MSK PROTOCOL COVER SHEET

A Randomized Phase II Double-Blinded Study of the Efficacy of Oleogel-S10 (AP101) Gel for the Treatment of Grade 2/3 Radiation Dermatitis in Breast Cancer Patients

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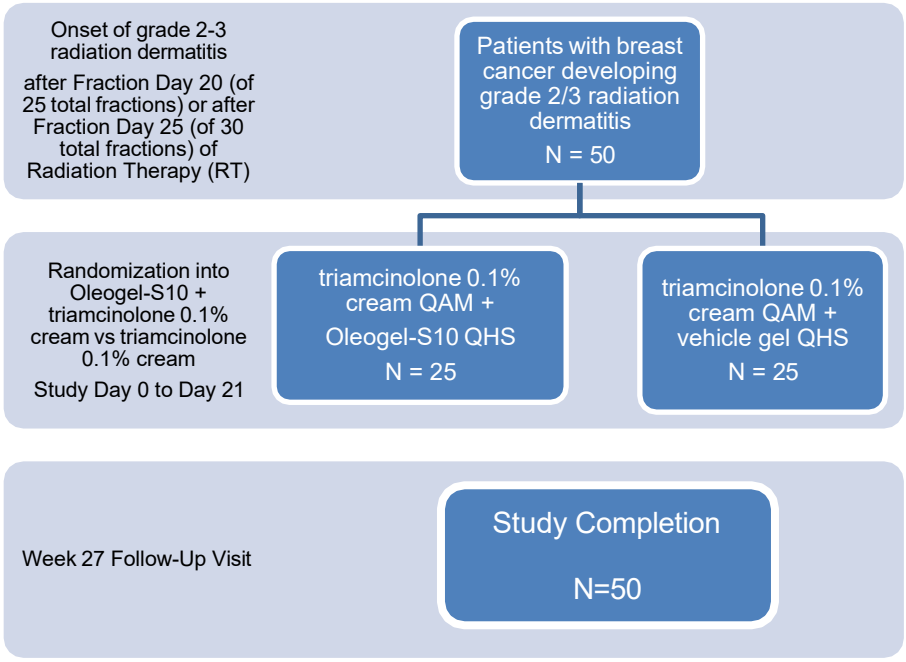
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: A Randomized Phase II Double-Blinded Study of the Efficacy of Oleogel-S10 (AP101) Gel for the Treatment of Grade 2/3 Radiation Dermatitis in Breast Cancer Patients.

Funding: Amryt Research

Total Study Follow-up per Patient: 27 weeks

Schema:



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- To assess the efficacy of topical Oleogel-S10 gel vs placebo (vehicle gel) when added to standard of care (triamcinolone 0.1% cream) in reducing radiation wound body surface area, when applied for 14 days to the radiated area of skin in patients with breast cancers and grade 2/3 dermatitis.

Secondary Objectives:

- To assess the efficacy of topical Oleogel-S10 gel vs placebo (vehicle gel) when added to standard of care (triamcinolone 0.1% cream) in reducing radiation wound

body surface area, when applied for 21 days to the radiated area of skin in patients with breast cancers and grade 2/3 dermatitis.

- To determine the effect of topical Oleogel-S10 gel vs placebo (vehicle gel) when added to standard of care (triamcinolone 0.1% cream) on the time to resolution of grade 2/3 radiation dermatitis via standardized photography.
- To evaluate adverse events (AEs) as determined by CTCAE v5.0 grading
- To assess health-related quality of life (HRQoL), as assessed by PRO-CTCAE (Appendix III) and the Radiation-Induced Skin Reaction Assessment Scale (RISRAS) (Appendix IIB).

Exploratory Objectives:

- To characterize time to resolution of ARD in intertriginous vs non-intertriginous skin and with respect to radiation dose.
- To characterize late effects of radiation, such as fibrosis, telangiectasias, hyperpigmentation, and dermatitis.
- To characterize the typical timeline of AE occurance.
- To assess patient compliance with the application of topical Oleogel-S10 gel or placebo

3.0 BACKGROUND AND RATIONALE

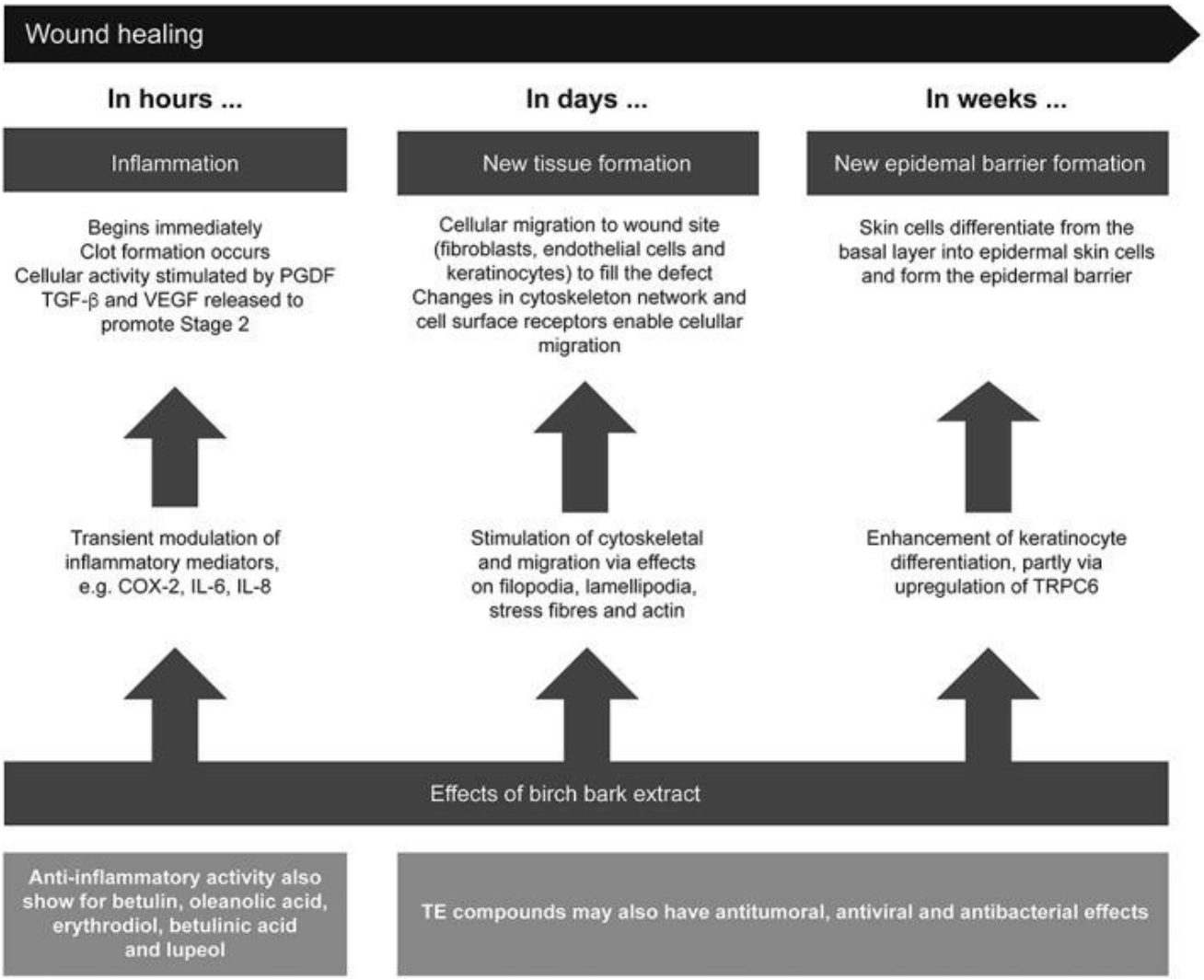
Radiation therapy (RT) is an essential treatment for people with cancer, but is associated with significant toxicities. After breast-conserving surgery, radiotherapy to the conserved breast halves reduces the rate at which the disease recurs and the breast cancer death rate by about a sixth[1].

