by Preferred Term using the MedDRA coding dictionary. Adverse events will then be grouped by MedDRA Preferred Term into frequency tables according to System Organ Classification (body system).

Adverse events that started after the initiation of treatment (on or after the day of the baseline visit) and those that were present at Baseline and increased in severity during the treatment period will be considered as treatment-emergent adverse events. Events ending prior to the day of the baseline visit and events present at Baseline that do not increase in severity during treatment will be considered as medical history and will not be included in the presentation of treatment-emergent adverse events.

The following AE will be produced:

- All treatment-emergent AEs;
- Treatment-emergent AEs by relatedness;
- Treatment-emergent AEs by severity (CTCAE grade);
- Serious treatment-emergent AEs;
- Grade 3 or higher treatment-emergent AEs
- Treatment-emergent AEs of special interest;
- Common treatment-emergent AEs by cycle.

The number and percentage of patients experiencing treatment-emergent adverse events will be presented for the Safety Population for each body system and preferred term by treatment group. Treatment-emergent adverse events will also be summarized for each severity, and relationship to study medication. When an adverse event occurs more than once, the maximum severity and causality will be counted. Deaths, serious adverse events, DLTs, and discontinuations due to an adverse event will be provided in separate listings for the Safety Population.

The maximum grade of the following adverse events of special interest will be summarized in separate tables:

Common side effects
- Pruritus
- Skin discomfort
- Skin stinging or burning
- Eye irritation or stinging

Less common side effects
- Scalp xerosis and flaking
- Erythema
- Irritant dermatitis

Rare but serious side effects
- Hypercalcemia
- Hypercalciuria
- Renal stones
- Increased thirst
- Increased frequency of urination
- Changes in pulse
- Weakness
- Drowsiness
- Bone pain
- Renal Insufficiency

Common side effects will be reported by cycle and grade in separate tables. The rest will be reported in a table of AEs of special interest.

7.5.2 Dose-Limiting Toxicity (DLT)

Toxicities will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE v 4.0). 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 topical Compound 31543 and not the taxane-based regimen as best determined by investigators.

7.5.3 Laboratory Assessments

Laboratory variables will be examined using CFB at each time point for the Safety Population by dose cohort. A summary of laboratory values categorized according to the CTCAE v4.0; categorized by the worst on-study toxicity grade, dose cohort, and cycle. Laboratory variables with CTCAE grading for both low and high values will have both reported separately; e.g., glucose will be reported as hypoglycemia and hyperglycemia. Laboratory variables without CTCAE grading will be presented to show the number and percent of subjects with high, normal, and low (or normal/abnormal) laboratory results by cycle. The laboratory assessments are given in Appendix A.

7.5.4 Pharmacokinetics

Details and results of the PK analyses will be presented in a separate document.

7.5.5 Vital Signs

Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats/min), respiration rate (breaths/min), temperature (°C), and weight (kg), and CFB in each vital sign, will be listed and summarized for the Safety Population by cohort and visit. Height will be recorded and included in listings only.

7.5.6 Physical Examinations

Physical examination findings (normal or abnormal) for each body system will be listed.

7.6 Efficacy

All efficacy assessments will be provided for the FAS and the Evaluable Population.

7.6.1 Subjective record of hair and scalp

Summary statistics for Questions 1a, 1b, and 1c (related to fullness, thickness, and volume) and frequencies for Questions 2 and 3 (Yes / No for hair falling out and hair thinning) will be provided for the FAS by cohort and visit. Summary statistics for Questions 5a, 5b, and 5c (related to comfort with the study drug, overall confidence in hair condition, and overall feeling regarding health of a scale of 1-10) will be provided for the FAS and the Evaluable Population by cohort and visit.

7.6.2 Photographic record of hair and scalp

Global photographic review will be conducted by one dermatologist reviewer and photographs will be evaluated using a 7-point evaluation scale given in the following table.

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

The reviewer will compare the photographs acquired at baseline, Week 7 and Week 15. Photographs acquired at Week 27 and Week 54 will be assessed in a similar manner, 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. Summary statistics for photographic assessments will be provided for the FAS and the Evaluable Population by cohort and visit. Summary statistics for photographic assessments will be provided for the FAS and the Evaluable Population by cohort and visit.

7.7 Interim Analysis

The Cohort Review Committee (CRC), comprised of the Berg medical monitor, Berg Pharma Clinical & Regulatory Consultant, 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 cohort will also be reviewed by the CRC and considered in any decision to escalate the dose. 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 (e.g., observation of non-linear PK, AEs in subjects who receive more than one dose of topical Compound 31543). The decision to proceed with the next cohort will require unanimous agreement of the members of the CRC.

8 DATA HANDLING

8.1 Data Calculations and Definitions

8.1.1 Baseline Values

A patient's Baseline value will be the last measurement taken before initiation of treatment.

8.1.2 Change from Baseline (CFB)

CFB will be calculated at each post-baseline visit for non-missing continuous data as:

CFB = Post-Baseline value – Baseline value.

8.2 Missing Data

There will be no imputation of missing data.

9 CHANGES FROM THE PROTOCOL

No changes in the analyses described in the protocol are planned. If changes are made prior to completion of the study, this document will be amended and such changes will be described. Any changes in the analyses made after completion of the study will be noted in the study report.

10 APPENDIX A – LABORATORY TESTS

The following laboratory tests will be performed Pre-Study and at Weeks1, 3, 5, 7, 11, 15, 27 and 54.

CBC WITH DIFF	COMPREHENSIVE CHEMISTRY PANEL
WBC	Albumin
Platelet Count	Alkaline phosphatase
Hemoglobin	ALT (SGPT)
RBC	AST (SGOT)
Hematocrit	Blood urea nitrogen (BUN)
MCV	Calcium
MCH	Carbon Dioxide
MCHC	Chloride
RDW	Creatinine
Lymphocytes	Glucose
Monocytes	Potassium
Neutrophils	Sodium
Eosinophils	Total bilirubin
Basophils	Total protein
Large Unstained Cells (LUC)	
Absolute Neutrophil Count	
Absolute Lymphocyte Count	
Absolute Monocyte Count	
Absolute Eosinophil Count	
Absolute Basophil Count	
Absolute Large Unstained Cells	

APPENDIX A– LABORATORY TESTS (Continued)

URINALYSIS	MICROSCOPIC URINALYSIS
Specific Gravity	RBC, Urine
Color	WBC, Urine
Clarity	Epithelial
pH, Urine	Crystals, Urine
Albumin, Urine	Casts
Glucose, Urine	Bacteria
Ketones, Urine	Yeast
Bilirubin, Urine	Small Round Cells
Blood, Urine	Pathological Casts
Urobilinogen, Urine	Sperm
Leukocyte Esterase, Urine	Other
Nitrite, Urine	