STATISTICAL ANALYSIS PLAN

Study Title:	**A Randomized, Double-Blind, Vehicle-Controlled, Parallel-Group Phase 2 Study of the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of RTA 408 Lotion in the Treatment of Patients at Risk for Radiation Dermatitis**
Name of Test Drug:	RTA 408 Lotion
Indication:	Radiation Dermatitis
Sponsor:	Reata Pharmaceuticals, Inc.
Protocol No.:	RTA 408-C-1306
Protocol Version/Date	Version 4.0 (October 17, 2014)
Author Biostatistician:	[redacted]
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CONFIDENTIAL AND PROPRIETARY INFORMATION

SPONSOR APPROVAL

A Randomized, Double-Blind, Vehicle-Controlled, Parallel-Group Phase 2 Study of the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of RTA 408 Lotion in the Treatment of Patients at Risk for Radiation Dermatitis

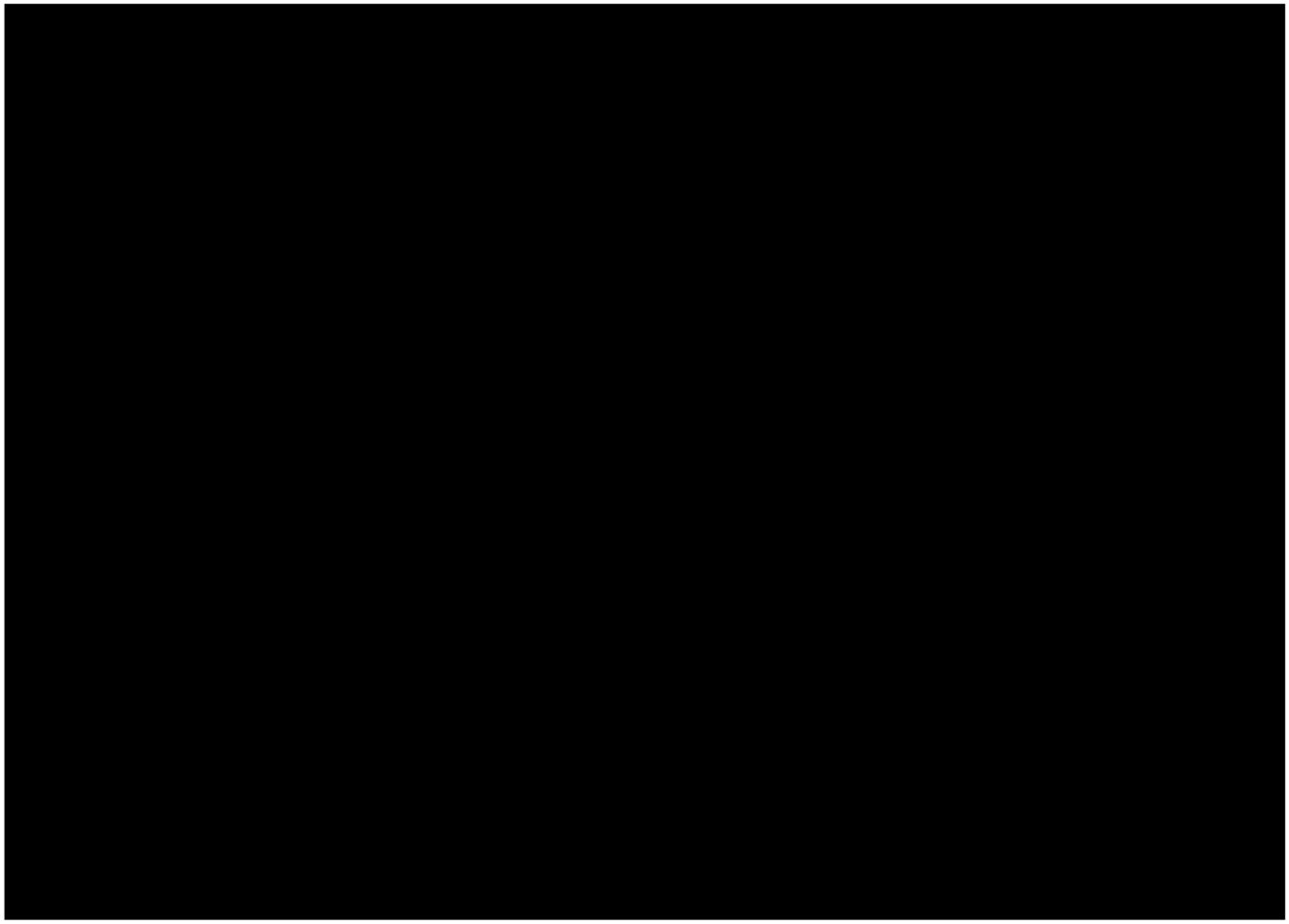

TABLE OF CONTENTS

1. INTRODUCTION

Study 408-C-1306 is a randomized, double blind, vehicle-controlled, parallel-group Phase 2 study designed to study the efficacy, tolerability and safety of two concentrations of RTA 408 Lotion (3% and 0.5%) versus vehicle in patients with breast cancer for whom radiation is recommended. This document describes the statistical analysis methods and data presentations that Reata Pharmaceuticals, Inc. (Reata) will use to analyze data from the study. [redacted], [redacted] is the blinded study statistical group responsible for conducting the analyses described in this document. [redacted] will remain blinded to study treatment assignments until after the database is locked. Study related documents include the study protocol and case report form.