Memorial Sloan Kettering Cancer Center Department of Radiation Oncology annually treats 1000 post-mastectomy patients (~400 at MSK Main; ~600 at MSK regionals) and ~1400 post-lumpectomy patients (~500 at MSK Main; ~900 at MSK Regionals) with breast cancer with external beam radiation, of whom approximately 43.8% are expected to develop grade 2-3 acute radiation dermatitis (ARD) with moist desquamation, providing a compelling rationale for effective prophylactic skin interventions and highlighting a need for therapeutic development. Standard of care guidelines for radiation dermatitis prevention have been developed at MSKCC for patients receiving post-mastectomy radiation therapy. These guidelines recommend application of topical steroids twice daily from day 0 of radiation through two weeks after completion of radiation. While topical steroids are established as an effective prophylactic therapy for acute radiation dermatitis[2] in post-mastectomy patients by reducing the incidence of moist desquamation (g2-3 ARD) from 66.7% to 43.8%, there is a paucity of therapies to expedite healing of acute (grade 2 to 3) radiation dermatitis wounds. Furthermore, MSKCC patients receiving radiation therapy without mastectomy (e.g., after lumpectomy) are routinely treated with topical steroids.

Topical Oleogel-S10 would augment the wound care armamentarium to treat ARD wounds. Oleogel-S10 is a sterile gel consisting of 10% dry triterpene extract (TE) refined from Betulae cortex (birch

bark) of which 72% to 88% is betulin, and the remaining ingredients are primarily betulinic acid, lupeol, oleanolic acid, erythrodiol, and residue of the extraction solvent and 90% sunflower oil.

Oleogel-S10 Mechanism of Action[3]:



In January 2016 Oleogel-S10 received a marketing authorization in the European Economic Area under the tradename Episalvan® for the treatment of partial thickness wounds in adults (Episalvan EPAR, first published 05Feb2016) and on 9/10/2018, the US FDA granted Investigational New Drug (IND) clearance to Oleogel-S10.

Pivotal clinical studies were performed in patients with split-thickness skin graft (STSG) donor sites wounds and in patients with Grade 2a burn wounds[4]. The primary efficacy end-point in the two pivotal studies on STSG donor sites wounds were intra-individual difference in time to wound closure (at least 95% epithelialization) between wound halves, either treated with Oleogel-S10 (AP101) gel and non-adhesive wound dressing, or with non-adhesive wound dressing alone. In

both pivotal studies, Oleogel-S10 gel met the primary end-point and was significantly superior in both studies compared to standard dressing. In the first study, the mean time from surgery to wound closure was 17.1 days with standard of care treatment and 15.5 days when the wound was treated with Oleogel-S10 gel every 3 to 4 days or more frequently depending on dressing changes[5]. The mean intra-individual difference in time to wound closure between the wound halves was -1.4 days. The difference was statistically significant ($p<0.0001$). The results in the second study were consistent with the first study. The mean time from surgery to wound closure was 16.0 days with standard dressing and 15.1 days when the wound was treated with Oleogel-S10 gel. The mean intra-individual difference in time to wound closure between the wound halves was -0.8 days and again statistically significant ($p<0.0232$)[4].

In the pivotal study performed in patients with Grade 2a partial thickness burn wounds who received Oleogel-S10 application at least every other day with dressing changes[6], the primary endpoint was percentage of patients showing earlier healing of the Oleogel-S10 gel treated wound half compared with the Octenilin® Wound Gel treated half. 85.7% of all treated patients had faster healing with Oleogel-S10 gel[6]. According to the mean expert evaluation, the mean time from the burn accident to wound closure was 7.6 days for Oleogel-S10 gel and 8.8 days for Octenilin® Wound Gel[4].

We hypothesize application of topical Oleogel-S10 to grade 2 – 3 acute radiation dermatitis wounds after radiation for breast cancer would expedite wound healing, leading to improvements in patients' quality of life.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Design: This is a single-center, prospective, randomized, double-blind study.

Purpose: This study is designed to to evaluate the efficacy of topical Oleogel-S10 gel when used as an adjunctive treatment to topical corticosteroids (indicated for the treatment of skin dermatoses) for the treatment of grade 2/3 radiation dermatitis

Patient population: Patients 18 years or older with breast cancer and radiation dermatitis grade 2/3.

Duration and follow-up: A total of 50 patients with breast cancer experiencing grade 2/3 radiodermatitis during their last 5 fractions of radiation therapy (i.e., after fraction day 20 (when completing 25 total fractions) or after fraction day 25 (when completing 30 total fractions inlusive of a 5 fraction boost)) of radiation therapy will be enrolled, such that 25 patients with breast cancer will be randomized to triamcinolone 0.1% cream once every morning (QAM) and vehicle gel once prior to bedtime (QHS) and 25 patients will be randomized to triamcinolone 0.1% cream QAM and topical Oleogel-S10 gel QHS for a 3 week period. The primary assessment will be measured at Calendar Day 14 after start of

topical application of Oleogel-S10 gel or vehicle gel. Completion of the study will be followed by a safety visit at 7 weeks (Day 49). Each patient will be on treatment for 21 days unless they experience any progression of RD to grade 4+, or intolerable or serious treatment-related AE. At 24 weeks (Day 168) after completion of radiation the patient will return to the clinic to assess for effects of the investigational treatment on the late effects of radiation.

4.2 Intervention

Patients who are receiving radiation therapy for breast cancer will be treated with either triamcinolone 0.1% cream QAM and vehicle gel QHS; or triamcinolone 0.1% cream QAM and topical Oleogel-S10 gel QHS for 21 days. At the time of grade 2/3 RD, patients will be enrolled into the study. All patients will have standard of care (SOC) triamcinolone 0.1% cream applied to the area of radiation QAM. Patients randomized into Oleogel-S10 will have Oleogel-S10 applied onto the area of radiation QHS. Those randomized to the comparator arm will have a vehicle/placebo gel applied to the area of radiation QHS, once a day for 21 days. For both study arms, treatment will continue for a period of 21 days, or until progression of RD to grade 4+, intolerable adverse event (AE) or serious AE related to the investigational agent.

Enrolled patients will be treated with our standard MSK fractionation for PMRT of 50Gy/2Gy per fraction or post-lumpectomy with dose and fractionation per physician discretion allowing both a 3D conformal and IMRT/VMAT planning technique. A chest wall boost for PMRT is allowed if indicated. Hypofractionation for PMRT will not be allowed. The use of bolus for our PMRT or post-lumpectomy patients is standardized by our MSK bolus guidelines policy. The thickness of bolus will be noted for each patient.

Standardized photos, grading with CTCAE, PRO-CTCAE and Radiation-Induced Skin Reaction Assessment Scale (RISRAS) will be obtained every week from day 0 of trial through day 21; and then subsequently at the week 7 safety visit (Day 49), and 24- week (Day 168) long-term follow up visit.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

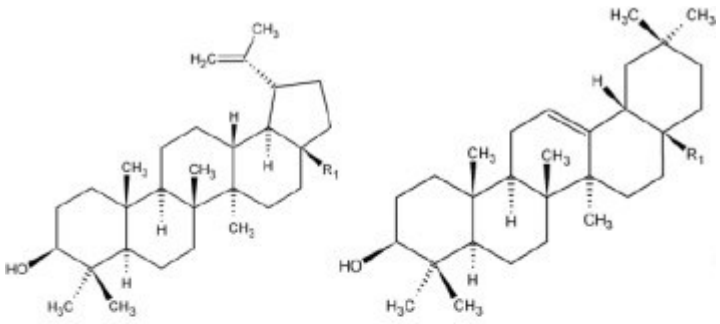
5.1 Study drug, packing, and labeling

Oleogel-S10

The study drug to be used in the course of this study is Oleogel-S10 which is a gel of 10% Triterpene Extract (Birch bark extract) and 90% sunflower gel[7].

The investigational product, Oleogel-S10, is a colourless to slightly yellowish, opalescent gel packed in white collapsible aluminium tubes containing 23.4 g gel each. Tamper-evident aluminium membranes close the tubes, which are fitted with white polypropylene screw caps. The single-use tubes are packed in cardboard boxes. The investigational product will be packed and labelled according to applicable regulatory requirements.

Oleogel-S10 Structural Formula:



lupane oleanane

Triterpene family	Triterpene	R_1 (C_{28})
Lupane	Lupeol	CH_3
	Betulin	CH_2OH
	Betulinic acid	COOH
Oleanane	β-amyrin	CH_3
	Erythrodiol	CH_2OH
	Oleanolic acid	COOH

Description of the Vehicle

For clarification, please note that the term “vehicle” describes the placebo throughout this protocol.

The sterile vehicle gel matches Oleogel-S10 in texture and visual appearance. 100 g of the vehicle gel will consist of 85 g sunflower oil, 5 g Cera flava/yellow wax, and 10 g Carnauba wax.

