RTA 408

408-C-1306

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

VERSION 4.0

SPONSOR APPROVAL AND SIGNATURE PAGE

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for RTA 408. I have read the 408-C-1306 clinical study protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

2. SYNOPSIS

Name of Sponsor/Company:
Reata Pharmaceuticals

Name of Investigational Product:
RTA 408 Lotion

Name of Active Ingredient:
RTA 408

Title of Study:
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

Study center(s): Up to 35 study centers in the US

Studied period (years): < 1	**Phase of development:**
Estimated date first patient enrolled: June 2014	2
Estimated date last patient completed: May 2015	

Objectives:

Primary:

- To determine the time-averaged 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

Secondary:

- To determine the mean maximum radiation dermatitis grade measured with CTCAE of RTA 408 Lotion (0.5% and 3%) 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)

Methodology:
This double-blind, randomized, 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 and 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). 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 radiation treatment initiation 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 drug 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. 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 drug. A follow-up visit will occur 4 weeks after the last application of study drug.

Number of patients (planned):

Approximately 177 patients will be enrolled in this study with 59 patients in each of the three groups

Diagnosis and main criteria for inclusion:

Key inclusion criteria:

1. Adult female patients (18 to 80 years of age, inclusive);
2. Patients diagnosed with ductal carcinoma *in situ* or non-inflammatory breast adenocarcinoma who have been referred for post-operative radiotherapy to one breast and have had no prior radiation treatment to that breast;
3. Patients planning to undergo 3D conformal radiation therapy to the whole breast (as part of breast-conservation therapy / lumpectomy) or chest wall (as part of post-mastectomy irradiation), with or without treatment of regional lymph nodes (i.e., axillary, supraclavicular, or internal mammary), using one of the following treatment schedules:
    a. 45 – 50.4 Gy in 1.8 Gy per day, in addition to a mandatory 10-16 Gy boost
    b. 46 – 50 Gy in 2 Gy per day, in addition to a mandatory 10-16 Gy boost;
4. Patients who received breast-conservation therapy / lumpectomy must be receiving ≥ 107% of the total radiation dose (calculated from the total radiation dose including boost) to any portion of the breast, based on radiation inhomogeneity, **and/or** have a breast volume ≥ 1200 cc;
5. Female patients of childbearing potential who are willing to practice methods of birth control from screening through 1 month after applying the final dose of study drug;
6. Female patients of childbearing potential who are non-pregnant, non-lactating and have a negative pregnancy test result prior to enrollment in the study;
7. Patients willing and able to give written informed consent for study participation;
8. Patients willing and able to cooperate with all aspects of the protocol.
9. Patients for whom at least 14 days have elapsed since breast conservation surgery, mastectomy surgery and/or chemotherapy prior to randomization;
10. Have adequate hematologic and organ function at screening as follows:
    - Hematologic: Absolute neutrophil count ≥ 1.5 x 10^3 /μL, platelets > 100 x 10^9/L, hemoglobin ≥ 9 g/dL;
    - Hepatic: total bilirubin ≤ 2 times (X) upper limit of normal (ULN), ALT and AST ≤ 2X ULN;
    - Renal: serum creatinine ≤1.5 mg/dL

Key exclusion criteria:

1. Patients with TNM Classification T4 or Stage IV breast cancer;
2. Patients with prior radiation therapy to the breast treated in this study;
3. Patients with type V or VI skin according to the Fitzpatrick scale;
4. Patients with current bilateral breast cancer who are receiving radiation treatment in both breasts;
5. Patients receiving partial breast irradiation therapy;
6. Patients with uncontrolled diabetes (HbA1c > 11.0%, historical values within 6 months of screening are acceptable);
7. Patients with collagen vascular disease or vasculitis;
8. Patients with concurrent active malignancy other than adequately treated basal cell carcinoma of the skin or carcinoma *in situ* of the cervix;
9. Patients with active and not adequately treated bacterial, fungal, or viral skin infections, at the investigator's discretion;
10. Patients with known active hepatitis B or hepatitis C infection;
11. Patients who intend to use any other topical cream, lotion or preparation applied to the radiation treatment area;
12. Patients with known or suspected active drug or alcohol abuse;
13. Patients with any abnormal laboratory test value which, in the opinion of the investigator, would put the patient at risk by trial enrollment;
14. Participation in other interventional clinical studies within 30 days prior to consent;
15. Patients with known hypersensitivity to excipients in the drug product;
16. Patients receiving concomitant chemotherapy during the course of the planned radiation treatment regimen. Patients are eligible if they are receiving sequential, neoadjuvant or adjuvant chemotherapy that is not anticipated to be delivered during the time course of the radiation treatment regimen;
17. Patients unable to comply with the requirements of the study protocol or are unsuitable for the study for any reason in the opinion of the investigator;
18. Patients receiving any form of brachytherapy radiation treatment including a brachytherapy boost;
19. Patients receiving reverse-planned intensity modulated radiation treatment (IMRT).

Investigational product, dosage and mode of administration:

RTA 408 Lotion (0.5% and 3%) will be applied topically 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. 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. If patients develop grade 2 or higher radiation dermatitis and the radiation dermatitis is believed to be inadequately controlled in the opinion of the Investigator, additional topical creams, lotions, hydrocortisone or other escape medications may be prescribed and then must be documented.

Duration of treatment:

RTA 408 Lotion will be administered topically to the radiation area twice daily: prior to initiation of radiation treatment (approximately 1 week), during radiation treatment (approximately 6 weeks), and after completion of radiation treatment (2 weeks). In cases where radiation treatment is delayed (e.g., delayed radiation treatment initiation or radiation treatment interruptions), the study drug application period may be extended from the expected 8-9 weeks up to a maximum of 13 weeks.

Reference therapy, dosage and mode of administration:

Vehicle lotion will be applied topically 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. 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. If patients develop grade 2 or higher radiation dermatitis and the radiation dermatitis is believed to be inadequately controlled in the opinion of the Investigator, additional topical creams, lotions, hydrocortisone or other escape medications may be prescribed and then must be documented.

Criteria for evaluation:

Efficacy: Time-averaged change in dermatitis grade (CTCAE v4.03), Change in mean maximal dermatitis grade, percentage of patients with maximal dermatitis grade < 2, duration of CTCAE grade ≥ 2.

Safety: Results of vital sign assessments, physical examinations, laboratory test results (clinical chemistry, hematology, urinalysis), concomitant medications, adverse events and serious adverse events

Pharmacokinetic variables: RTA 408 plasma concentration-time data

Statistical methods:

Sample size: [redacted]

Statistical analysis: A statistical analysis plan (SAP) detailing the analyses described below will be developed prior to the database lock. The SAP will serve as the final arbiter of all statistical analyses. Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation geometric mean (where applicable), frequency counts and percentages.

Primary efficacy analysis: For the primary efficacy analysis, a longitudinal mixed-model will be used to analyze the CTCAE dermatitis grades 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; smoking status, breast cancer treatment prior to radiation therapy, and other covariates (such as cumulative radiation exposure) will be evaluated for inclusion in the model as covariates. A generalized mixed model will be used as the primary longitudinal model with additional sensitivity analyses performed as appropriate. A hierarchical approach will be used for analysis of the primary endpoint to control the type I error. RTA 408 treatment arms will be compared

with vehicle utilizing a hierarchical testing strategy to control the overall type I error. The primary efficacy analyses will first test the difference between RTA 408 Lotion pooled and vehicle lotion. If the first comparison is statistically significant, RTA 408 Lotion 3.0% will be compared to vehicle lotion. Otherwise, the second comparison will not be performed or the p-value will be considered nonsignificant. Similarly, only if the second comparison is statistically significant, RTA 408 lotion 0.5% will be compared to vehicle lotion.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
3D	Three-dimensional
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BUN	Blood urea nitrogen
cc	Cubic centimeters
CFR	Code of Federal Regulations (US)
cm	Centimeter
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ET	End of treatment
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Gy	Gray
HbA1c	Hemoglobin A1c
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
hr	Hour
ICH	International Conference on Harmonization
IFNγ	Interferon-gamma
IMRT	Intensity modulated radiation treatment
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LLOQ	Lower limit of quantitation