This version of the SAP describes the analyses planned prior to the database lock. Unless otherwise specified, the analyses described in this document will be performed after database lock for inclusion in the final clinical study report (CSR). Any substantive changes made to the statistical analysis plan after database lock will be clearly documented and a justification will be given in the CSR.

This SAP is based on Version 4 of the study protocol dated October 17, 2014. If the protocol is subsequently amended, this SAP may be amended as well. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing. All analyses will be conducted using SAS version 9.2 or higher.

1.1 Study Objectives

1.1.1 Primary Objectives

The primary objectives of this study are the following:

- To determine the time-averaged (averaged effect over time) effect on radiation dermatitis grade measured with Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03) following 3D conformal radiation therapy to the breast and concomitant administration of RTA 408 Lotion (0.5% and 3%) compared to administration of vehicle.
- To evaluate the safety of RTA 408 Lotion

1.1.2 Secondary Objective

The secondary objectives of this study are the following:

- To determine the mean maximum radiation dermatitis grade measured with CTCAE of RTA 408 Lotion (0.5% and 3%) on weekly visits compared to administration of vehicle
- To determine the proportion of patients with treatment success, defined as post-baseline maximum dermatitis grade < 2 using the CTCAE criteria following administration of RTA 408 Lotion compared to administration of vehicle
- To determine the mean duration of grade ≥ 2 radiation dermatitis using the CTCAE criteria following administration of RTA 408 Lotion compared to administration of vehicle
- To determine the extent of systemic exposure to RTA 408 following administration of RTA 408 Lotion following radiation therapy

- To evaluate patient-reported outcomes (Skindex-16)

1.2 Study Design

This randomized, double-blind, vehicle-controlled, parallel-group study will assess the safety, tolerability and efficacy of RTA 408 Lotion (0.5% or 3%) versus vehicle in the treatment of patients at risk for radiation dermatitis. Eligible patients will be randomized using a 1:1:1 assignment ratio to receive RTA 408 Lotion 0.5%, RTA 408 Lotion 3%, or vehicle 1 week (± 2 days) prior to initiation of radiation therapy. Randomization will be stratified by smoking status (smoker or ex-smoker versus non-smoker) and breast cancer treatment prior to radiation therapy (mastectomy versus lumpectomy/partial mastectomy).

Study drug application will start approximately 1 week prior to scheduled initiation of radiation therapy with twice daily applications continuing throughout the duration of radiation therapy (i.e., 5-6 weeks) and two weeks following completion of radiation therapy, for an expected total of up to 9 weeks of study drug application. In cases where radiation treatment is delayed (e.g., delayed start of radiation treatment or radiation treatment interruptions), the total study drug application period may be extended from the expected 8-9 weeks up to a maximum of 13 weeks. Study lotion is to be applied twice daily.

On days of morning radiation treatments, the patient will apply the study drug at the radiation treatment center immediately after the radiation therapy concludes and at night before bed. On days of afternoon radiation treatments, the patient will apply the study drug in the morning at least 4 hours before radiation treatment and at night before bed. For each application of study drug treatment, a thin layer of lotion will be applied to the irradiated area. RTA 408 Lotion or vehicle lotion should never be applied immediately before radiation treatment, and any residual lotion from a prior application should be removed prior to radiation treatment.

Following randomization, patients will be assessed in person at weekly visits during administration of study treatment. A follow-up visit will occur 4 weeks after last application of RTA 408 Lotion or vehicle. Due to the variation in radiation treatment schedules, exact study days or procedures may be shifted to fall within a window of 2 days based on radiation treatment schedules. However, all enrolled patients must continue to apply RTA 408 Lotion for two weeks after the completion of radiation. If a radiation therapy treatment break is extended beyond 5 days, the medical monitor should be consulted to determine if application of study drug should continue.

1.2.1 Study Visits and Assessments

Detailed overall schedule of assessments for the study are included in Appendix 1.

1.2.2 Discontinuation of Treatment

Discontinuation refers to a patient stopping administration of study drug. Reasons for study drug discontinuation may include the following:

- Occurrence of an adverse event or change in medical status that leads the investigator to be concerned about the patient's welfare
- Noncompliance with study procedure
- Pregnancy during the study

- Investigator unblinding of patient

Patients who are discontinued from study drug should still attend all study visits and undergo all study assessments, if possible.

1.2.3 Patient Termination

Termination refers to a patient stopping study drug and all study assessments and visits. Reasons for study termination include the following:

- Failure to return for follow-up
- Death
- Withdrawal of consent
- Investigator decision

Patients who terminate the study for any reason may not re-initiate study drug at any time.

1.2.4 Randomization and Blinding

The study will be conducted using double-blind procedures with limited access to the randomization code. Patients will be randomly assigned to RTA 408 Lotion 0.5%, 3% or vehicle using a 1:1:1 assignment ratio. Randomization will be stratified by smoking status (smoker or ex-smoker versus non-smoker) and breast cancer treatment prior to radiation therapy (full mastectomy versus partial mastectomy or lumpectomy). Randomization occurs approximately one week prior to the start of radiation treatment (Day 1).