The SoC cream used in all patients is Triamcinolone acetonide
MF: $C_{25}H_{32}ClFO_5$; IUPAC Name: [(8S,9R,10S,11S,13S,14S,16S,17R)-17-(2-chloroacetyl)-9-fluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] propanoate.

Chemical Properties:
Oleogel-S10
Extract (as dry extract, refined) from birch bark from Betula pendula Roth, Betula pubescens Ehrh. as well as hybrids of both species (yield 10-20% (w/w)), quantified to 72% to 88% betulin. Extraction solvent: n-Heptane.

Triamcinolone acetonide

Triamcinolone acetonide is a derivative of prednisolone with high glucocorticoid activity and low mineralocorticoid activity. Triamcinolone acetonide is the acetonide salt form of triamcinolone, a topical synthetic corticosteroid with anti-inflammatory, antipruritic, and vasoconstrictive properties. Triamcinolone acetonide exerts its effect by binding to cytoplasmic glucocorticoid receptors and subsequently activates glucocorticoid receptor–mediated gene expression. This results in synthesis of certain anti-inflammatory proteins, with inhibition of synthesis of certain inflammatory mediators. Specifically, triamcinolone acetonide appears to induce phospholipase A2 inhibitory proteins, thereby controlling the release of the inflammatory precursor arachidonic acid from membrane phospholipids by phospholipase A2.

Because triamcinolone is fluorinated and also contains a substituted 17-hydroxyl group, it is not metabolized in the skin. Repeated application results in a cumulative depot effect in the skin, which may lead to a prolonged duration of action and increased systemic absorption. As circulating levels are below the level of detection, the use of pharmacodynamic endpoints for assessing the systemic exposure of topical triamcinolone is necessary. Once in the systemic circulation, triamcinolone is metabolized in the liver, but systemic metabolism has not been fully quantified. Excretion of triamcinolone acetonide and its metabolites occurs via the urine and bile.

Molecular weight
Oleogel-S10
Betulin (main component): 442.73 g/mol
Triamcinolone acetonide: 466.974 g/mol

Formulation and excipients:
Oleogel-S10
Birch bark extract (TE): 10 mg/100 mg; Sunflower oil, refined: 90 mg/100 mg

The extract with the oil forms a colorless to slightly yellowish, opalescent gel without any further ingredients. Oleogel-S10 is a gel with the active substance birch bark extract (triterpene extract, TE).

Triamcinolone acetonide
Triamcinolone acetonie is a colorless cream. 1 mg of Triamcinolone Acetonide per gram in a base containing Emulsifying Wax, Cetyl Alcohol, Isopropyl Palmitate, Sorbitol Solution, Glycerin, Lactic Acid, Benzyl Alcohol and Purified Water.

Pharmaceutical Properties
Oleogel-S10
TE is a dry extract (refined) from Betulae cortex (birch bark) from Betula pendula Roth, Betula pubescens Ehrh. as well as hybrids of both species (yield 10-20% (w/w)), quantified to 72% to 88% betulin (also called triterpene dry extract from birch bark). TE contains about 90% of the triterpenoids betulin (72% to 88%), betulinic acid (0.5% to 6%), lupeol (2% to 8%), oleanolic acid (0.1% to 2%), and erythrodiol (0.5% to 2%). Numerous biological effects

are reported for these substances. Besides antibacterial, antimycotic, antiviral, anti-inflammatory effects and antitumour effects, the triterpenes also display wound healing-promoting effects. Oleogel-S10 is applied topically. The effects of TE were investigated by preclinical in vitro and in vivo studies as well as by clinical phase 2 and 3 studies in different indications, including a phase 2 study in epidermolysis bullosa (EB).

Non-clinical Studies
Parenteral 14- and 28-day repeated dose toxicity studies in rats and dogs, respectively, showed no systemic test substance related changes except for those expected due to the insolubility of the TE extract at the injection site. Dermal application to intact or abraded minipig skin did not result in any systemic toxicity or adverse local reactions in a 4-week local tolerability study. A 39-week study in 24 Göttingen minipigs to measure the dermal safety of Oleogel-S10 versus sunflower oil control and sham-treated animals following daily non-occlusive administration to intact skin representing 10% of the body surface area, is ongoing. An interim report at 3-months indicates no significant treatment-relate findings including the analysis from skin biopsies taken at this timepoint. Systemic toxicity was assessed in juvenile rats following daily oral administration (by gavage) of TE in sunflower oil. The objective of this GLP study was to investigate the potential toxicity once daily from Day 10 to at least Day 63 of age, inclusive, and to assess the reversibility of any observed effects over a 28-day treatment-free period. Significant systemic exposure was achieved although both Cmax and AUC were lower at Day 63 due to differences in absorption by the immature and mature intestinal tract. At the doses tested (30, 100 or 300 mg/kg/day) TE was well tolerated, with no adverse effect on growth or development. For the females, minimal to moderate periportal vacuolation was seen in the liver at all dose levels, which was considered not to be adverse as the change typically reversed after a 28-day treatment-free period and there were no corresponding liver enzyme changes in the females. Based on the above findings in these juvenile animals, the No Observed Adverse Effect Level (NOAEL) was considered to be 300 mg/kg/day. At this dose, mean total systemic exposure (AUC0-24) of betulin, the primary component of TE, on Day 63 of age was 3,140 ng.h/mL and 2,110 ng.h/mL in males and females, respectively far in excess of any systemic exposure anticipated in the clinical study. A further 6-month systemic toxicity study in adult rats is currently ongoing. A study to investigate the effects of systemic exposure of TE on fertility and early embryonic development was completed and showed there was no negative impact when TE was delivered orally. Additionally, Oleogel-S10/TE did not act as a sensitiser, was not phototoxic, and was negative in all genotoxicity studies.

Clinical Studies
A phase 2 study in EB patients (12 wounds of 10 patients) (Schwieger-Briel 2017), as well as observations in 4 additional single case reports suggest that Oleogel-S10 may accelerate the healing of EB partial thickness wounds. Oleogel-S10 was well tolerated and no adverse drug reactions were observed. That Oleogel-S10 can accelerate the wound healing process was demonstrated in other wound types. In one phase 2 (24 patients) and three clinical phase 3 trials (280 patients) in partial thickness wounds, Oleogel-S10 showed a faster healing than standard treatment: in split-thickness skin graft donor site wounds the 17-day healing period with standard treatment was reduced by 1 to 2 days (Barret 2017), in Grade 2a burn wounds the 9-day healing period with standard treatment was reduced by 1 day. The studies compared intra-individually the difference in time to wound healing between wound halves treated with Oleogel-S10 versus wound halves treated with standard of care. The number of adverse events such as wound infections was lower on wound halves treated with Oleogel-

S10 compared to those treated with standard of care. The most frequently observed adverse reactions were wound complication (in 2.9% of patients), pain of skin (2.5%) and pruritus (1.3%). Adverse reactions were administration site reactions only. Clinical studies in further indications showed that TE was safe and well tolerated in atopic dermatitis (33 patients), psoriasis (24 patients), and actinic keratosis (151 patients). In summary, pharmacological data obtained with *in vitro* and *in vivo* model systems supports the potential utility of topically applied Oleogel-S10 in the treatment of grade 2 to 3 radiation dermatitis wounds.

Triamcinolone acetonide
Triamcinolone acetonide is indicated for the treatment of the following: moderate-to-severe inflammatory manifestations (including pruritus), corticosteroid-responsive dermatologic disorders (such as alopecia areata), atopic dermatitis, contact dermatitis, generalized exfoliative dermatitis, Rhus dermatitis (caused by plants such as poison ivy), seborrheic dermatitis, eczema (including severe hyperkeratotic eczema, severe nummular eczema, and severe eczematous conditions of the hands or feet), granuloma annulare, keloids, cutaneous lichen planus, lichen simplex chronicus, lichen striatus, subacute cutaneous and discoid lupus erythematosus, pretibial myxedema, necrobiosis lipoidica diabeticorum, pemphigoid, pemphigus, pityriasis rosea, sarcoidosis, sunburn, and urticaria.

Labeling: Medication labels will comply with US legal. They will supply no information about the patient. The same storage conditions will be described on each medication label.