Abbreviation or Specialist Term	Explanation
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
µg	Microgram
mL	Milliliter
µM	Micromolar
mm Hg	Millimeters of mercury
n	Number of patients
NCI	National Cancer Institute
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
ng	Nanogram
Nrf2	Nuclear factor erythroid-derived 2-related factor 2
NO	Nitric oxide
NOAEL	No observed adverse effect level
NQO1	NAD(P)H:quinone oxidoreductase 1
PD	Pharmacodynamic
PK	Pharmacokinetic
RBC	Red blood cell
RT	Radiation therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedure
STAT	Skin toxicity assessment tool
TBL	Total bilirubin
TNM	Cancer classification system based on assessment of the Tumor, lymph Nodes, and Metastases
US	United States
WBC	White blood cell
WK	Week
WOCBP	Women of child bearing potential

5. INTRODUCTION

5.1. Background on RTA 408

Natural triterpenoids, such as oleanolic acid and ursolic acid, are derived from plant extracts and have been used extensively in Asian medicine for their anti-inflammatory and anticancer properties (Liu 1995). A series of semi-synthetic triterpenoids was prepared based on the structure of oleanolic acid and tested to identify compounds optimized for their ability to inhibit the induction of nitric oxide in primary mouse macrophages treated with interferon-gamma (IFN-γ) (Honda 1999). RTA 408 is a novel oleanane triterpenoid and part of this class of compounds. Mechanistic studies have revealed that RTA 408 and the semi-synthetic triterpenoids are potent activators of nuclear factor erythroid derived 2-related factor 2 (Nrf2) and inhibitors of nuclear factor kappa light-chain-enhancer of activated B-cells (NF-κB), and thus induce an antioxidant and anti-inflammatory phenotype.

The transcription factor Nrf2 regulates the expression of numerous antioxidant and anti-inflammatory genes. Activation of Nrf2 induces the expression of a battery of cytoprotective genes, which results in a coordinated cellular effort to protect against oxidative insult, highlighted by increased anti-oxidative capacity, induction of glutathione synthesis, and conjugation and efflux of potentially harmful molecules. RTA 408 and the semi-synthetic oleanane triterpenoids are among the most potent activators of Nrf2 identified to date (Sporn 2011, Dinkova-Kostova 2005). The structure and activity profile of this class resembles that of the cyclopentenone prostaglandins, the endogenous regulators of Nrf2, which also inhibit NF-κB and play an important role in the resolution of inflammation (Levonen 2004, Cernuda Morollon 2001, Cuzzocrea 2003, Kawamoto 2000, Rossi 2000, Straus 2000). RTA 408 exhibits efficacy in a broad range of animal models of diseases involving inflammation and oxidative stress, including models of radiation-induced skin and organ damage, cancer, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, rheumatoid arthritis, multiple sclerosis, asthma, and sepsis.

Reata has demonstrated that topical dermal administration of RTA 408 activates the Nrf2 pathway and increases expression of Nrf2 target genes in both the dermis and epidermis of various nonclinical species (Reisman 2013), as well as in human skin explants *ex vivo*. RTA 408 is highly effective in rodent models of radiation-induced dermatitis and also protects against organ damage from whole-body irradiation and radiation-induced oral mucositis.

Dermal application of RTA 408 Lotion was well-tolerated in a variety of nonclinical studies. In dermal Good Laboratory Practice (GLP) toxicity studies with up to 13 weeks of twice-daily dosing, no evidence of skin toxicity related to RTA 408 Lotion was observed in either rats or minipigs with doses as high as 8% RTA 408 Lotion. Further, in marked contrast to the negligible systemic exposure that has been observed in the Phase 1 clinical study with dermal dosing of RTA 408 Lotion to healthy volunteers, meaningful systemic exposure was observed in rats and minipigs. In the 14-day dermal GLP toxicity studies, systemic exposures, based on the area under the curve ($AUC_{(0\text{-}24hr)}$), of up to 5.3 hr*µg/mL in rats and 4.9 hr*µg/mL in minipigs at the maximum feasible dose of 8% RTA 408 Lotion were not associated with any adverse effects and consequently, the no-observed-adverse-effect-level (NOAEL) was 8% for both species. In the 13-week minipig dermal GLP toxicity study, systemic exposures ($AUC_{(0\text{-}24hr)}$) up to

1.7 hr*µg/mL were also not associated with any adverse findings, and thus, the NOAEL was also 8% RTA 408 Lotion. In the 13-week rat dermal GLP toxicity study, systemic exposures exceeded those associated with adverse effects in chronic oral toxicity studies in rats (*i.e.*, 4.6 hr*µg/mL in the 13-week dermal study vs. 2.3 hr*µg/mL in the 6-month oral dosing study). The liver and kidney were identified as target organs in the 13-week rat dermal GLP toxicity study, consistent with findings from the oral toxicity studies, and the resulting NOAELs were 0.3% RTA 408 Lotion in females and < 0.3% RTA 408 Lotion in males. Furthermore, the systemic toxicity potential of RTA 408 has been extensively studied in rats and monkeys, with daily oral administration for up to six months in rats and nine months in monkeys. Overall, based on an integrated assessment of the nonclinical data, and based on the demonstrated low systemic exposure to RTA 408 in healthy human volunteers after topical administration, it is concluded that RTA 408 Lotion has an acceptable safety profile for topical use as indicated in this Phase 2 study in female patients at risk for radiation dermatitis.

A Phase 1 study (408-C-1305) was completed to evaluate the safety, local pharmacodynamics (PD), and systemic pharmacokinetics (PK) of RTA 408 following topical application of RTA 408 Lotion to healthy volunteers. The Phase 1 study was conducted in three parts. In Part A of the study, RTA 408 Lotion Vehicle and RTA 408 Lotion (0.5%, 1%, and 3%) were each concurrently applied to a small skin surface area (four individual 4-cm^2 sites; 16 cm^2 total area) twice daily for 14 days. The maximum tolerated drug concentration in Part A was 3% RTA 408 Lotion. In Part B, RTA 408 Lotion (3%) was applied topically twice daily for 14 days to a larger skin surface area (~100 cm^2). In Part C, 3% RTA 408 Lotion was applied topically twice daily for 28 days to an even larger skin surface area (~500 cm^2). Approximately 32 healthy adult volunteers were enrolled in the Phase 1 study with 12 volunteers in Part A, 10 volunteers in Part B, and 10 volunteers in Part C.

Overall, RTA 408 Lotion, at doses as high as 3%, was well tolerated and elicited a significant pharmacodynamic response in the skin. No drug-related SAEs were observed in the study. Two drug-related AEs were reported from a single healthy volunteer enrolled in Part C of the study. In this subject, mild erythema at the dose site and mild, intermittent pruritus at the dose site were observed within the first 2 weeks of dosing and both resolved spontaneously with continued application of RTA 408 Lotion. No drug-related systemic AEs were observed in any subject. The local pharmacodynamic response was assessed in skin biopsy samples collected during each part of the study. Administration of RTA 408 Lotion significantly increased protein levels of NAD(P)H:quinone oxidoreductase 1 (NQO1, a prototypical Nrf2 target gene) in skin, consistent with the known pharmacology of RTA 408.

RTA 408 Lotion produced very low systemic exposures to RTA 408. The highest dose evaluated in the Phase 1 study was 3% RTA 408 Lotion applied to a 500-cm^2 skin area twice daily for 28 days. Plasma concentrations of RTA 408 were near or below the lower limit of quantitation (LLOQ; 0.075 ng/mL) for all healthy volunteers. Only 1 volunteer demonstrated measurable RTA 408 concentrations in plasma samples collected in the study; the subject was enrolled in the Part C cohort that received the highest dose evaluated, and had measurable plasma RTA 408 concentrations only on Day 28. The maximal plasma RTA 408 concentration observed in the healthy volunteer with RTA 408 plasma concentrations was 0.0943 ng/mL (0.00017 µM), and the total $AUC_{(0\text{-}24hr)}$ was 0.0019 hr*µg/mL.