In this double-blind study all patients, investigators, site personnel and laboratories with direct involvement in the conduct of the study or their designees will be blinded to treatment assignments. Appropriate measures will be taken to ensure the blind is maintained for the patients and personnel mentioned previously to reduce potential bias. To maintain the blind, blinded study drug kits will be distributed to patients as directed by the IWRS. Treatment assignments will be managed by an IWRS system. Additionally, some Sponsor personnel who are not part of day-to-day activities will be unblinded to individual treatment assignments.

1.3 Sample Size and Power

2. PLANNED ANALYSIS

2.1 Final Analysis

The randomization will be released and final analysis will be conducted after all patients have completed the study and the database has been locked.

2.2 Endpoint Measures

2.2.1 Efficacy Endpoints

The primary efficacy endpoint is dermatitis grade (CTCAE v4.03).

The secondary efficacy endpoints are mean maximal dermatitis grade, proportion of patients with maximal dermatitis grade < 2, duration of CTCAE grade ≥ 2, proportion of patients who develop moderate erythema, the proportion of patients who develop dry desquamation and the proportion of patients who develop moist desquamation.

2.2.2 Radiation Dermatitis Assessment

The CTCAE v4.03 radiation dermatitis grade will be assessed by a local, trained physician, nurse or appropriately trained site staff member. Radiation dermatitis scoring will be evaluated as follows (National Cancer Institute, 2010):

CTCAE Radiation Dermatitis Grade

Grade 0	No radiation dermatitis
Grade 1	Faint erythema or dry desquamation
Grade 2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
Grade 3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
Grade 4	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Grade 5	Death

Components of the CTCAE radiation dermatitis grade will be recorded separately by a local, trained physician, nurse or appropriately trained site staff member. These components include: the severity of erythema, the extent and severity of dry desquamation, the extent and severity of moist desquamation, the presence of edema.

2.2.3 Safety Endpoints

Safety endpoints include vital sign measurements, results of physical examinations, laboratory test results (clinical chemistry, hematology, urinalysis and microscopy), concomitant medications, adverse events, and serious adverse events.

2.2.4 Pharmacokinetics Endpoints

Pharmacokinetics endpoints include RTA 408 plasma concentration data for each analyte.

2.3 Changes from Protocol-Specified Analysis

There are no planned changes to analyses from what is described in the protocol.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

3.1 Analysis Considerations

All individual data will be listed as recorded in the database. All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

Only patients in the appropriate analysis set will be included in summary statistics. For endpoints discussed in this SAP, all available data from scheduled visits for each patient will be included in summaries.

Individual patient data will be presented in data listings. The listings will include all available data for all patients.

Continuous data will be summarized by treatment using descriptive statistics (number, mean, standard deviation [SD], minimum, median, and maximum). Categorical data will be summarized by treatment using frequency tables (number and percentage).

3.2 Analysis Populations

Additional analysis populations may be defined as needed.

3.2.1 Intent-to-treat Population (ITT)

The intent-to-treat (ITT) population includes all randomized patients whether or not they received study drug. Patients will be summarized according to the treatment to which they were randomized.

3.2.2 Safety Population

The safety population includes all patients who received at least 1 dose of study drug. Patients will be summarized according to the treatment they actually received.

3.3 Strata and Covariates

Randomization is stratified by smoking status (smoker or ex-smoker versus non-smoker) and breast cancer treatment prior to radiation therapy (full mastectomy versus partial mastectomy or lumpectomy).

Smoking status and breast cancer treatment prior to radiation therapy will be used as covariates in the primary efficacy analysis.

No other covariates will be considered for the primary analysis. However, other covariates may be considered in a post hoc manner.

3.4 Examination of Patient Subsets

Subsets of interest include: (1) smoking status (current or previous smoker vs never smoked), (2) breast cancer treatment prior to radiation therapy (breast conservation vs mastectomy), (3) chest wall separation (≤23 cm vs>23 cm), and (4) breast volume (>1200 cc vs ≤1200 cc) for breast conservation patients. Other subsets of interest may be defined as needed.

3.5 Multiple Comparisons

To maintain control of the family-wise error (FWE) rate at the alpha = 0.05 level with respect to the primary endpoint, a fixed sequential step down test procedure will be used. The first step is to compare RTA 408 Lotion pooled versus vehicle lotion for the primary endpoint. If significant at the 0.05 level, the second step of the test is to compare RTA 408 Lotion 3.0% versus vehicle lotion for the primary endpoint. If significant at the 0.05 level, the third step of the test is to compare RTA 408 Lotion 0.5% versus vehicle lotion for the primary endpoint. No other adjustments for multiplicity will be considered.

3.6 Missing Data

Missing data will not be imputed for safety endpoints. Missing efficacy endpoints will be imputed using the worst-observation reported for each patient. Sensitivity analyses for efficacy endpoints will be performed with no imputation for missing data. Additional sensitivity analyses may be considered as needed.

3.7 Visit Windows

3.7.1 Definition of Study Day

Study day is the day relative to the first dose of study drug administration. Study day for events on or after the date of the first dose will be defined as the number of days from the date of the first dose of study drug, plus 1 day, so that the date of the first dose will be defined as Day 1.

For events before the date of the first dose, study day will be calculated as the difference in days between the date of the first dose and the date of interest. Thus, the day before the date of the first dose will be defined as Day -1.