5.2 Drug supply and storage
The drug will be shipped by Amryt Pharma directly to the MSKCC pharmacy. It will be received by a designated person at the MSKCC pharmacy, handled and stored properly and safely, and kept in a secured location to which only the investigator/pharmacist and/or designated assistants will have access. Upon receipt, Oleogel-S10 and vehicle gel should be stored according to the instructions specified on the drug labels [Store at below 30°C (86°F)]. Study tubes will be coded (no identifiable information regarding contents of vehicle or Oleogel-S10); both vehicle and Oleogel-S10 will have similar texture and color and will be indistinguishable.

Triamcinolone acetonide should be stored according to the instructions specified on the drug labels. At the baseline visit, patients will receive a calculated number of tubes of Oleogel-S10 gel or vehicle gel and one 454g jar of of triamcinolone acetonide 0.1% cream (standard of care). Additional jar(s) will be made available to the patients as needed, after they have used up the initial jar (as per study instructions) and returned the empty container to the study staff. Topical Triamcinolone are stored at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]

These instructions will also be made clear to the patient for storage and self-administration of Oleogel-S10 or Vehicle placebo gel at home (Patient Information Sheet, Appendix IV). At visits 1-3, a 7-day supply of study drug will be dispensed. Daily dose is 0.002 gram per cm^2 of acute radiation dermatitis; total dispensed drug dose is 0.014 gram/cm^2 x ___cm^2 of acute radiation dermatitis.

5.3 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit using information provided by the patient and/or caregiver in the Medication Application Diary (Appendix V). This record will capture information of medication used, dosages administered, and intervals between visits and the completion of the study. Patient is required to bring the investigational medication tubes to study visits for drug diary review and drug accountability return.

5.4 Medication administration
All participants will initiate treatment within 3 days of informed consent/ registration (exceptions can be made per PI discretion); first day of medication application will be considered Study Day 1.

Oleogel-S10 gel administration
The Oleogel-S10 gel will be self-administered once daily in the evening for the Oleogel-S10 group for the entire course of treatment by the patient (or caregiver), as per the instructions provided. The gel is applied to the wound surface at a thickness of approximately 1 mm and covered by Mepilex® Transfer dressing when possible. The gel is to be re-applied at each evening wound dressing change, until the wound is healed.

Fresh wounds should achieve hemostasis prior to application of Oleogel-S10. If necessary, wounds should be cleaned according to standard procedures, using e.g.gentle soap and water, prior to application of Oleogel-S10.

Oleogel-S10 gel is in tubes for single use only such that a new tube should be opened for each dressing change. Once opened, the product should be used immediately. Used tubes will be returned at following study visit for accountability.

Vehicle gel administration
The vehicle gel will be self-administered once daily in the evening for the placebo group for the entire course of treatment by the patient (or caregiver), as per the instructions provided. The gel is applied to the wound surface at a thickness of approximately 1 mm and covered by Mepilex® Transfer dressing when possible. The gel is to be re-applied at each evening wound dressing change, until the wound is healed.

Fresh wounds should achieve hemostasis prior to application of vehicle. If necessary, wounds should be cleaned according to standard procedures, using e.g.gentle soap and water, prior to application of vehicle.

Vehicle gel is in tubes for single use only such that a new tube should be opened for each dressing change. Once opened, the product should be used immediately. Used tubes will be returned at following study visit for accountability.

Triamcinolone 0.1% cream administration
Triamcinolone 0.1% cream will be self-administered once daily in the morning in both patient groups for the entire course of treatment by the patient (or caregiver), as per the instructions provided. The cream is applied to the wound surface at a thickness of approximately 1 mm and covered by Mepilex® Transfer. The cream is to be re-applied at each morning wound dressing change, until the wound is healed.

5.5 Supportive care guidelines and concomitant medications

Participants must be instructed not to apply any (new) topical additional medications, including over-the-counter products during the trial without prior consultation with the investigator. All topical products applied to the skin within 14 days of screening should be recorded. This includes all moisturizers, sunscreen, sunblock etc. If concomitant therapy must be added or changed, including over-the-counter medications, or alternative therapies, the reason and name of the drug/therapy should be recorded by the investigator.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

Any patients age 18 years and older with breast cancer undergoing post-mastectomy radiation therapy (PMRT) or post-lumpectomy RT will be considered for participation.

6.1 Participant Inclusion Criteria

- Patients who are receiving PMRT to the chest wall or post-lumpectomy RT to the whole breast breast cancer of any stage
- Age ≥ 18 years
- Patients who develop ARD grade 2/3 after fraction day 20 (when receiving 25 total fractions) or after fraction day 25 when receiving (30 total fraction inclusive of a 5 fraction boost) of radiation therapy with all locations of desquamation
- Able to self-administer topical interventions or provide for another person to apply the topical intervention
- Patients may be started on any topicals prior to study enrollment. Once patient is enrolled on study (on or before Day 1), patient must be able to discontinue other topicals (including topical steroids, Silvadene, calcineurin inhibitors) to the treatment area
- Patients have completed surgery or chemotherapy ≥ 4 weeks prior to start of radiation therapy. Patients may receive antibody-drug conjugates at any time before/during/after study.
- Women of childbearing potential (WCBP) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 0) and documented monthly.
- WCBP must agree to abstrain from sex or use a highly effective method of birth control* from the time of consent through visit 5.

  *Adequate contraceptive methods include those with a low failure rate, i.e., less than 1% per year, when used consistently and correctly, such as abstinence from sexual intercourse, and some double barrier methods (condom with spermicide) in conjunction with use by the partner of an intrauterine device, diaphragm with spermicide, oral contraceptives, birth control patch or vaginal ring, or injectable or implanted contraceptives. Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence

(e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

A woman that is postmenopausal (≥2 years since last menstrual period) or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy) is not considered a WCBP.

6.2 Participant Exclusion Criteria

- Patients who are receiving radiation therapy for inflammatory breast cancer or malignant fungating wound
- Known history of allergy to any ingredient of the study medication
- Patients with collagen-vascular disease/vasculitis
- Patients receiving hypofractionated radiation therapy
- Special populations:
    - patients who, in the opinion of the investigator have a condition that precludes their ability to provide an informed consent

7.0 RECRUITMENT PLAN

A member of the patient's treatment team, a protocol investigator, or research staff, at Memorial Sloan Kettering Cancer Center (MSKCC) will identify potential research subjects. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects may also be referred to the investigator/research staff of the study by the treating physician or any MSKCC physician. Generally, the patient's primary radiation oncologist and primary dermatologist will identify potential research subjects.

The participating investigators may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study, and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

The following procedure will be employed in enrolling all participants into the study. (Potentially) eligible patients identified by the mechanism described in the preceding paragraphs, will be offered participation in the study. This will be accomplished by the treating physician, clinician, or research staff, in person. The purpose of the study will be explained to the patient and informed consent will be obtained from willing participants. (Potential participants will also be offered the opportunity to consider participation and review the consent documents (e.g. at home) with the option of providing consent in the future.) Subsequently, a consenting professional will call potential adult study participants to invite them to participate. Patients may be screened by the research team at the patient's location (e.g., in radiation oncology unit or dermatology unit). If they agree to enroll, then the eligible

participants will be scheduled for in-person consenting (if not already performed) and baseline assessments. The patient will be transferred to the dermatology clinic for enrollment and study assessments, when possible on the same day, or within the study window. This visit will preferably coincide with patients' standard-of-care visit. Potential participants who decline participation will not be contacted again for the purpose of recruitment into the study.

We will only retain participants' basic information (e.g. questionnaire responses, eligibility checklist, etc.) that is needed for study reporting purposes. These records will be maintained on a secured Dermatology shared drive. We will also maintain a list of all participants approached throughout the entire study to record reasons for refusal and avoid re-approaching healthy volunteers that have been identified as ineligible or refusing participation. This list will be destroyed at the completion of the study.

The investigators participating in this research include physicians and research staff from Memorial Sloan Kettering Cancer Center, as listed on the face page of this protocol, who have successfully completed training for protection of human research subjects in compliance with MSKCC clinical research policy. Written consent will be obtained by one of these individuals or his/her designee, who must also have successfully completed training for protection of human subjects in compliance with MSKCC clinical research policy.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or in the medical record to confirm that the patient is eligible, and to contact the patient regarding research enrollment. If the patient turns out to be ineligible for the research study, the study personnel will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed

Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

7.2 Randomization

This is a randomized double-blind label comparison of topical Oleogel-S10 versus vehicle gel, when added to standard of care (topical triamcinolone). After eligibility is established and immediately after consent is obtained, patients will be registered in the Clinical Trial Management System (CTMS). After registration, patients will be randomized in the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block. Patients' treatment assignments can be viewed in the CRDB only by CRDB staff.