5.2. Background on Radiation-Induced Dermatitis

Radiation dermatitis is experienced by almost all patients (up to 95%) receiving radiation therapy for cancer (Ryan 2012). Radiation dermatitis can be a serious condition because, in addition to its direct physical complications and the resulting impact on overall quality of life, it can also be a dose-limiting toxicity requiring changes to the prescribed course of radiation therapy. The most common strategy employed in an attempt to prevent or minimize radiation dermatitis involves moisturization of the irradiated area, use of a mild soap to keep the area clean, and minimizing exposure to potential mechanical irritants, such as scratching and rough clothing. However, this strategy has been shown to lack clinically significant efficacy (Salvo 2010). Consequently, there is a clinical need for new treatments that are effective in protecting against radiotherapy-induced oxidative stress and the subsequent development of radiation dermatitis.

RTA 408 Lotion has shown significant efficacy in mouse models of radiation dermatitis with both fractionated and acute radiation regimens. In these models, disease severity was evaluated using a 5-point clinical scoring scale, similar to the CTCAE scale used in clinical practice. In the fractionated radiation dermatitis model, RTA 408 Lotion was effective in decreasing the severity of dermatitis in mice that received a cumulative radiation dose of 60 Gray (Reisman 2014). Specifically, RTA 408 Lotion treatment was associated with a lower incidence of animals that developed severe dermatitis and improved histology scores compared with vehicle controls. Further, RTA 408 Lotion is unlikely to interfere with radiation therapy, as RTA 408 has demonstrated enhanced therapeutic efficacy when orally administered concomitantly with radiation therapy in a mouse xenograft cancer model, and an oral dosage form of RTA 408 is currently being studied in a Phase 1 study in patients with advanced cancers. Based on these data, Reata believes that RTA 408 Lotion may effectively prevent and mitigate radiation dermatitis in oncology patients undergoing radiation therapy.

5.3. Rationale

This randomized, double-blind, vehicle-controlled, parallel-group trial will 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 therapy is recommended. The primary outcome will be the change in dermatitis grade measured with Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03) following administration of RTA 408 Lotion compared to administration of vehicle.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Study Objectives

The primary objectives of this study are the following:

1. To determine the time-averaged 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.
2. To evaluate the safety of RTA 408 Lotion

6.2. Secondary Study Objectives

The secondary objectives of this study are the following:

1. To determine the mean maximum radiation dermatitis grade measured with CTCAE of RTA 408 Lotion (0.5% and 3%) compared to administration of vehicle
2. 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
3. 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
4. To determine the extent of systemic exposure to RTA 408 following administration of RTA 408 Lotion following radiation therapy
5. To evaluate patient-reported outcomes (Skindex-16)

7. INVESTIGATIONAL PLAN

7.1. Overall 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.

7.2. Number of Patients

Approximately 177 patients (59 per treatment group) are to be enrolled in this study.

7.3. Treatment Assignment

Patients who qualify for the study will be randomized with a 1:1:1 assignment ratio to receive RTA 408 Lotion 0.5%, RTA 408 Lotion 3%, or vehicle. 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). Treatment assignments will be managed by an IWRS system.

7.4. Criteria for Study Termination

Although the Sponsor intends to complete the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons, or if required by regulatory agencies. If the Sponsor discontinues the study, all study treatment will be discontinued, and the investigator will be responsible for any additional therapy to be administered.

7.5. Schedules of Assessments

Table 3 lists the overall schedule of assessments for the study.

Table 3: 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 (described in Section 9.8 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.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

All patients must meet all of the following criteria to be included in the study:

1. Adult female patients (18 to 80 years of age, inclusive);
2. Patients diagnosed with ductal carcinoma in situ or non-inflammatory breast adenocarcinoma who have been referred for post-operative radiotherapy and have had no prior radiation treatment to that breast;
3. Patients planning to undergo 3D conformal radiation therapy to the whole breast (as part of breast-conservation therapy / lumpectomy) or chest wall (as part of post-mastectomy irradiation), with or without treatment of regional lymph nodes (i.e., axillary, supraclavicular, or internal mammary), using one of the following treatment schedules:
    a. 45 – 50.4 Gy in 1.8 Gy per day, in addition to a mandatory10-16 Gy boost
    b. 46 – 50 Gy in 2 Gy per day, in addition to a mandatory 10-16 Gy boost;
4. Patients who received breast-conservation therapy / lumpectomy must be receiving ≥ 107% of the total radiation dose (calculated from the total radiation dose including boost) to any portion of the breast, based on radiation inhomogeneity, **and/or** have a breast volume ≥ 1200 cc;
5. Female patients of childbearing potential who are willing to practice methods of birth control from screening through 1 month after applying the final dose of study drug;
6. Female patients of childbearing potential who are non-pregnant, non-lactating and have a negative pregnancy test result prior to enrollment in the study;
7. Patients willing and able to give written informed consent for study participation;
8. Patients willing and able to cooperate with all aspects of the protocol;
9. Patients for which at least 14 days have elapsed since breast conservation surgery, mastectomy surgery and/or chemotherapy prior to randomization;
10. Have adequate hematologic and organ function at screening as follows:
    a. Hematologic: Absolute neutrophil count ≥ 1.5 x 10^3 /μL, platelets > 100 x 10^9/L, hemoglobin ≥ 9 g/dL;
    b. Hepatic: total bilirubin ≤ 1.5 times (X) upper limit of normal (ULN), ALT and AST ≤ULN;
    c. Renal: serum creatinine ≤1.5 mg/dL

8.2. Patient Exclusion Criteria

All patients with any of the following conditions or characteristics must be excluded from the study:

1. Patients with TNM Classification T4 or Stage IV breast cancer;
2. Patients with prior radiation therapy to the breast treated in this study;
3. Patients with type V or VI skin according to the Fitzpatrick scale;
4. Patients with current bilateral breast cancer who are receiving radiation treatment in both breasts;
5. Patients receiving partial breast irradiation therapy;
6. Patients with uncontrolled diabetes (HbA1c > 11.0%, historical values within 6 months of screening are acceptable);
7. Patients with collagen vascular disease or vasculitis;
8. Patients with concurrent active malignancy other than adequately treated basal cell carcinoma of the skin or carcinoma in situ of the cervix;
9. Patients with active and not adequately treated bacterial, fungal, or viral skin infections, at the investigator's discretion;
10. Patients with known active hepatitis B or hepatitis C infection;
11. Patients who intend to use any other topical cream, lotion or preparation applied to the radiation treatment area;
12. Patients with known or suspected active drug or alcohol abuse;
13. Patients with any abnormal laboratory test value which, in the opinion of the investigator, would put the patient at risk by trial enrollment;
14. Participation in other interventional clinical studies within 30 days prior to consent;
15. Patients with known hypersensitivity to excipients in the drug product;
16. Patients receiving concomitant chemotherapy during the course of the planned radiation treatment regimen. Patients are eligible if they are receiving sequential, neoadjuvant or adjuvant chemotherapy that is not anticipated to be delivered during the time course of the radiation treatment regimen;
17. Patients unable to comply with the requirements of the study protocol or are unsuitable for the study for any reason in the opinion of the investigator;
18. Patients receiving any form of brachytherapy radiation treatment including a brachytherapy boost;
19. Patients receiving reverse-planned intensity modulated radiation treatment (IMRT).

8.3. Patient Re-screening

Reasons for study re-screening include the following:

- At the discretion of the investigator, a patient's planned radiation regimen is changed from a non-allowed regimen to a regimen listed in Section 8.1;
- Patients initially qualified for the study, but radiation treatment was delayed such that patients did not begin study drug for >45 days after Screening;
- Patients have experienced logistical/operational issues and the medical monitor has been notified;
- Patients have no changes in their radiation treatment plan and have undergone prior chemotherapy, but did not initially qualify for the study due to bone marrow toxicity associated with chemotherapy (absolute neutrophil count $\geq 1.5 \times 10^3$ /μL, platelets $> 100 \times 10^9$/L, hemoglobin ≥ 9 g/dL);
- Patients had untreated bacterial, fungal, or viral skin infections and since have undergone treatment for this condition;
- Patients who may undergo re-screening with the approval of a medical monitor.