3.7.2 Definition of Study Baseline

Unless otherwise noted, study baseline is defined as the last observation obtained prior to administration of the first dose on Study Day 1.

Change from baseline is defined as post-baseline assessment minus baseline assessment. The baseline value will not be used to impute the post-baseline values.

3.7.3 Unscheduled Visits

The CRF nominal study visits will be used for all safety analyses. Unscheduled visits will be reflected in summarization of changes to worst post-baseline measures.

Additionally, for missing scheduled assessments with an unscheduled assessment available after the previous scheduled visit but before the next scheduled visit, the closest unscheduled assessment will be used in the place of missing scheduled efficacy assessments

All unscheduled visits will be listed.

3.8 Rounding

The method of rounding for data presentation is provided in Appendix 3.

4. BASELINE CHARACTERISTICS AND PATIENT DISPOSITION

4.1 Disposition of Patients

A disposition summary will include:

- Number and percentage of patients randomized in each cohort
- Number and percentage of patients in the safety analysis set
- Number and percentage of patients completing treatment
- Number and percentage of patients discontinuing treatment
- Number and percentage of patients by reason for discontinuing treatment
- Number and percentage of patients completing study
- Number and percentage of patients terminating study
- Number and percentage of patients by reason for terminating study

Disposition summaries will be presented by randomized treatment. Percentages will be based on the number of randomized patients.

A listing of patient disposition will include the randomization date, date of the last dose of study drug, study completion status, and reason for termination (if applicable).

4.2 Demographics and Baseline Characteristics, Baseline Disease Characteristics, and Radiation Treatment Plan

Demographic and baseline characteristics summaries, for patients in the safety analysis set, will include:

- Age (years at study baseline)
- Sex
- Race
- Ethnicity
- Smoking status
- Fitzpatrick skin Type

Baseline disease characteristics will be provided in a separate summary. Continuous statistics will be provided for:

- Time since diagnosis (years)
- Time since surgery (days)

- Breast volume after surgery (cc)
- Chest wall separation (cm)

Frequency tables (number and percentage) will be provided for discrete measures:

- Breast cancer treatment prior to radiation therapy
- Breast cancer stage
- T/N/M clarification
- Post-mastectomy reconstruction
- Prior receipt of radiation treatment

Radiation treatment plan will be provided in a separate summary. Continuous statistics will be provided for:

- Total planned radiation (Gy)
- Total planned radiation boost (Gy)
- Total radiation (regular + boost) (Gy)
- Planned bolus use (days)
- Radiation treatment surface area (cm^2)
- Radiation inhomogeneity (%)

Frequency tables (number and percentage) will be provided for discrete measures:

- Planned radiation treatment area

All will be summarized by randomized treatment group without stratification and stratified by smoking status and breast cancer treatment prior to radiation therapy, respectively.

4.3 Study Drug Exposure

Study treatment exposure (i.e. RTA 408 Lotion 0.5%, RTA 408 Lotion 3%, or vehicle lotion), including treatment duration will be summarized by treatment group with descriptive statistics. Similarly, the incremental and cumulative radiation exposure will be summarized by treatment group. The number of patients with interruptions in radiation treatment due to radiation tolerability will be tabulated overall and by study visit. Total study treatment exposure for each patient is calculated as follows: (last date of study treatment) – (first date of study treatment) +1. Additionally, treatment compliance will be summarized, and the number of treatment compliant patients (i.e., ≥75% compliant with dosing) will be tabulated. Compliance is calculated as [(total exposure days) – (total missed doses)] / (total exposure days).

4.4 Inclusion and Exclusion Criteria

A listing will be provided for all randomized patients who did not meet all study entry criteria as defined by inclusion and exclusion criteria.

4.5 Medical History

Medical history will be coded using MedDRA, version 16.0 or higher. Medical history will be summarized by SOC and PT, and will be presented by treatment. Percentages will be based on the number of patients in the safety analysis set. Medical history tables will be sorted alphabetically and all data will be listed chronologically.

4.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary (December, 2012) for anatomical therapeutic chemical classification (ATC) and preferred drug name. A patient who used multiple medications will be counted only once for each ATC and preferred drug name. ATC and preferred drug name within each ATC will be sorted alphabetically. Coded prior and concomitant medications will be summarized by treatment. Percentages will be based on the number of patients in the safety analysis set.

Prior medications are defined as those medications disclosed as not being taken on Study Day 1 on the CRF, with an onset date prior to the date of randomization. Concomitant medications are defined as any medications that was either taken on or after Study Day 1, or was started before Study Day 1 but was ongoing at time of the first dose administration.

4.7 Protocol Deviations

Protocol deviations as captured on the CRF will be listed. All protocol deviations will be reviewed by the Sponsor according to their SOPs. Major protocol deviations will be identified by the Sponsor prior to database lock, and will be flagged in the listing.

5. EFFICACY ANALYSIS

The primary population for efficacy analyses will include all randomized patients in this trial (intent-to-treat population, ITT population). The ITT analysis will be done by randomized treatment, and for each patient subset of interest defined in section 3.4.

Summary statistics will be presented by randomized treatment group, and will include an additional column to summarize the pooled RTA 408 patients.