7.3 Blinding

The study will be conducted using a double-blind design. The randomization process that occurs on screening visit will blind the participant. The investigators will be unaware of the treatment assignment of participants unless unblinding is performed.

7.4 Unblinding

Participant unblinding will be performed after all study assessments have been completed (after completion of Visit 6) by the PI only. The PI will seek MSK IRB approval prior to unblinding the participant. The study team will work with CRDB staff for unblinding after MSK IRB approves of it. Both the participant and the PI will be informed by CRDB personnel which arm the participant was randomized to.

In case of emergency, emergency unblinding may be exercised when the PI believes that awareness of the subject's medication is beneficial to the management of the adverse event. When an emergency unblinding has taken place, the treatment identification information is only unmasked to the PI, and other personnel remains masked. The study team must discuss and receive approval from the PI before unblinding. Unblinding will be completed by contacting CRDB personnel.

For participants whose treatment assignment has been unblinded due to emergency, the participant may continue the study treatment if the PI believes that the study medication is beneficial to the management of the patient's wellbeing.

8.0 INFORMED CONSENT PROCEDURES

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

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

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

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

9.0 PRE-TREATMENT/INTERVENTION

Patients may be screened and consented starting from up to 3 days before study initiation.

The following initial baseline procedures can take place at any time during this period, or on the day of initiation:

1. Medical history, including concomitant medications

2. Study assessments (serve as baseline measures for the study):
    - Patient-reported Outcomes (Appendix):
        - PRO-CTCAE™ for acute radiation dermatitis wound
        - Radiation-induced skin reaction assessment scale (RISRAS)
    - Clinical assessments (Appendix)
        - Skin examination with calculation of surface area with ruler and device measurement of radiation dermatitis and wound
        - The radiation dermatitis will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0
        - Radiation-induced skin reaction assessment scale (RISRAS)
    - Standardized photography

- The affected area of chest including the acute radiation dermatitis wound including wound will be photographed.

Visit # **Study day:**	Pre-study Screening Day -3 to Day 1 (In-Person)
Reason for visit	
Informed consent	**X**
Medical history	**X**
Vital signs	**X**
Skin examination	**X**
Patient- and Physician-reported outcomes questionnaires PRO-CTCAE, CTCAE, and RISRAS	**X**
Standardized photography	**X**
Pregnancy test for women of childbearing potential	**X**

10.0 TREATMENT/INTERVENTION PLAN

All patients will receive topical triamcinolone 0.1% cream application in the morning. Patients randomized to the Oleogel-S10 arm will be prescribed once nightly use of topical Oleogel-S10 gel and those randomized to the SOC arm will apply vehicle gel for 21 ± 2 days. Oleogel-S10 will be provided as topical gel. Triamcinolone 0.1% cream will be provided as a cream.

Once daily (at least 60 minutes before bedtime), patients will be instructed to apply a 1 mm thick layer of the topical Oleogel-S10 gel to the area of acute radiation dermatitis. Patients will receive detailed instructions at the baseline visit and receive clear, written instructions on the standarized application technique (see Patient Information Sheet, Appendix IV). Approximately 0.1g of Oleogel-S10 or vehicle gel per cm^2 of wound will be applied. Patients will be instructed to apply 1 fingertip unit (approximately 0.5g) per $250cm^2$ of wound.

In the treatment group, patients will not be allowed to apply topical emollients to the treated area during the study, but if desired, they may apply to untreated areas. Patients will be advised not to use products with chemicals or perfumes.

We do not anticipate the need for any adjustments to the treatment plan as consequence of adverse reactions to Oleogel-S10 (see section 15.0), but any patients with adverse cutaneous reactions to treatment with Oleogel-S10 will be advised to return to clinic to see a

dermatologist right away. Adverse event reporting will be based on CTCAE v5.0, as applicable. There will be six on-site visits. In the case of pandemic clinic closures, on-site visits may be converted to virtual visits in the case the patient does not have a same-day standard of care or treatment visit.

Patients will also be asked to use a diary to improve their compliance with the application of triamcinolone 0.1% cream, Oleogel-S10 gel, vehicle gel, as well as to record fingertip units of study gel applied, any adverse effects of treatment, and will be asked to bring diaries to all patient visits.

Skin examinations will be part of the evaluation performed during baseline visit at day 1, day 7, day 14, day 21, day 49, and Day 168. Patients will also complete adapted PRO-CTCAE™ questionnaires to measure dermatology-specific patient-reported symptoms and outcomes at each of the aforementioned visits for the area of ARD. Study questionnaires should take the participant no more than 10 minutes to complete at each time point. Standarized photography will be performed day 1, day 7 ± 1 days, day 14 ± 2 days, day 21 ± 2 days, day 49 ± 3 days, and Day 168 ± 7 days. Patients will be enrolled in the radiation oncology or dermatology clinics, and their clinical response will be assessed in the Dermatology clinic of Memorial Sloan-Kettering Cancer Center located in Manhattan or Basking Ridge. Visits Day 1 and Day 14 will be in-person visits. Visits Day 7, 21, 49, and 168 may be conducted in-person or virtual per patient preference.

Measurement of Wound Surface Area

Wound surface area will be measured at each visit via Canfield Scientific, Inc, a HIPAA-compliant 3D imaging system that uses machine learning and computer vision to measure wounds. The Canfield software calculates the area once the user manually outlines the wound edge. Noncontiguous areas will each be outlined and the sum of the total area involved will be used. 3D Canfield photography is the gold standard wound imaging software for clinical trials.

The investigator and authorized site study team members will receive a standardized training before start of the study. The ‘Photo Documentation Manual’ (Appendix) will provide a detailed description of the Canfield software, instructions for use, and a standard operating procedure of wound photography.

Common Terminology Criteria for Adverse Events (CTCAE) v5.0

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which is routinely utilized for Adverse Event (AE) reporting in oncologic patients. A grading (severity) scale is provided for each AE term.

PRO-CTCAE

PRO-CTCAE is a patient-reported outcome measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials. It was designed to be used as a companion to the

Common Terminology Criteria for Adverse Events (CTCAE), the standard lexicon for adverse event reporting in cancer trials. PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical trials.

Radiation-induced Skin Reaction Assessment Scale (RISRAS)

RISRAS is a tool developed for clinical and research practice with reliability and validity testing[8]. RISRAS measures both the subjective symptoms and objective signs of radiation-induced skin reactions[8]. This tool consists of a patient symptom scale for self-report and a healthcare professional assessment scale to measure the signs[8].

11.0 EVALUATION DURING TREATMENT/INTERVENTION

Table 1. Assessments: 6 study visits

Visit #	1	2	3	4	5	6
Study Day	Day -3 to Day 1*** (In-Person)	Day 7 ± 1 days (In-person or Virtual)	Day 14 ± 2 days (In-Person)	Day 21 ± 2 days (In-person or Virtual)	Day 49 ± 3 days (In-person or Virtual)	Day 168± 7 days (In-person or Virtual)
Reason for visit	Screening and Pre-treatment baseline evaluation	Interval follow-up evaluation	Interval follow-up evaluation	Treatment ends	Safety follow-up	24-week Long-term follow-up
Informed consent	X					
Medical history	X					
Vital signs	X	X	X	X	X	X
Skin examination	X	X	X	X	X	X
Pregnancy test for women of childbearing potential	X				X	
Patient- and Physician-reported outcomes questionnaires PRO-CTCAE, CTCAE, and RISRAS	X	X	X	X	X	X

Standardized photography with wound measurements	X*	X**	X*	X**	X**	X**
Drug diary return		X	X	X		
Drug accountability		X	X	X		
Drug dispensed	X	X	X			
Drug applied	Begin on Day 1	X	X	Completed this visit		

Footnotes:
**Photos to be examined and measured via Canfield 3D imaging software*
***Photos to be examined and measured via Canfield 3D imaging software OR via Patient-Submitted Home Photos*
****Screening and Day 1 Visit can be combined to occur on the same date.*

12.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study (and will not be replaced) if:
- They develop an adverse event necessitating discontinuation of topical interventions.
- They develop a grade 2 or higher dermatologic adverse event that has an attribution by the investigator of at least 'possibly' treatment-related.
- They require greater than 14 days off therapy due to a treatment-related adverse event.
- They have RD progression to grade 4.
- They develop new cutaneous metastases within the treatment area.