8.4. Patient Withdrawal and Discontinuation

Patients have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. Furthermore, the investigator may discontinue a patient from study drug or terminate the patient from the study. The reason for a patient's withdrawal or discontinuation from the study will be recorded in the Electronic Case Report Form (eCRF).

8.4.1. Patient Discontinuation Criteria

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

- Occurrence of an adverse event (AE) or change in medical status that leads the investigator to be concerned about the patient's welfare
- Noncompliance with study procedures
- 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.

The CTCAE version 4.03 will be used to define patient stopping criteria for systemic adverse events, except where related to transaminase laboratory values. The criteria for a stopping criteria for adverse events related to transaminase laboratory values will be defined using the FDA Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" (July 2009) rather than CTCAE.

The determination stopping criteria will be defined in each patient as all toxicity ≥ Grade 3 (using CTCAE, version 4.03), except as noted below:

- Grade ≥ 3 skin toxicity, with the patient allowed to continue at the discretion of the investigator;
- Nausea and vomiting will be considered stopping criteria if Grade 3 toxicity persists after optimal medical therapy.

Any hepatobiliary disorders of ≥ Grade 2 (from CTCAE, version 4.03, pages 24 – 25) will be considered adequate stopping criteria. Note that laboratory measurements are included in a separate section of the CTCAE.

Changes in ALT, AST, and total bilirubin levels must meet one of the following criteria to be considered a DLT:

- ALT or AST > 8X ULN
- ALT or AST > 5X ULN for more than 2 weeks
- ALT or AST > 3X ULN and (total bilirubin > 2X ULN or INR > 1.5)
    - (Repeat testing every 72 to 96 hours until transaminase levels are below three times the ULN for at least one week or patient withdraws consent.)
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
    - (Repeat testing every 72 to 96 hours until transaminase levels are below three times the ULN for at least one week or patient withdraws consent.)

8.4.2. Patient Study Termination Criteria

Termination refers to a patient stopping study drug and all study assessments and visits. Reasons for patient 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.

9. TREATMENT OF PATIENTS

9.1. Description of Study Drug

Reata will provide sufficient quantities of 0% (vehicle), 0.5%, and 3% (w/w) RTA 408 Lotion to allow for completion of the study. [redacted] RTA 408 Lotion and vehicle lotion [redacted] are packaged in a high-density polyethylene (HDPE) bottle with dispensing cap. The lotion bottle is to be shaken well before each use.

9.2. Concomitant Medications

9.2.1. Excluded Medications

Patients taking these medications or treatments will be ineligible for enrollment in the study:

- Any other investigational drug;
- Systemic drugs, vitamins or herbal preparations intended to treat radiation dermatitis (including curcumin);
- Use of deodorant containing aluminum chlorohydrate within the radiation treatment area;
- Any other topical cream, lotion or preparation applied to radiation treatment area except as noted below (Section 9.2.2) or as discussed and approved by the medical monitor.

Investigators must discuss study continuation with a medical monitor if their patients use these medications during the study.

9.2.2. Permitted Medications

Prophylactic anti-emetics will be allowed, at the discretion of the treating physician, after the patient has experienced ≥ CTCAE grade 1 nausea or vomiting.

Other allowed concomitant medications include:

- Antibiotics;
- Vitamins or minerals;
- Pain medication as authorized by the treating physician;
- Other medications intended to manage concurrent diseases, as authorized by the treating physician;
- Hormonal antagonists (including tamoxifen, aromatase inhibitors and/or herceptin);
- Any required immunizations and/or vaccinations;
- Oral, implantable or injectable contraceptives.

Patients may take ibuprofen, aspirin and/or over-the-counter cough / cold medications, but these concomitant medications must be recorded. Patients taking medication chronically should be maintained on those same doses and dose schedules throughout the study period, as medically feasible.

If patients develop Grade 2 or higher radiation dermatitis and the radiation dermatitis is believed to be inadequately controlled in the opinion of the Investigator, additional topical creams, lotions, hydrocortisone or other escape medications may be prescribed and then must be documented in the CRF. Patients should apply escape medications 1-3 hours after study drug application. Any residual escape medication should be removed prior to study drug application. However, in patients with radiation dermatitis < Grade 2, no concomitant medications may be prescribed or administered to prophylactically prevent the incidence of Grade 2 or higher radiation dermatitis.

9.3. Treatment Compliance

The investigator or his/her designated and qualified representatives will only dispense study drug to patients enrolled in the study in accordance with the protocol. 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. The study drug must not be used for reasons other than that described in the protocol. A maximum of 14 consecutive missed doses (7 days of twice daily dosing) or no more than 28 total non-consecutive missed doses are permitted during the study. Additionally, a maximum of 6 total missed doses is permitted in the 7 day run-in period prior to the start of radiation treatment. Patients who exceed the number of allowed missed doses will be considered not compliant with dosing and will have a protocol deviation recorded, but these patients will be encouraged to continue with dosing and will not be discontinued from the study.

In cases where radiation treatment is delayed (*e.g.*, delayed start of radiation treatment or radiation treatment interruptions), the study drug application period may be extended from the expected 8-9 weeks up to a maximum of 13 weeks. 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.

9.4. Randomization

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).

9.5. Blinding

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 will be unblinded to individual treatment assignments.

9.5.1. Patient Unblinding

Although there is no known antidote to RTA 408, under rare circumstances unblinding may be considered medically necessary. Unless faced with a life-threatening medical situation, the investigator should contact the medical monitor to discuss if there is a medically compelling reason to unblind the patient's treatment assignment. After the discussion, the investigator may proceed to unblind the patient, as appropriate. If unblinding is required, the investigator will utilize the IWRS to perform the unblinding. If a study drug assignment is unblinded, a description of the event that required unblinding must be documented by the investigator in the patient's source documents. Patients must discontinue taking study drug if their treatment assignment has been unblinded to the investigator (or designee). Such patients must undergo the same early termination procedures as those patients who discontinue taking study drug for other reasons. Patient treatment assignments must not be unblinded in the case of an AE or SAE, except as described above.

9.5.2. Unblinding for Regulatory Submission

In situations where a regulatory body requires unblinding and reporting of a particular serious adverse event, the appropriate bodies (e.g., ethics committees, IRBs) must be provided with unblinded information according to the applicable regulatory requirement. This information must not be conveyed to investigator, site personnel or patient; therefore, this type of unblinding does not necessitate that the patient discontinue taking study drug. In cases when unblinded information must be conveyed to local health authorities, personnel without direct involvement in the conduct of the study must be responsible for unblinding the patient's treatment using the IWRS and conveying the necessary information.

9.6. Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

- Patient re-screening;
- Management of an adverse event or serious adverse event;
- Performance of additional laboratory tests for clinically abnormal test values or to confirm a possible pregnancy;
- Any time the investigator feels that it is clinically appropriate for patient safety.

9.7. Pregnancy

9.7.1. Women of Childbearing Potential

Women of childbearing potential (WOCBP) are female patients who are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy), do not have fallopian inserts with confirmed blockage and are not postmenopausal for at least 1 year.

9.7.2. Methods of Birth Control

During screening, while taking study drug and until the final visit indicated in Table 3, per the International Conference on Harmonization (ICH) M3 Guidance for Industry (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf), WOCBP must practice one of the following highly effective methods of birth control:

- Use double-barrier contraception method defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]);
- Established use of hormonal contraceptives (oral, parenteral, vaginal or transdermal) for at least 3 months prior to study drug administration;
- Use of an intrauterine device;
- Have a partner who has had a vasectomy (applies to any and all partners);
- Abstain from sexual intercourse completely.

9.7.3. Suspected Pregnancy

During the study, all WOCBP must be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, late or missed menstrual period).