5.1 Primary Efficacy

The primary efficacy outcome of this study is the radiation dermatitis grade measured with Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03) following 3D conformal radiation therapy to the breast and concomitant administration of RTA 408 Lotion (0.5% and 3%) compared to administration of vehicle. Radiation dermatitis scoring is assessed by a local, trained physician, nurse or appropriately trained site staff member based on CTCAE v4.03 on a scale of 0 to 5 (National Cancer Institute, 2010). Following randomization, patients will be evaluated in person at weekly visits during the administration of the study treatment up to a maximum of 13 weeks.

Longitudinal mixed-models will be used to analyze the dermatitis scores over time, incorporating the repeated measures design of the study. Treatment group and week of visit will constitute the main fixed effects of the model; study subject will represent the random effect; site, smoking status, and breast cancer treatment will be evaluated for inclusion in the model as covariates. The distribution of residuals will be examined using a Shapiro-Wilks test. Interactions of time and treatment effect will also be examined in the mixed-model.

A sensitivity analysis will be performed using the same model, except cumulative radiation (expressed as a categorical variable in 2.5 Gy increments from 0 to 70 Gy) will be used as a fixed effect instead of visit week. Only those CTCAE grades collected from baseline to the last day of radiation treatment for each patient will be considered for this sensitivity analysis.

The mean CTCAE dermatitis scores will also be plotted in a scatter plot by cumulative radiation exposure overall and by patient subsets of interest.

RTA 408 treatment arms will be compared with vehicle utilizing a hierarchical testing strategy described in Section 3.6.

5.2 Secondary Efficacy

The following secondary efficacy endpoints will be analyzed for all randomized patients (i.e., ITT population). Interpretations of significance levels (i.e. P-values) will be done with caution since there is no formal control of type I error for multiple comparisons on the secondary efficacy endpoints.

5.2.1 Mean Maximum Radiation Dermatitis Grade of RTA 408 Lotion Compared to Administration of Vehicle

The first secondary efficacy endpoint is the mean maximum dermatitis grade. A maximum CTCAE grade per patient evaluated at weekly visits during the study will be identified.

Descriptive statistics will be summarized for the maximum dermatitis grade overall and by each of the subgroups of interest, breaking down by the 3 treatment groups.

An analysis of Covariance (ANCOVA) model will be conducted to compare the mean maximum dermatitis grade among the RTA408 0.5%, RTA408 3% and vehicle groups, adjusted for site, smoking status, breast cancer treatment prior to radiation therapy and total duration (in weeks) of study drug use. Pairwise RTA 408 lotion group comparisons with vehicle group will be estimated using the difference in adjusted means (and 95% confidence intervals, CI) from the ANCOVA model.

5.2.2 Proportion Patients with Post-baseline Maximum Dermatitis Grade <2 Using the CTCAE Criteria

Descriptive statistics (frequencies and percentages) by treatment groups will be provided overall and stratified by smoking status and breast cancer treatment prior to radiation therapy, respectively. In addition, logistic regression analysis will be performed to assess the dermatitis scores over time for the proportion of patients with success, where success is defined as CTCAE dermatitis score <2. The logistic regression model will include covariates for site, smoking status (smoker or ex-smoker vs non-smoker) and breast volume with fixed effects for treatment group, visit, and the interaction between treatment group and visit. To visualize the grade patterns in RTA408 groups and the vehicle group, a bar chart will be plotted for the proportions of CTCAE dermatitis scores by treatment groups and study visit.

5.2.3 Mean Duration of Grade ≥ 2 Radiation Dermatitis Using the CTCAE Criteria

The total duration is defined as the spanning from first onset date with CTCAE grade ≥ 2 to last resolved date (i.e., next dermatitis assessment date after the last grade ≥ 2). Descriptive statistics by treatment groups will be summarized for the total duration, overall and by subgroups of interest for the subset of patients with at least one CTCAE grade ≥ 2. In addition to the descriptive analyses, the mean duration across 3 treatment groups will be compared using an ANCOVA model in a similar manner to the analysis in Session 5.2.1.

5.2.4 Dermatitis Assessment

Proportion of patients who develop moderate erythema, the proportion of patients who develop dry desquamation and the proportion of patients who develop moist desquamation (according to eCRF) will be analyzed in a similar manner to the analysis in Session 5.2.2.

5.2.5 Patient-reported Outcomes (Skindex-16)

The Skindex-16 quality-of-life tool will be used to assess patient responses to skin toxicity during and after radiation therapy. The Skindex-16 is a short 16-item patient-completed assessment using numerical analogue scales (0=never bothered to 6=always bothered). Responses to the Skindex-16 are categorized into three subscales: symptom, emotional and functional. Refer to Appendix C for the Skindex-16 assessment. The Skindex-16 assessment will be scored using the tool's scoring algorithm which averages all responses for the total Skindex-16 score. Subscale scores will be calculated as follows: symptom subscale as the mean of questions 1–4, emotional subscale as the mean of questions 5–11 and functional subscale as the mean of questions 12–16.

Descriptive statistics (means and standard deviation, minimum, median, and maximum) will be summarized for the total score and each subscale score for the available patient-reported data, by treatment groups. Analysis of variance (ANOVA) will be used to compare the total and subscale scores among the three treatment groups.

6. PHARMACOKINETIC ANALYSIS

Descriptive statistics will be summarized for RTA 408 plasma concentration by treatment group overall and by patient subsets of interest.