Patients will be removed from the study and replaced if:
- They enroll in an alternate systemic clinical trial which prohibits concurrent topical clinical trial participation.
- They choose to withdraw consent for continued participation.
- Death occurs unrelated to the RD.
- They are lost to follow-up before RD can be evaluated.

All patients who receive Oleogel-S10 or vehicle and report using the treatment will be evaluable for toxicity.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

The primary outcome of this study is the efficacy of Oleogel-S10 in reducing radiation dermatitis grade 2-3 wound size in patient with breast cancer undergoing external beam radiation therapy. Clinical assessment at all study visits, including wound

surface area and adverse events will be performed by a dermatologist. Wound size will be measured using a HIPAA compliant 3D clinical imaging system.

The following are the secondary outcomes:

- Time to complete resolution of grade 2/3 radiation dermatitis assessed via standardized 3D clinical imaging. We will continue to monitor the study lesion area after the Day 14 (primary outcome) time point. Lesional area will monitored and imaged at all study visits through Day 168. A wound will be considered completely healed when wound size is 0 cm^2.
- Differences in adverse events at Day 21, as determined by the CTCAE v5.0; and health-related quality of life (HRQoL): as assessed by PRO-CTCAE (Appendix) and the Radiation-Induced Skin Reaction Assessment Scale (RISRAS).

The tertiary objectives of this study are to determine the effect of topical Oleogel-S10 gel on the late effects of radiation, such as fibrosis, telangiectasias, hyperpigmentation, and dermatitis.

Criteria for evaluation of clinical efficacy:

Wound surface area:
The PI or a trained designee will measure the subject's wound and calculate surface area via the 3D Canfield Imaging Software for in person visits and via patient-submitted photographs for virtual visits, when applicable.

Time to healing of wound:
Wounds in both groups will be measured and photographed at baseline/Day 1, Day 7, Day 14, Day 21, Day 49, and Day 168. Measurements will be taken via Canfield 3D Imaging softwares on baseline/Day 1, Day 7*, Day 14, Day 21*, Day 49*, Day 168*. A wound will be considered healed when wound size is 0 cm^2. (*Only for patients who present in person; otherwise wounds will be examined via patient-submitted home photos reviewed during virtual visit.)

CTCAE Grading:
Efficacy will be considered a mean improvement score in the CTCAE grade of each term of 0.3 or greater at Visit 5.The PI or a trained designee will assess the subject's skin for adverse events and late effects for the below parameters using the CTCAE version 5.0 grading (severity) scale shown in Appendix I:

- Dermatitis radiation
- Body odor
- Pain of skin
- Pruritus
- Skin hyperpigmentation*

- Skin hypopigmentation*
- Dry skin
- Skin atrophy
- Hyperkeratosis
- Skin induration (fibrosis)
- Skin ulceration
- Telangiectasia

Note: A "0" grade will be used to document subjects with no presence of the CTCAE skin adverse event symptoms for radiation dermatitis, body odor, pain of skin, pruritus, skin hyperpigmentation, skin hypopigmentation, dry skin, skin atrophy, hyperkeratosis, skin induration, skin ulceration, telangiectasia.

A percent body surface area for skin hyperpigmentation and skin hypopigmentation will be recorded and mean improvement will be calculated at visit 5.

Subject Questionnaires:
The subject will complete the below questionnaires for adverse events and late effects:

- PRO-CTCAE questionnaire (see Appendix III)
- Radiation-Induced Skin Reaction Assessment Scale (RISRAS) (see Appendix IIB)

The PI or a trained designee will complete the below questionnaires for adverse events and late effects:

- Radiation-Induced Skin Reaction Assessment Scale (RISRAS) (see Appendix)

Patient Compliance:

Study personnel will evaluate the patient diary for compliance with application of the topical Oleogel-S10 gel or placebo. If the patient diary is incomplete, the study participant will be asked about compliance since the last study visit.

Criteria for evaluation of clinical safety:

CTCAE Grading:
Safety will be assessed by the PI or trained designee for adverse events, graded via the CTCAE v5.0.

Breast cancer recurrence and survival
Loco-regional recurrence and (disease-specific and overall) survival data will be collected through Visit 6 (24-week Long-term follow-up). We will explore differences in survival between the Oleogel-S10 and vehicle groups, controlling for stage of breast cancer at study treatment inception.

13.2 Criteria for Study Endpoint Evaluability

The efficacy and tolerability analysis will be evaluated for all intent-to-treat subjects, defined as all subjects who use standard of care or Oleogel-S10 topical and have baseline and at least one post-baseline data point.

In case of early subject withdrawal, subjects may be replaced based upon overall enrollment numbers.

14.0 BIOSTATISTICS

The primary objective of this study is to assess the efficacy of topical Oleogel-S10 gel vs placebo (vehicle gel) when added to standard of care (triamcinolone 0.1% cream) in reducing radiation wound surface area, when applied for 14 days to the radiated area of skin in patients with breast cancers and grade 2/3 dermatitis. For the primary objective we are measuring radiation wound size at baseline (day 1) and and follow-up (day 14 +/- 3 days). We are estimating percent change in radiation wound size between the two time points as:

$$\text{Percent change from baseline} = \frac{(\text{Baseline size} - \text{Follow-up size}) \times 100}{\text{Baseline size}}$$

A mean percent change will be estimated for both Oleogel-S10 and vehicle control arms.

We plan to enroll and randomize 50 participants. If we lose ~10% of our participants between baseline and follow-up due to attrition, we will have an effective sample size of 44 participants for primary endpoint evaluation. With 22 participants per treatment arm and an average percent reduction in the vehicle control arm of 0.2 or 20%, a common standard deviation of 0.2, and an alpha level of 5%; based on a two-sided means test we have >80% power to detect a mean difference of greater than 0.18 (Table). Estimates of percent reduction and standard deviation in the vehicle control arm were arrived at by the principal investigator's experience treating these lesions in this patient population. To test the differences in mean percent change between the treatement groups at day 14, we will perform an independent sample Student's t-test.

Alpha-level	Power	N	AP-101	Vehicle	Delta	Average % change vehicle arm	Average % change Oleogel-S10 arm	Common SD
0.05	0.7364	44	22	22	0.16	0.2	0.36	0.2
0.05	0.7865	44	22	22	0.17	0.2	0.37	0.2
0.05	0.8305	44	22	22	0.18	0.2	0.38	0.2

0.05	0.8682	44	22	22	0.19	0.2	0.39	0.2
0.05	0.8997	44	22	22	0.20	0.2	0.4	0.2

Secondary Objectives are to describe the resolution rate of grade 2/3 radiation-induced dermatitis. Evaluation of the safety of Oleogel-S10, and the patient reported symptoms will be assessed using the CTCAE v5.0 grading, the PRO-CTCAE (Appendix) and the Radiation-Induced Skin Reaction Assessment Scale (RISRAS).

The efficacy of topical Oleogel-S10 gel vs placebo (vehicle gel) when added to standard of care (triamcinolone 0.1% cream) in reducing radiation wound surface area, when applied for 21 days to the radiated area of skin in patients with breast cancers and grade 2/3 dermatitis will be assessed as a secondary outcome, with the above methods used for the primary outcome.

Time to lesion resolution is defined as time from radiation therapy grade 2/3 dermatitis assessement to complete resolution of the radiation dermatitis. Assessments and quantification will be accomplished through the use of 3D clinical imaging for in-person visits and home photography for virtual visits. Patients with lesions that do not resolve at the time of study completion, or who are lost to follow-up, are to be censored at the last date of physician assessment and imaging. The proportion of patients who achieve resolution of the dermatitis will be calculated along with their 95% confidence intervals for both treatment arms. The rate of overall lesion resolution will be estimated by the Kaplan-Meier method. A logrank test will be used to compare the distributions of resolution rates by treatment arm.

The rates of adverse events and the rates of grades 3-5 adverse events will be tabulated using the CTCAE v5.0. These adverse events will be presented on an individual basis and summarized using descriptive statistics. The proportion of patients with these toxicities and the severity will assessed at each study time point along with exact binomial confidence intervals. The proportion of pariticipants with adverse events by treatment group at each evaluation time point will be evaluated using chi-square statistics or Fisher's exact tests. The distribution of patient-assessed Radiation-Induced Skin Reaction Assessment Scale (RISRSAS) scores will be assessed at each study time point. T-tests or Wilcoxon rank-sum tests will be used to assess differences in RISRAS scores.