If a patient or investigator suspects that the patient may be pregnant, the study drug must be withheld until the results of a serum pregnancy test are available. If pregnancy is confirmed with a positive serum pregnancy test result, the patient must discontinue applying study drug and be discontinued from the study. The investigator must immediately report a pregnancy associated with study drug exposure and record the event. Protocol-required last-day-of-treatment and early-termination procedures must be performed on the patient. Other appropriate follow-up procedures should be considered if indicated.

Pregnancy is not considered an AE; however, the investigator must follow a pregnant patient and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. Reata or designee may contact the investigator to request additional information throughout the course of the pregnancy.

The following pregnancy outcomes must be considered SAEs and will require additional reporting in the CRF and on an SAE form:

- Congenital anomaly/birth defect
- Stillbirth
- Spontaneous miscarriage

9.8. Study Procedures

9.8.1. Informed Consent

Written informed consent (see Section 16.3) must be obtained from the patient before any study-related procedures are performed.

9.8.2. Inclusion/Exclusion

Inclusion and exclusion criteria should be reviewed at the times indicated in Table 3. Patients must meet all of the inclusion and none of the exclusion criteria for entry into the study.

9.8.3. Demographics and Baseline Disease Characteristics

Demographic data includes sex, age, race and ethnicity and will be collected at the times indicated in Table 3. Baseline disease characteristics will be collected at the time point indicated in Table 3.

9.8.4. Concomitant Medications

The name, dose, and frequency must be recorded for all medications that the patient is taking or applying to the treatment area. All allowed and excluded medications should be recorded including all prescription drugs, herbal products, vitamins, minerals and over-the-counter medications. Trade or generic drug names should be used where possible. Concomitant medications will be collected at the times indicated in Table 3.

9.8.5. Medical History

A complete medical history (e.g., per patient report) that includes all medical history within the past 5 years must be collected. Medical history includes collection of surgery type (lumpectomy, partial mastectomy, or full mastectomy). If the patient is to undergo post-mastectomy reconstruction before radiation treatment, the type of reconstruction should be recorded as well. Medical history also includes date of breast cancer diagnosis, clinical stage at diagnosis, date of breast surgery, and breast surgery type. Medical history will be recorded at the times indicated in Table 3.

9.8.6. Height

Height in centimeters should be measured without footwear, or limb prosthetics at the time indicated in Table 3.

9.8.7. Weight and Body Mass Index (BMI)

Weight in kilograms should be measured at the times indicated in Table 3. Weight should be measured without footwear, or limb prosthetics. Body mass index (BMI) will be calculated automatically each time the weight is recorded.

9.8.8. Vital Signs

Vital sign measurements include the patient's heart rate (beats/minute taken for at least 15 seconds), blood pressure (mm Hg) and oral, tympanic or temporal body temperature (°C or

°F). Blood pressure should be taken after the patient has rested in a sitting position for at least 5 minutes. The same arm (usually the non-dominant arm if appropriate) and the appropriate size cuff should be used for each measurement. Vital sign measurements should be taken at the times indicated in Table 3.

9.8.9. Physical Exam

A comprehensive physical examination must be performed by a physician, physician assistant or registered nurse practitioner at the time points indicated in Table 3. If the physical exam is to be performed as part of the practice of medicine and would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, the physical exam may be performed and the results subsequently used for determining study eligibility without first obtaining consent as long as the exam is done within the study screening timeframe, and the site's IRB is in agreement. The examination must include the following organ or body system assessments: general appearance, head, eyes, ears, nose, throat, neck, musculoskeletal, cardiovascular, lymphatic, respiratory, abdomen, dermatologic, extremities and neurological. Assessments of any specific signs or symptoms reported by the patient must also be performed and documented along with any other findings of note. Findings at Screening must be characterized as either normal or abnormal, and if abnormal, a description of the abnormality must be provided. Each body system must be assessed for clinical significance. Clinically significant findings at Screening must be included in the patient's medical history. New clinically significant findings after first dose must be included as adverse events.

9.8.10. Fitzpatrick Skin Score

Determination of the Fitzpatrick skin score must be performed at the time point indicated in Table 3. Patients with type V or VI skin are excluded from the study. Refer to Appendix A for the Fitzpatrick Skin Scale.

9.8.11. Pregnancy Test

WOCBP (see Section 9.7.1) will complete a pregnancy test at the time points indicated in Table 3. Negative test results are required on Day 1 (Study Visit 2) before study drug administration. Any patient who becomes pregnant during the study must discontinue taking study drug immediately. See Section 9.7 for a description of procedures to be followed in case of pregnancy.

9.8.12. Smoking Status

The smoking status of the patient (current smoker, former smoker, or never smoked) is to be recorded at the time points indicated in Table 3.

9.8.13. Study Drug Administration

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 should self-administer the lotion at the time points indicated in Table 3. Study drug is to be applied twice daily. The amount of lotion used will depend on the size of the radiation treatment area. 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. A thin layer of lotion will be applied to the indicated or planned radiation treatment area, which includes any regional irradiated lymph nodes. 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. On the last day of study drug administration, patients will only have a morning study drug application as the study drug will be collected that day. If patients develop grade 2 or higher radiation dermatitis and the radiation dermatitis is believed to be inadequately controlled in the opinion of the Investigator, additional topical creams, lotions, hydrocortisone or other escape medications may be prescribed and then must be documented. Patients should continue study drug administration in addition to escape medications prescribed by the Investigator. Patients should apply escape medications 1-3 hours after study drug application. Any residual escape medication should be removed prior to study drug application.

9.8.14. Study Drug Dispensation

Study drug will be dispensed to the patient along with the dosing diary and collected from the patient at the time points indicated in Table 3.

9.8.15. Adverse Event Collection

Patients should be observed for general appearance, presence of illness or injury, or signs indicative of a concurrent illness at the time points indicated in Table 3. Patients should be instructed to volunteer any information regarding AEs at any time during the study, or query the patients with an open question regarding any AEs they may be experiencing (*e.g.*, "How do you feel?" or "How have you been feeling since your last visit?"). Any findings are to be documented.

9.8.16. Clinical Chemistry

Samples will be collected for the following clinical chemistry analyses at the time points indicated in Table 3: urea nitrogen (BUN), creatinine enzymatic, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, sodium, potassium, calcium, phosphorus, uric acid, cholesterol, total protein, albumin, chloride and bicarbonate.

9.8.17. Hematology

Samples will be collected for the following hematology assessments at the time points indicated in Table 3: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, bands (if detected), lymphocytes, monocytes, basophils (if detected), eosinophils (if detected), absolute platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC).

9.8.18. Urinalysis and Microscopy

Samples will be collected for the following urinalysis assessments at the time points indicated in Table 3: specific gravity, ketones, pH, protein, blood, glucose, urobilinogen and bilirubin.

9.8.19. Chest Wall Separation

Chest wall separation measurements must be collected by CT scanning at the time points indicated in Table 3. Institutions may use their local SOP for determination of chest wall separation as measured by CT. Chest wall separation will be reported in centimeters (cm).

9.8.20. Breast Volume

Breast volume measurements in patients that have undergone breast conserving surgery must be collected by CT scanning at the time points indicated in Table 3, which should correspond with the radiation treatment planning visit. Breast tissue should be defined per the RTOG contouring guidelines (RTOG 2009), but sites may use their local SOP for calculating breast volume.

9.8.21. Radiation Treatment

Planned radiation treatment must be no more than 7.5 weeks, and the dates of radiation treatment will be recorded in the eCRF at the time points indicated in Table 3. The dates of missed radiation treatment, the type of radiation treatment (regular radiation or boost treatment), and the use of a bolus will also be recorded in the eCRF. For patients for whom a bolus is used, an indicator other than redness of the skin surface (e.g., dosimeter at the skin surface) may be considered for decisions regarding radiation treatment dose and frequency.

9.8.22. Radiation Treatment Area

The surface area (cm^2) of the breast skin region treated with radiation must be measured and recorded as indicated in Table 3. The area (cm^2) of the breast skin area treated with radiation will be measured as defined in the study manual. The radiation treatment area surface measurements can occur at any time before Day 1 of radiation treatment.