7. SAFETY ANALYSIS

Safety data (including AEs, laboratory data, vital signs, electrocardiogram [ECG] data, echocardiogram data, and physical examinations) will be listed and summarized for patients in the safety analysis set. All safety data collected on or after the date of the first dose of study drug through completion of the study will be summarized by treatment.

The CRF nominal study visits will be used for all safety analyses. Unscheduled visits will be reflected in summarization of changes to worst post-baseline measures where appropriate.

7.1 Adverse Events

New or worsening radiation dermatitis signs/symptoms should not be captured as individual AEs, but rather are captured in the Dermatitis Assessment documentation as these signs/symptoms are being assessed as study endpoints.

AEs will be summarized by treatment as defined by the safety analysis set.

7.1.1 General Considerations for Analysis of Adverse Events

General considerations for AE summaries and calculations are:

- Multiple events by preferred term (PT) and system organ class (SOC) will be counted once only per patient for each treatment.
- For summaries by severity, only the most severe event will be counted per patient for each treatment.
- For summaries by relationship, only the most related event will be counted per patient for each treatment.
- An AE with a missing resolution date or incomplete date that is not identified as continuing will be assumed to be continuing and no duration will be calculated.
- AEs will be summarized by the highest dose received.
- Only treatment-emergent adverse events (TEAEs) will be included in summaries.

7.1.2 Adverse Event Dictionary

AEs will be coded using MedDRA® (Medical Dictionary for Regulatory Activities) version 16.0 or higher. Tables and listings will present data at the SOC and PT level.

7.1.3 Treatment-Emergent Adverse Events

7.1.3.1 Definition of Treatment-Emergent

Treatment-emergent adverse events are events that either:

- Date of onset on or after the date of the date of first dose and not more than 30 days after the date of the last dose of study drug, or
- Had no recorded date of onset with a stop date after the first dose of study drug, or
- Had no recorded date of onset or stop date

7.1.3.2 Incomplete Dates

If the date of onset is incomplete, then the month and year of onset (or year alone if month is not recorded) determines whether the event is treatment-emergent. The event is treatment-emergent if the month and year of onset (or year of onset) of the event is:

- The same as or after the month and year (or year) of the first dose of study drug, and
- The same as or before the month and year (or year) of the date of the last visit.

7.1.4 **Adverse Event Severity**

The investigator will grade the severity of the AEs as Grades 1, 2, 3, 4, or 5 based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

7.1.5 **Relationship of Adverse Events to Study Drug**

Association or relatedness to the study medication will be graded by the investigator as either probably, possibly, unlikely, or unrelated according to criteria specified in the study protocol.

7.1.6 **Serious Adverse Events**

As defined in the protocol and captured on the CRF, an SAE is an adverse event that results in any of the following:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in a congenital anomaly or birth defect in an offspring of a patient taking study drug;
- Is an important medical event.

7.1.6.1 Summaries of Adverse Events

Treatment-emergent AEs will be summarized by treatment at onset of the AEs. For each treatment, SOC, and PT, the number and percentage of patients reporting an event will be calculated. In summary tables, SOC will be presented alphabetically and events within SOC will be presented by decreasing frequency count based on the number of events in the total group.

Summary tables (number and percentage of patients) of AEs (by SOC and PT) will be provided by treatment as follows:

- All treatment-emergent AEs
- All treatment-emergent related AEs (probably or possibly related)
- All treatment-emergent AEs by severity
- All treatment-emergent serious adverse events (including deaths)
- All treatment-emergent adverse events leading to discontinuation of study drug

Listings will be provided showing:

- All AEs

- Serious adverse events (including deaths)
- AEs leading to discontinuation of study drug

7.1.6.2 Additional Analysis of Adverse Events

No additional analysis of AEs is planned.

7.2 Clinical Laboratory Evaluations

Laboratory data will be summarized at baseline and at each time point by treatment. Only values obtained at scheduled assessment times will be included in by-visit summary statistics. When appropriate, change from baseline to worst post-baseline (including unscheduled visits) value will be summarized. Specific assessment times are given in Appendix 1 of this analysis plan.

Continuous laboratory data results which are less than the lower limit of quantification or above the upper limit of quantification will be imputed to the value of the lower or upper limit plus or minus one significant digit, respectively (e.g., if the result of a continuous laboratory test is < 20, a value of 19 will be assigned). A baseline value is defined as the last available measurement obtained prior to administration of the first dose. If multiple values for a given lab test exist for a particular day, the last one drawn will be used for summarization.

7.2.1 General Considerations for Analyses of Laboratory Data

Clinical laboratory results will be provided by a central lab. Clinical laboratory test results, including results from hematology, chemistry and urinalysis will be listed by patient.

7.2.2 Summaries of Laboratory Results

Selected laboratory evaluations and change from baseline will be summarized by treatment, laboratory category (hematology, chemistry), test, and study visit using continuous statistics. Laboratory tests to be summarized are provided in Appendix 2.

Due to the nature of urinalysis parameters, summaries of continuous statistics will not be provided.

7.2.3 Laboratory Abnormalities

Laboratory results are not captured on the CRF. All flags with respect to normal or abnormal results will be identified by the central lab.