For the patient reported outcomes (PRO-CTCAE and RISAS) we will use descriptive statistics and graphical methods to show the measures at each time point and to display the the trends in these measures across the evaluation time points. For each intstrument, we will initially use ANOVA methods with repeated measures and a time component to assess whether there are any significant changes over time. If we observe significant changes, we will explore the subject-specific graphs to see if there is a consistent pattern in the changes (i.e., trending upward, trending downward, upward then levelling off, etc). We will also use random effects models to investigate any longitudinal associations. This method can

account for the serial correlation, time-varying covariates and missing interval measures from any of the study participants.

We will invariably have some missing data during the course of the follow-up. We will try to determine whether these data are missing at random. With quality of life measures, patients with lower initial quality of life measures might be more prone to missingness. If we find a single missing quality of life instrument for a given time point for a participant, we will assume that this is missing at random. If we observe more than one missing instrument for a participant, we will attempt to determine whether refusal to complete the instrument is associated with disease severity and/or overall quality of life. If we see a general pattern of missingness within the study population, we will estimate the degree and direction to which this is occurring.

As an exploratory objective, we will assess wound resolution in intertriginous vs non-intertriginous skin and with respect to radiation dose and late effects of radiation, such as fibrosis, telangiectasias, hyperpigmentation, and dermatitis. We will also characterize the timeline to onset of these AEs. The absolute number, distribution and the proportion of participants who experience these adverse events will summarized by study time point. The radiation dose to the skin will be recorded to evaluate if treatment hotspots impact dermatitis healing rates. We will record V110 to the skin of all patients enrolled on the trial retrospectively. The skin organ at risk volume will be defined as the 5mm from the patient surface encompassing the entire treatment portal.

The analysis of this exploratory objective will be similar to the secondary objective with elapsed time to resolution of radiation dermatitis defined as time from radiation therapy grade 2/3 dermatitis assessement to complete resolution of the radiation dermatitis. Lesions will be categorized as in intertriginous vs non-intertriginous by the study investigator based on visual skin examination at Study Day 1. Lesion resolution will be assessed by Canfield imaging. Patients with lesions that do not resolve at the time of study completion, or who are lost to follow-up, are to be censored at the last date of physician assessment and imaging. The proportion of patients who achieve resolution of the dermatitis will be calculated along with their 95% confidence intervals for both treatment arms and by categorization of intertriginous vs non-intertriginous areas. The rate of overall lesion resolution will be estimated by the Kaplan-Meier method. A logrank test will be used to compare the distributions of resolution rates by treatment arm and by intertriginous vs non-intertriginous areas.

Patient compliance with the application of the topical Oleogel-S10 gel or placebo will be assessed at study visits 2, 3, & 4 (Day 7 +/-1 day, Day 14 +/- 2 days, & Day 21 +/- 2 days). For each pariticipant the total days compliant from Baseline to Day 21 will be summed. We will calculate the proportion of days compliant with application of topical Oleogel-S10 gel or placebo for each participant. We will also evaluate the distributions of compliance for the treatment and placebo arms, and compare mean or median compliance using a t-test or a Wilcoxon rank sum test.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

15.1 Oleogel-S10

Safety
Intensive non-clinical in vitro and in vivo experiments in different species of different ages and different routes of administration up to long-term chronic use raise no concerns for conducting clinical trials. In single and repeated dose experiments, in safety pharmacology tests, and in the genotoxic evaluation no adverse effects have been observed. Taking results of all toxicological experiments together, and keeping in mind that the intended route of TE is the Oleogel-S10 topical application, TE can, therefore, be considered as safe when applied to the skin, including abraded skin. In clinical trials in patients with partial thickness wounds Oleogel-S10 was well tolerated. The most common adverse events related to Oleogel-S10 concerned 25 patients out of 280 (9%), comprising pain of skin (2.9%) and pruritus (1.4%).

Adverse Reactions Reported in Clinical Trials with Donor Site Wounds and Grade 2a Burns

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infections and infestations		Wound infection
Immune system disorders		Hypersensitivity
Skin and subcutaneous tissue disorders	Pain of skin	Dermatitis
	Pruritus	Rash pruritic
		Purpura
General disorders and administration site conditions		Pain
Injury, poisoning and procedural complications	Wound complication*	

* Wound complication comprises different kinds of local complications such as post-procedural complications, wound necrosis, wound secretion, impaired healing, or inflammation of wound

Deaths, serious adverse events and adverse events that led to discontinuation
The number of patients in the pooled analysis (study BSH-12, BSG-12 and BBW-11) who experienced one or more serious AEs (SAEs) was low (15 or 5.4% of the patients). The most frequently reported SAEs were wound infection (4 or 1.4% of patients) and condition aggravated (2 or 0.7% of patients). All other SAEs were reported for 1 (0.4%) patient each. None was considered related to treatment except for one SAE (wound necrosis), for which causality between treatment and event was reported as “yes: unknown” by the investigator. Wound necrosis was experienced by a 79-year-old male in the Grade 2a burn wound study BBW-11 (Patient B-02-02). Both the wound half treated with Oleogel-S10 and the wound half treated with standard of care (Octenilin® wound gel with fatty gauze dressing) had changed to Grade 2b and required skin grafting resulting in prolonged hospital stay. A change in burn wound depth from Grade 2a to Grade 2b was expected for up to 30% of patients in the study. Skin grafting is the standard treatment for Grade 2b burn wounds.

No deaths were reported in the treatment phase of the studies. Two deaths in the 12 months follow-up period were considered not related to the treatment. CTCAE Version 5 will be utilized for toxicity evaluation.

15.2 Triamcinolone acetonide

Topical application of triamcinolone acetonide cream results in a markedly (~90%) lower relative bioavailability than oral administration. Because triamcinolone is fluorinated and also contains a substituted 17-hydroxyl group, it is not metabolized in the skin. Repeated application results in a cumulative depot effect in the skin, which may lead to a prolonged duration of action and increased systemic absorption. As circulating levels are below the level of detection, the use of pharmacodynamic endpoints for assessing the systemic exposure of topical triamcinolone is necessary. Once in the systemic circulation, triamcinolone is metabolized in the liver, but systemic metabolism has not been fully quantified. Excretion of triamcinolone acetonide and its metabolites occurs via the urine and bile.

Absorption after topical application of triamcinolone is increased in areas that have skin damage, inflammation, or occlusion or in areas where the stratum corneum is thin, such as the eyelids, genitalia, axillae, and face. The use of occlusive dressings with the application of triamcinolone enhances penetration into the skin and may increase the chance of systemic absorption. Ointments have a hydrating effect, are lipophilic, and enhance the penetration of triamcinolone into the skin. Triamcinolone gels, foams, and solutions also have enhanced topical penetration versus cream preparations. Once absorbed, maximal vasoconstrictive effects of triamcinolone occur within 1.5 hours of application. Anti-inflammatory effects are usually not seen for hours after triamcinolone application since the mechanism of action requires alterations in synthesis of proteins.

Corticosteroid Hypersensitivity

Triamcinolone is contraindicated in any patient with a history of corticosteroid hypersensitivity and hypersensitivity to triamcinolone or any ingredients in the preparation. Although true corticosteroid hypersensitivity is rare, patients who have demonstrated a prior hypersensitivity reaction to triamcinolone should not receive any form of triamcinolone. It is possible, although also rare, that such patients will display cross-hypersensitivity to other corticosteroids. It is advisable that patients who have a hypersensitivity reaction to any corticosteroid undergo skin testing, which, although not a conclusive predictor, may help to determine whether hypersensitivity to another corticosteroid exists. Such patients should be carefully monitored during and following the administration of any corticosteroid.

Cushing's Syndrome, Hepatic Disease, Hypothalamic-Pituitary-Adrenal (HPA) Suppression, Occlusive Dressing, Skin Abrasion

Systemic absorption of topical corticosteroids has produced reversible HPA suppression and/or manifestations of Cushing's syndrome in some patients. Triamcinolone acetonide has

been shown to suppress the HPA axis at doses as low as 2 g/day. Conditions that increase systemic absorption include application of high-potency corticosteroids, use over large surface areas, prolonged use, use in areas where the epidermal barrier is disrupted (i.e., skin abrasion), use in pediatric patients, use in patients with hepatic disease, and the use of an occlusive dressing. Triamcinolone acetonide preparations should not be used with occlusive dressings. Patients receiving large doses of a potent topical corticosteroid such as triamcinolone should be evaluated periodically for evidence of HPA axis suppression and manifestations of Cushing's syndrome. If these effects are noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less-potent corticosteroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation. Infrequently, signs and symptoms of withdrawal may occur, requiring supplemental systemic corticosteroids.