9.8.23. Weigh Study Drug

The combined weight of the study drug and the lotion bottle (without box) must be recorded at the times listed in Table 3. Empty lotion bottles will not be provided to sites, and sites should not attempt to tare the scale with an empty lotion bottle before weighing. Study drug and lotion bottle weight should be recorded in units of grams, with 0.1 gram precision.

9.8.24. Pharmacokinetic (PK) Blood Samples

Blood samples for the determination of plasma RTA 408 and potential metabolite concentrations will be drawn at the time points indicated in Table 3. Blood sample collection instructions will be provided in the laboratory manual. The date and time of collection of all PK blood samples should be recorded; however, any deviations from the protocol-specified sampling times will not be considered protocol deviations. Sample time deviations will be summarized in the study report. Dates in the case report form should be recorded in an unambiguous format (e.g., DD MMM YYYY) and time should be recorded to the nearest minute (e.g., HH:MM using the 24-hour clock). Blood samples not drawn should be recorded as such. The date and time of the last two applications of study drug should also be collected on the PK case report form.

9.8.25. Dermatitis Assessment

The CTCAE v4.03 radiation dermatitis grade will be assessed by a local, trained physician, nurse or appropriately trained site staff member. Components of the CTCAE will be recorded separately by a local, trained physician, nurse or appropriately trained site staff member. Dermatitis assessment at each visit is performed before initiation of radiation therapy. Dermatitis assessments must be performed by trained evaluator(s) at each time point indicated in Table 3. These components include the severity of erythema, the extent and severity of dry desquamation, the extent and severity of wet desquamation and the presence of edema. Refer to Section 13.2.2.1 for the CTCAE scoring.

New or worsening of radiation dermatitis signs/symptoms should not be captured as individual AEs, but rather are captured in the Dermatitis Assessment process and documentation. These signs / symptoms are being assessed as study endpoints. Thus, if investigators seek to enter "radiation dermatitis", "erythema", "desquamation" or other signs / symptoms of radiation dermatitis as adverse events, they should first discuss the signs/symptoms with the medical monitor. The investigator, in coordination with the medical monitor, will determine the process for capturing these signs/symptoms.

9.8.26. Photographs of Radiation Treatment Area

Optional photographs may be collected at Sponsor-qualified sites at the times indicated in Table 3. The local, trained physician, nurse or appropriately trained site staff member who performs the dermatitis assessment should also collect photographs of the patient. Details of photography assessments will be outlined in a study specific manual. On Day 1 of radiation treatment and the last day of radiation treatment, photographs must be collected prior to radiation treatment.

9.8.27. Skindex-16 Assessment

The Skindex-16 quality-of-life tool will be used to assess patient responses to skin toxicity during and after radiation therapy at the time points indicated in Table 3. 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. The tool should be completed by the patient prior to initiation of that day's planned radiation therapy. Refer to Appendix B for the Skindex-16 assessment.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

RTA 408 Lotion 0.5% or 3% and Lotion Vehicle will be used in this study. The investigational product consists of a preserved lotion formulation containing RTA 408 (0%, 0.5% or 3%), [redacted]

10.2. Study Drug Packaging and Labeling

The study drug will be supplied in a HDPE bottle with dispensing cap. [redacted] Bottles of study drug will be contained in a carton or kit. The label on each kit and bottle will contain the following information:

- Protocol 408-C-1306
- Medication ID number
- Contents: 45 grams of RTA 408 Lotion or Vehicle
- SHAKE WELL PRIOR TO USE. FOR TOPICAL USE ONLY.
- Caution Statement: New Drug – Limited by Federal Law to Investigational Use.
- [redacted]
- Reata Pharmaceuticals, Inc., Irving, TX

10.3. Study Drug Storage

The stability of the drug product is being evaluated in ongoing studies.

Investigative sites must store the investigational product in a secure locatio [redacted] Sites must maintain a temperature log of the storage conditions. Temperature logs must be available for review at each monitor site visit. When a temperature within the storage location at the site is noted to be outside the excursion range for 24 hours or more, or exceeds 40°C, the Sponsor must be notified.

10.4. Study Drug Administration

Please refer to Section 9.8.13 for details on study drug administration. Instructions will be provided to the patient regarding how to apply the lotion at each study drug administration time point listed in Table 3.

10.5. Study Drug Accountability

The investigator, or designee, will maintain a record of all study drug received, dispensed, and returned to the Sponsor or its designee. No study drug shall be destroyed by the clinical site

unless directed to do so by the Sponsor or its designee. All study drug containers will be weighed prior to dispensation and upon collection.

10.6. Study Drug Handling and Disposal

At the conclusion of the study, the Sponsor or its designee will direct the site regarding the final disposition of any remaining study drug.

11. PHARMACOKINETIC, PHARMACODYNAMIC, AND EFFICACY ASSESSMENTS

11.1. Pharmacokinetic Samples

Pharmacokinetic samples will be analyzed for RTA 408 using a validated analytical method. Samples may be analyzed for potential metabolites of RTA 408 using non-validated analytical methods.

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety assessments. Safety parameters include weight, BMI, vital sign measurements, physical examination results, adverse events, serious adverse events and laboratory test results (clinical chemistry, hematology, urinalysis and microscopy).

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom or disease temporally associated with the use of the study drug, whether or not it is considered to be study-drug related. Included in this definition are any newly-occurring events or previous condition that has increased in severity or frequency since the administration of study drug.

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. Thus, if investigators seek to enter "radiation dermatitis", "erythema", "desquamation" or other signs/symptoms of radiation dermatitis as adverse events, they should first discuss the signs/symptoms with the medical monitor. The investigator in coordination with the medical monitor will determine how these signs/symptoms are to be recorded.

All AEs that are observed or reported by the patient during the study (from the time of first dose until the final visit indicated in Table 3) must be reported, regardless of their relationship to study drug or their clinical significance.

12.2.1.2. Serious Adverse Event

A serious adverse event (SAE) is any AE occurring at any dose and regardless of causality that:

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

The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above, however, they may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies which occur during the study (from the time of administration of the first dose of study drug until the final visit indicated in Table 3). Certain pregnancy outcomes will require submission as an SAE. (See Section 9.7)

The investigator is responsible for reporting to Reata or designee all AEs and SAEs that are observed or reported by the patient during the study (from the time of first dose until the final visit indicated in Table 3), regardless of their relationship to study drug or their clinical significance. All SAEs reported or observed during the study must be followed to resolution or until the investigator deems the event to be chronic or the patient to be stable. Reata or designee may contact the investigator to obtain additional information on any SAE which has not resolved at the time the patient completes the study.

12.3. Eliciting Adverse Event Information

At every study visit, patients must be asked a standard, non-directed question, such as, “How do you feel?” or “How have you been feeling since your last visit?” to elicit any medically related changes in their well-being. They may also be asked if they have been hospitalized, had any accidents, used any new medications or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products and minerals). Responses to questions asked must be documented in the source documents.

In addition to patient observations, AEs must be documented for any clinically significant diagnosis resulting from abnormal laboratory test values, physical examination findings, or ECG abnormalities, or from other documents that are relevant to patient safety.

12.4. Assessment of Causality

The investigator must use the following classifications and criteria to characterize the relationship or association of the study drug in causing or contributing to the AE:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Unlikely: This relationship suggests that the temporal sequence of the event with study drug administration makes a causal relationship improbable and/or other factors also provide plausible explanations.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of study drug administration, and/or, follows a known response pattern to the study drug, but could have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with study drug administration seems likely.

12.5. Assessment of 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. If the criteria in the CTCAE version 4.03 do not apply, severity should be defined as follows:

Table 4: AE Severity Grades

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

The NCI CTCAE, version 4.03 will be provided to the investigator.

12.6. Recording Adverse Events

All conditions present prior to the first dose of study drug should be documented as medical history. Documentation of AEs shall continue until the final visit indicated in Table 3, regardless of the relationship of the AE to study drug. Information to be collected includes type of event, date of onset, date of resolution, investigator-specified assessment of severity and relationship to study drug, seriousness, as well as any action taken.