7.2.4 Treatment-Emergent Abnormalities

Treatment-emergent laboratory abnormalities are defined as values with any shift from a normal at baseline (Day 1) to abnormal at any time post-baseline up to and including the last dosing date. Additionally, a shift from a low non-normal baseline value to a high non-normal post baseline value (and vice versa) will also be considered treatment emergent. If the relevant baseline laboratory values are missing, then any abnormality will be considered treatment emergent.

7.2.5 Summaries of Laboratory Abnormalities

The number and percentage of patients with laboratory normality and abnormality categories (Normal, Low, High) as well as the treatment-emergent shift will be summarized by treatment, laboratory category (hematology, chemistry, and urinalysis), test, and study visit. In addition to

by-visit frequencies, the most abnormal (low or high separately) as well as the shift to most abnormal (low or high) will be summarized.

7.3 Vital Signs

Vital signs assessments include systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg), oral body temperature (°C), heart rate (HR, bpm), respiration rate (RR, breaths/min), height (m), weight (kg), and BMI (m2/kg).

Vital signs will be summarized at baseline and at each time point along with the change from baseline by treatment. Only values obtained at scheduled assessment times will be included in by-visit summary statistics. Specific assessment times are given in Appendix 1 of this analysis plan. All data will be listed.

8. REFERENCES

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9. APPENDICES

Appendix 1. Overall Schedule of Assessments

Appendix 2. List of Laboratory Tests

Appendix 3. Programming Specifications

Appendix 1. Overall Schedule of Assessments

Assessment	Screening Period	Randomization and Run In Period	Day 1 of Radiation Treatment	Concurrent with RT					Last day of RT	After RT	Last day of Study Drug	ET / Follow-up
Study Visit	1[a]	2[b]	3[c]	4[d]	5[d]	6[d]	7[d]	8[e]	9[e]	10[f]	11[g]	12[h]
Visits or Visit Procedures may fall within a window of ±2 days for a total of 2 days[i]	Up to 45 days	Randomization Visit - First Day of Study Lotion Application for Run-In Period 7 days prior to RT[b]	RT WK 1[c]	RT WK 2	RT WK 3	RT WK 4	RT WK 5	RT WK 6	Last Day of RT[d]	Post-RT WK 1	Post-RT WK 2 / End of Study Drug Administration	Post-RT WK 6/ ET / Follow-up Visit
Informed consent	X											
Inclusion/ Exclusion	X	X										
Demographics and baseline disease characteristics	X											
Fitzpatrick skin type	X											
Prior and Concomitant medications	X	X	X			X			X		X	X
Medical history[j]	X											
Height	X[k]											
Weight and BMI	X[k]					X			X			X
Vital signs	X[k]					X			X		X	X
Physical exam	X[k]											X
Smoking status	X											
Chest wall separation	X											
Measurement of radiation treatment skin surface area[l] (Prior to RT)	←----------X[l]----------→											
Breast volume (lumpectomy and breast-conserving surgery patients)[m]	X											
Randomization		X										
Pregnancy test WOCBP[n]	X[v]	X			X					X		X
Dispense/ Weigh study drug[o]		X				X			X			
Study drug application/diary[p]		←----------X----------→										
Collect / Weigh study drug						X			X		X	
Radiation treatment[q]			X	X	X	X	X	X	X			
Dermatitis assessment[r]			X	X	X	X	X	X	X	X	X	X
Skindex-16 assessment[s]			X						X		X	X
Adverse event collection		X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry	X[t]					X			X		X	X
Hematology	X[t]					X			X		X	X
Urinalysis and microscopy	X[t]					X			X		X	X
PK sample[u]			X			X			X		X	X
Photograph collection			X[v]						X[v]		X	X
End of Study												X

[a] The Screening Period (Visit 1) may last up to 45 days prior to Randomization (up to 52 days prior to Day 1 of RT).

[b] Visit 2 (7 days prior to radiation treatment) is the day of randomization and application of the first dose, and must occur at least 5 and no more than 9 days prior to the first day of radiation treatment. If the start of radiation treatment is delayed, patients should continue administering study drug twice daily until the first dose of radiation up to a maximum of 14 days. If the time from randomization to first dose of radiation exceeds 14 days, the medical monitor should be contacted to decide on an appropriate action. Patients may be randomized after meeting the inclusion / exclusion criteria and before study drug lotion is first administered as long as patients apply study drug lotion for at least 5 days prior to the first day of radiation treatment. Patients with either morning or afternoon randomizations may apply lotion in the clinic and again before bedtime for two doses on that day.

[c] Visit 3 should occur on the day of the first radiation treatment. If radiation treatment is in the morning, the radiation treatment will be the third to last procedure (radiation treatment > study drug application > PK). If radiation treatment is in the afternoon, radiation treatment will be the second to last procedure, and the last procedure will be PK, as study drug will have been applied at least 4 hours prior to radiation treatment.

[d] Study visits during radiation treatment therapy must occur weekly beginning with Day 1 of radiation treatment.

[e] At the end of radiation treatment, patients must complete Visit 9 assessments. Visit 9 must be the last day of the 10 – 16 Gy boost. Visit 8 is needed for patients who require radiation therapy for 6 weeks. If radiation therapy is extended longer than 6 weeks, then assessments at Visit 8 should be repeated weekly until the end of radiation visit (Visit 9). A weekly study visit should not be performed if the visit falls 1 or 2 days prior to the last day of radiation (Visit 9), or 1-2 days after the last day of radiation.