While an AE is ongoing, changes in the severity (*e.g.*, worsening and improving) should be noted in the source documents but, when documenting the AE, only the total duration and greatest severity should be recorded in the case report form. AEs characterized as intermittent require documentation of onset and duration.

All drug-related (Possible or Probable, see Section 12.4) AEs and abnormal laboratory test results reported or observed during the study must be followed to resolution (either return to baseline or within normal limits). All other AEs will be followed throughout the study.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications or progression of disease states must also be reported. Preexisting conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the patient experiences a

worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (*e.g.*, "worsening of…").

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory test values are only considered to be AEs if they are judged to be clinically significant (*i.e.*, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory test values are the result of pathology for which there is an overall diagnosis (*e.g.*, increased creatinine levels in renal failure), only the diagnosis should be reported as an AE.

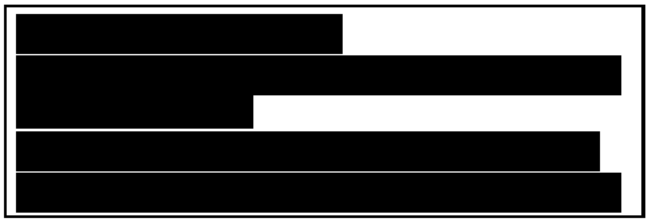
New or worsening radiation dermatitis signs/symptoms should not be captured as individual AEs, but rather are captured in the Dermatitis Assessment documentation as these signs / symptoms are being assessed as study endpoints. Thus, if investigators seek to enter "radiation dermatitis", "erythema", "desquamation" or other signs / symptoms of radiation dermatitis as adverse events, they should first discuss the signs/symptoms with the medical monitor. The investigator in coordination with the medical monitor will determine how these signs/symptoms are to be recorded.

Elective procedures (surgeries or therapies) that were scheduled prior to the start of AE collection are not considered AEs. These elective procedures should not be recorded as AEs, but should be documented in the patient's source documents as elective (*e.g.*, elective periodontal surgery). However, if a pre-planned procedure is performed early (*e.g.*, as an emergency) because of a worsening of the preexisting condition, the worsening of the condition should be captured as an AE.

12.7. Reporting Serious Adverse Events

Any AE the investigator considers serious according to the previously described criteria must be reported within 24 hours from the time when site personnel first learn about the event.

Table 5: SAE Reporting Contact Information



For questions regarding SAE reporting, contact your study manager, monitor, or

Any additional information that becomes available later should be submitted to the above number within 1 working day of receipt.

Reata or designee will notify regulatory agencies of any fatal or life-threatening unexpected events associated with the use of the study drug as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within the timeframe established by the appropriate regulatory agency. For other SAEs that do not meet the fatal or life-threatening unexpected criteria, but are reported to be associated with the use of the study drug, Reata or designee will notify the appropriate regulatory agencies in writing within the timeframe established by those regulatory agencies. Reata or designee will provide copies of any reports to regulatory agencies regarding serious and unexpected SAEs to the investigators for review and submission to their institutional review board (IRB).

Principal investigators are responsible for informing their IRB of any SAEs at their site. SAE correspondence with regulatory authorities or IRBs must be submitted to Reata or designee for recording in the study file.

13. STATISTICS

13.1. Sample Size

13.2. Study Variables

13.2.1. Pharmacokinetic Variables

The pharmacokinetic variables include RTA 408 plasma concentration data for each analyte.

13.2.2. Efficacy Variables

The efficacy variables include the time-averaged change in dermatitis grade (CTCAE v4.03), change in mean maximal dermatitis grade, percentage of patients with maximal dermatitis grade < 2, and duration of CTCAE grade ≥ 2.

13.2.2.1. 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):

Table 6: 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 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 wet desquamation and the presence of edema.

13.2.2.2. Skindex-16 assessment

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 B for the Skindex-16 assessment.

13.2.3. Safety Variables

The safety variables 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.

13.3. Statistical Analyses

A statistical analysis plan (SAP) detailing the analyses will be developed prior to the database lock. All statistical analyses and data summaries will be performed using SAS® (Version 9.1 or higher) or other similar software. The SAP will serve as the final arbiter of all statistical analyses. Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation and geometric mean (where applicable). Categorical data will be summarized using number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation, geometric mean (where applicable), frequency counts and percentages.

13.3.1. Primary Efficacy Analysis

For the primary efficacy analysis, a longitudinal mixed-model will be used to analyze the CTCAE dermatitis grades 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; smoking status (smoker or ex-smoker versus non-smoker), breast cancer treatment prior to radiation therapy (full mastectomy versus partial mastectomy or lumpectomy), and other covariates (such as cumulative radiation exposure) will be evaluated for inclusion in the model as covariates. A generalized mixed model will be used as the primary longitudinal model with additional sensitivity analyses performed as appropriate. A hierarchical approach will be used for analysis of the primary endpoint to control the type I error. The primary efficacy analyses will first test the difference between RTA 408 Lotion pooled and vehicle lotion. If the first comparison is statistically significant, RTA 408 Lotion 3.0% will be compared to vehicle lotion. Otherwise, the second comparison will not be performed or the p-value will be considered nonsignificant. Similarly, only if the second comparison is statistically significant, RTA 408 lotion 0.5% will be compared to vehicle lotion.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

The study monitor, as a representative of the Sponsor, has the obligation to follow the study conduct closely. In doing so, the monitor will visit the principal investigator and study facilities periodically, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current knowledge of the study activity of the investigator and his/her staff through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigators and staff.

The Sponsor or designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the ICH guideline E6(R1): Good Clinical Practice: Consolidated Guideline and current standard operating procedures (Section 16.2).

Each investigator is expected to make a reasonable effort to accommodate the monitor when monitoring visits are necessary and to be available during the site visit. Furthermore, the monitor should be provided direct access to source data and documents for trial-related monitoring and internet during the visit.

14.2. Audits and Inspections

Principal investigators and institutions involved in the study will permit study-related monitoring, audits, and IRB review, and regulatory inspection(s), by providing direct access to all study records. In the event of an audit, the principal investigator agrees to allow the Sponsor, representatives of the Sponsor, the US Food and Drug Administration (FDA) or other relevant regulatory authorities access to all study records.

The principal investigator should promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or designee.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Quality Assurance

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Reata may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

15.2. Financial Disclosure

Principal investigators and sub-investigators are required to provide financial disclosure information prior to starting the study. In addition, the principal investigator and sub-investigators must provide the Sponsor or designee with updated information, if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

Any potential investigator who has a vested financial interest in the success of this study may not participate in this study.

15.3. Sponsor Obligations

The Sponsor or designee is not financially responsible for further testing/treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor or designee is not financially responsible for treatment of the patient's underlying disease.

15.4. Investigator Documentation

Before beginning the study, the principal investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the Code of Federal Regulations (CFR) by providing the essential documents to the Sponsor or designee, which include but are not limited to the following:

- An original investigator-signed investigator agreement page of the protocol;
- The IRB approval of the protocol;
- The IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardians;
- A Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572;
- Curricula vitae for the principal investigator and each sub-investigator listed on Form FDA 1572. A curricula vitae and current licensure, as applicable, must be provided. The curricula vitae must have been signed and dated by the principal investigators and sub-investigators within 2 years before study start-up to indicate the documents are accurate and current;

- Completed financial disclosure forms (Section 15.2) to allow the Sponsor or designee to submit complete and accurate certification or disclosure statements required under US Title 21 CFR 54. In addition, the investigators must provide to the Sponsor or designee a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study;
- Laboratory certifications and normal ranges for any laboratories used by the site for the conduct of this study.

15.5. Clinical Study Insurance

In accordance with the respective national drug laws, the Sponsor has taken out patient liability insurance for all patients who give their consent and enroll in this study. This insurance covers potential fatalities, physical injuries, or damage to health that may occur during the clinical study.

15.6. Use of Information

All information regarding RTA 408 supplied by Sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. Furthermore, the investigator is obligated to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of RTA 408 Lotion and may be disclosed to regulatory authority(ies), other investigators, corporate partners or consultants, as required.

16. ETHICS

16.1. Institutional Review Board (IRB) Review

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB before study start. Each site must provide the Sponsor or its designee a signed and dated statement that the protocol and informed consent have been approved by the IRB before consenting patients. Prior to study initiation, the investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with this protocol and to give access to all relevant data and records to the Sponsor, its designee and regulatory authorities as required.

The IRB chairperson or designee must sign all IRB approvals and must identify the IRB by name and address, the clinical protocol, and the date approval and/or favorable opinion was granted.

The principal investigator is responsible for obtaining reviews of the clinical research at intervals specified by the IRB, but not exceeding 1 year. The principal investigator must supply the Sponsor or designee with written documentation of reviews of the clinical research.

16.2. Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (e.g., US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

The principal investigator agrees to conduct the study in accordance with the ICH E6(R1) Guidance for Industry on Good Clinical Practice [http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf]. The principal investigator must conduct all aspects of this study in accordance with all national, state, and local laws or regulations, and the principles of the Declaration of Helsinki [http://www.wma.net/en/30publications/10policies/b3/].

16.3. Written Informed Consent

Because the study will be conducted under a United States Investigational New Drug Application, a signed informed consent form, in compliance with Title 21 of the United States Code of Federal Regulations (CFR) Part 50, will be obtained from each patient before the patient enters the study. An informed consent template may be provided by the Sponsor or designee to the investigators. The consent must be reviewed by the Sponsor or designee before IRB submission. Once reviewed, the consent will be submitted by the principal investigator to his or her IRB for review and approval before the start of the study. If the informed consent form is revised during the course of the study, all participants affected by the revision must sign the revised IRB-approved consent form.

Before enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the approved informed consent form. Once the principal investigator or designee

is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the informed consent form.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Any changes to the proposed consent form suggested by the investigator must be agreed to by the Sponsor before submission to the IRB, and a copy of the approved version and the notice of approval must be provided to the Sponsor's designated monitor after IRB approval.

The principal investigator or designee will provide a copy of the informed consent form (signed copy to be provided per applicable law) to the patient and/or legal guardian. The original form will be maintained in the patient's medical records at the site.

16.4. Confidentiality

All laboratory specimens, evaluation forms, reports and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA or applicable regulatory authorities, or the IRB.

The principal investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record or other unpublished confidential information disclosed to them for the purpose of the study. Prior written agreement from the Sponsor or designee must be obtained for the disclosure of any said confidential information to other parties.

16.5. Modification of the Protocol

Any changes, which arise after the approval of the protocol, must be documented as protocol amendments. FDA must be notified of protocol amendments. The changes will become effective only after approval of the Sponsor, the investigator and the IRB. In cases when the protocol is modified to enhance patient safety, changes may be implemented and the amendment must be immediately submitted to the IRB.

The investigator is responsible for informing the IRB of all problems involving risks to patients according to national legislation. In case of urgent safety measures, the Sponsor will immediately notify FDA in accord with 21 CFR 312.32.

16.6. Protocol Deviations

The principal investigator or designee must document any protocol deviation. The IRB must be notified of all protocol deviations in a timely manner by the investigator as appropriate. Protocol deviations will be documented by the responsible monitor during monitoring visits, and those observations will be communicated to the investigator.

If there is an immediate hazard to a patient the principal investigator may deviate from the protocol without prior Sponsor and IRB approval. The Sponsor and IRB must be notified of the deviation.

17. DATA HANDLING AND RECORDKEEPING

17.1. Retention of Records

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application submission or 2 years after formal discontinuation of the clinical development of the investigational product. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

17.2. Case Report Forms

All case report form data will be entered in paper or electronic forms at the investigational site. If an Electronic Data Capture system (EDC) is used to capture data electronically for all randomized patients, it will be 21 CFR Part 11 compliant.

18. PUBLICATION POLICY

Reata reserves the right to review all planned communications and manuscripts based on the results of this study. This reservation of the right is not intended to restrict or hinder publication or any other dissemination of study results, but to allow the Sponsor to confirm the accuracy of the data, to protect proprietary information, and to provide comments based on information that may not yet be available to the study investigators. Reata supports communication and publication of study results whatever the findings of the study. Reata also requires disclosure of any conflict of interest from all authors or investigators when manuscripts are submitted for publication.

Those individuals who have contributed greatly to this study, including lead external advisors and select principal investigators, may serve on any publications committee for the study.

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20. APPENDICES

APPENDIX A. FITZPATRICK SKIN TYPE ASSESSMENT

Study personnel will read the questions and possible answers below to each subject and record the answers. After all answers have been recorded, study personnel will tally the scores and record the Fitzpatrick Skin Type of the subject.

The worksheet is not to be handed to or completed by subjects.

Fitzpatrick Skin Type Worksheet

Name:						**Date:**
Score		**0**	**1**	**2**	**3**	**4**
	What is the color of your eyes?	Light Blue, Light Gray or Light Green	Blue, Gray, or Green	Light Brown, Hazel	Dark Brown	Brownish Black
	What is your natural hair color?	Sandy Red	Blond	Brown, Dark Blond	Dark Brown	Black
	What is the color of your unexposed skin?	Reddish	Very Pale, Pink	Pale with Beige Tint	Light Brown	Dark Brown
	Do you have Freckles on Sun exposed areas?	Many	Several	Some	Few	None
	What happens when you stay in the sun to long?	Intense Burn, Blistering, Peeling	Burn Followed by Peeling	Mild burn sometimes followed by peeling	Rarely Burns	Never Burns
	To what degree do you turn Brown?	Hardly or Not at all	Light Tan	Reasonable Tan	Tan Very Easily	Immediate Tan
	Do you turn brown several hours after sun exposure?	Never	Seldom	Sometimes	Often	Always
	How does your face respond to the Sun?	Very Sensitive	Sensitive	Normal	Normally Resistant	No problems
	When did you last expose yourself to the sun tanning bed or self-tanning creams?	More than 3 Months ago	2-3 Months ago	1-2 Months ago	Less Than 1 Month ago	Less than 2 Weeks ago
	Do you expose the area to be treated to the sun?	Never	Hardly Ever	Sometimes	Often	Always
Total Score: Skin Type:	Score 0-7 8-16 17-25 26-30 Over 30	Fitzpatrick Skin Type: I II III IV V-VI				

APPENDIX B. SKINDEX-16 ASSESSMENT

Patients should check one box for each question. Study personnel should specify that the patient answers should reflect the patient's responses during the past week. Patients should answer every question.

During the past week, how often have you been bothered by:

	Never Bothered						**Always Bothered**
Your skin condition **itching**	0	1	2	3	4	5	6
Your skin condition **burning** or **stinging**	0	1	2	3	4	5	6
Your skin condition **hurting**	0	1	2	3	4	5	6
Your skin condition **being irritated**	0	1	2	3	4	5	6
The **persistence / recurrence** of your skin condition	0	1	2	3	4	5	6
Worry about your skin condition (for example: that it spread, get worse, scar, be unpredictable, etc.)	0	1	2	3	4	5	6
The **appearance** of your skin condition	0	1	2	3	4	5	6
Frustration about your skin condition	0	1	2	3	4	5	6
Embarrassment about your skin condition	0	1	2	3	4	5	6
Being annoyed about your skin condition	0	1	2	3	4	5	6
Feeling depressed about your skin condition	0	1	2	3	4	5	6
The effects of your skin condition on your **interactions with others** (for example: interactions with family, friends, close relationships, etc.)	0	1	2	3	4	5	6
The effects of your skin condition on your **desire to be with people**	0	1	2	3	4	5	6
Your skin condition making it hard to **show affection**	0	1	2	3	4	5	6
The effects of your skin condition of your **daily activities**	0	1	2	3	4	5	6
Your skin condition making it hard to **work or do what you enjoy**	0	1	2	3	4	5	6