[f] Visit 10 should occur approximately 1 week (7 calendar days) after the completion of radiation therapy (Visit 9).

[g] Visit 11 should occur approximately 1 week (7 calendar days) after Visit 10 (*i.e.*, 2 weeks after the completion of radiation therapy).

[h] Follow-up visit will occur approximately 4 weeks after the final study drug application. These procedures should be performed at the end of study and for early termination.

[i] The ±2 day window is a two-day allowance within which the visit or visit procedures may occur around the scheduled visit date.

[j] Medical history includes collection of surgery type (lumpectomy, partial mastectomy (breast conserving surgeries), or full mastectomy). If the patient is to undergo post-mastectomy reconstruction before radiation treatment, the type of reconstruction should be recorded as well.

[k] Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent if done within the screening timeframe, and if the site's IRB is in agreement.

[l] The radiation treatment area surface measurements can occur at any time before first day of radiation treatment.

[m] Breast volume measurements are required for all patients who had breast conserving surgery (lumpectomy or partial mastectomy). Breast tissue should be defined per the RTOG contouring guidelines (RTOG 2009), but sites may use their local SOP for calculating breast volume.

[n] A serum pregnancy test will be performed at Screening for WOCBP or at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests, unless site/local authority mandates serum pregnancy testing.

[o] Study drug is to be dispensed to the patients at the scheduled study visits. Additional study drug will be dispensed to patients based on patient need, and will be recorded as an unscheduled study drug dispensation. Study drug (bottle + lotion) is to be weighed before study drug dispensing.

[p] When radiation treatment overlaps with study drug administration and radiation treatment is in the morning, RTA 408 Lotion or vehicle should be applied to the breast area immediately after radiation treatment concludes. If radiation treatment is in the afternoon, RTA 408 Lotion or vehicle should be applied at least 4 hours before radiation treatment. RTA 408 Lotion or vehicle should also be applied nightly.

[q] Planned radiation treatment must be no more than 7.5 weeks.

[r] Radiation dermatitis assessments must be performed PRIOR to initiation of that day's radiation treatment, and only by a trained evaluator. If radiation treatment is delayed or extended, dermatitis assessments should be performed weekly until the end of radiation treatment.

[s] The Skindex-16 must be completed prior to initiation of that day's radiation treatment.

[t] Screening lab assessments for chemistry, hematology, urinalysis, and serum pregnancy tests should be drawn ≤ 14 days prior to randomization in order to have current values for inclusion/exclusion assessment.

[u] A single PK collection will be obtained on Visit 3, Visit 6, Visit 9, Visit 11 and Visit 12. If patients are to receive a morning radiation treatment on any of these visits, the PK sample should be drawn after RTA 408 Lotion or Vehicle Lotion application, which occurs after the completion of radiation treatment. If patients are to receive an afternoon radiation treatment on any of these visits, the PK sample should be drawn after the radiation treatment.

[v] Optional photographs may be collected at Sponsor-qualified sites. On Day 1 of radiation treatment and the last day of radiation treatment, photographs must be collected prior to radiation treatment.

Appendix 2. List of Laboratory Tests

Blood samples will be collected throughout the study for hematology, chemistry, and urinalysis for clinical laboratory evaluation.

Test panels will include the following:

Hematology	Chemistry	Urinalysis
Hematocrit	Blood urea nitrogen (BUN)	Specific gravity
Hemoglobin	Creatinine	Ketones
HbA1C	Total bilirubin	pH
Red blood cell (RBC) count	Alanine aminotransferase (ALT)	Protein
White blood cell (WBC) count	Aspartate aminotransferase (AST)	Blood
Neutrophils	Alkaline phosphatase (ALP)	Glucose
Bands (if detected)	Ferritin	Urobilinogen
Lymphocytes	Sodium	Bilirubin
Monocytes	Potassium	
Basophils (if detected)	Calcium	
Eosinophils (if detected)	Inorganic phosphorus	
Absolute platelet count	Magnesium	
Mean corpuscular hemoglobin (MCH)	Chloride	
Mean corpuscular volume (MCV)	Bicarbonate	
Mean corpuscular hemoglobin concentration (MCHC)	Uric acid	
Reticulocyte count	Cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	
	Creatine phosphokinase (CPK)	
	Lactate dehydrogenase (LDH)	
	High-density lipoprotein cholesterol (HDL-C)	
	Low-density lipoprotein cholesterol (LDL-C)	
	Very-low-density lipoprotein cholesterol (VLDL-C)	
	Gamma-glutamyl transpeptidase (GGT)	
	Estimated glomerular filtration rate (eGFR) using the MDRD-4 formula	

Appendix 3. Programming Specifications

Continuous data will be listed corresponding to the precision measured or calculated. Measures of central tendency will be presented using one additional decimal place than the precision of the data. Variability summaries will be presented using two additional significant digits relative to the precision of the underlying data. Quartiles, the minimum, and the maximum will be presented using the precision of the data.

All percentages are to be expressed as integers with one decimal place. The convention for rounding percentages is as follows:

- Values greater than or equal to x.x5% are rounded up
- Values between 0 and x.x5% are rounded down
- Values that are between 0 and .5% should be displayed as "<0.5%"