Diabetes Mellitus

Topical corticosteroids, including triamcinolone, should be used with caution in patients with diabetes mellitus. Exacerbation of diabetes may occur with systemic absorption of the topical corticosteroid. Use of topical corticosteroids may further delay healing of skin ulcers in diabetic patients.

Pregnancy

Triamcinolone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Topical corticosteroids, including triamcinolone, should not be used in large amounts, on large areas, or for prolonged periods of time in pregnant women. Guidelines recommend mild to moderate potency agents over potent corticosteroids, which should be used in short durations. Fetal growth restriction and a significantly increased risk of low birthweight have been reported with the use of potent or very potent topical corticosteroids during the third trimester, particularly when using more than 300 g. There are no adequate and well-controlled studies of the teratogenic effects from topical application of triamcinolone in pregnant women. Corticosteroids have been shown to be teratogenic after dermal, oral, and subcutaneous administration in animal studies. Triamcinolone has greater potency and, thus, greater teratogenic potential than other topical corticosteroids. After subcutaneous administration of triamcinolone acetonide to pregnant mice and rabbits, increased malformations, such as cleft palate and skeletal abnormalities, were observed.

Fungal Infection, Herpes infection, Infection, Measles, Peripheral Vascular Disease, Varicella, Viral Infection

The normal inflammatory response to local infections can be masked by triamcinolone. Application of topical corticosteroids to areas of infection, including tuberculosis of the skin, dermatologic fungal infection, and cutaneous or systemic viral infection (e.g., herpes infection, measles, varicella), should be initiated or continued only if the appropriate anti-infective treatment has been instituted. If the infection does not respond to the antimicrobial therapy, the concurrent use of the topical corticosteroid should be discontinued until the

infection is controlled. Topical corticosteroids may delay the healing of noninfected wounds, such as venous stasis ulcers. Triamcinolone preparations should be used with caution in patients with markedly impaired circulation or peripheral vascular disease; skin ulceration has been reported in these patients following topical corticosteroid use.

Geriatric, Skin Atrophy

Topical corticosteroids should be used for brief periods or under close medical supervision in patients with evidence of preexisting skin atrophy. Geriatric patients may be more likely to have preexisting skin atrophy secondary to aging. Purpura and skin lacerations that may raise the skin and subcutaneous tissue from deep fascia may be more likely to occur with the use of topical corticosteroids in geriatric patients. Clinical trials of topical triamcinolone included insufficient numbers of elderly patients to perform a separate analysis of efficacy and safety in this population. On the basis of the available data, no dosage adjustments are required for elderly patients receiving topical triamcinolone. Use of lower-potency topical corticosteroids may be necessary in some patients.

Adverse Reactions

Previously observed adverse reactions for **triamcinolone acetonide** are listed below.

Severe

Skin atrophy / Delayed / 0-2.0
Papilledema / Delayed / Incidence not known
Increased intracranial pressure / Early / Incidence not known
Visual impairment / Early / Incidence not known
Ocular hypertension / Delayed / Incidence not known

Moderate

Erythema / Early / 1.0-10.0
Withdrawal / Early / Incidence not known
Pseudotumor cerebri / Delayed / Incidence not known
Hyperglycemia / Delayed / Incidence not known
Growth inhibition / Delayed / Incidence not known
Hypothalamic-pituitary-adrenal (HPA) suppression / Delayed / Incidence not known
Glycosuria / Early / Incidence not known
Adrenocortical insufficiency / Delayed / Incidence not known
Cushing's syndrome / Delayed / Incidence not known
Hypertension / Early / Incidence not known
Cataracts / Delayed / Incidence not known
Impaired wound healing / Delayed / Incidence not known
Skin ulcer / Delayed / Incidence not known

Tolerance / Delayed / Incidence not known
Contact dermatitis / Delayed / Incidence not known

Mild

Maculopapular rash / Early / 1.0-10.0
Pruritus / Rapid / 1.0-10.0
Skin irritation / Early / 2.0-10.0
Xerosis / Delayed / 1.0-10.0
Striae / Delayed / 0-2.0
Acneiform rash / Delayed / 0-2.0
Infection / Delayed / 0-2.0
Skin hypopigmentation / Delayed / 0-2.0
Folliculitis / Delayed / 0-2.0
Miliaria / Delayed / 0-2.0
Hypertrichosis / Delayed / 0-2.0
Telangiectasia / Delayed / 0-2.0
Vesicular rash / Delayed / 0.3-0.3
Ocular irritation / Rapid / 0.3-0.3
Alopecia / Delayed / 0.3-0.3
Headache / Early / 0.3-0.3

15.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other AEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

15.4 External SAE Reporting

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

15.5 Reporting to Amryt Pharma

Reporting of Serious Adverse Events: Within 5 days of first awareness of the event, the Investigator will report to Amryt by email to medinfo@amrytpharma.com any Serious Adverse Event ("SAE," as defined above) for which reporting is required under this provision. SAEs are to be reported for (1) Study subjects who are assigned or, in the case of a blinded Study, possibly assigned to receive the Amryt Product. The Principal Investigator should report an SAE as soon as it is determined to meet the definition, even if complete information is not yet available.

Lack of Effect: Even though there may not be an associated SAE, lack of effect of the Amryt Product may be reportable. As used in this Agreement, the term SAE will be understood to include reportable instances of lack of effect.

Reporting form to be used: MSKCC SAE form

Follow-up information: Investigator will assist Amryt in investigating any SAE and will provide any follow-up information reasonably requested by Amryt.

Regulatory Reporting: Reporting an SAE to Amryt does not relieve the investigator of responsibility for reporting it to FDA or other appropriate Regulatory Authorities as required.

Reporting of non-serious adverse events: Non-serious adverse events can be sent to Amryt at the end of the study when all data has been compiled and analysed.

Occupational exposure: Due to the low risk profile of the drug being used in this study, MSK staff working with and around the study drug will follow all routine procedures, precautions and reporting of exposure.

16.0 PROTECTION OF HUMAN PARTICIPANTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible side effects. Patients reserve the right to withdraw participation from this study at any time.

Risks: It's unlikely that significant risks will be associated with the limited use of topical Oleogel-S10 and topical triamcinolone planned in this study.

Benefits: The early use of topical Oleogel-S10 is hypothesized to wound size of acute radiation dermatitis with a positive safety profile. This would serve as a novel topical therapy for management of acute radiation dermatitis wounds and would improve patients' symptoms during treatment. Prophylactic and therapeutic topical corticosteroid (with triamcinolone) reduces severity of ARD and is standard of care.

Possible toxicities/ adverse events: Adverse events are rare. 1- <10% of patients developed local application-site side effects with Oleogel-S10 including pruritus and skin pain. Local application–site side effects anticipated with topical triamcinolone include dry skin, erythema, pruritus, skin peeling, and irritation. These adverse events are not expected to necessitate treatment interruption. These adverse effects are not expected to necessitate treatment interruption. Systemic toxicities, including wound infection and GI events, are rare. Toxicities are elaborated in section 11.0 of this protocol. The investigators will use a standardized form to assess adverse events during the visits, as well as rare reactions that could be reported by the patient.

Consent process: Participation in this protocol is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSKCC IRB guidelines.

Costs: Patients will not be charged for protocol related costs

Alternatives: There are no FDA-approved topical therapies for the treatment of acute radiation dermatitis wounds.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate personnel may review patient records as required.

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

Data forms will be developed for recording all information pertinent to the observations and tests described in this protocol. All study data will be collected by an assigned data manager who will enter this information into MSK Medidata in a timely and accurate manner. All data and forms gathered for this study will be collected and stored in a secure location in facilities of the Dermatology Service. Regular meetings attended by the data manager and the Principal Investigators will be held to review study progress and to manage any difficulties encountered.

The data manager will collect toxicity and self-reported compliance data via patient's diaries and patient interviews. Adverse events, including all toxic effects related to treatment will be recorded individually according to toxicity date.

All clinical photographs will be maintained in digital format in a computerized archive (DermagraphixTM). This system labels each clinical photograph with study subject MRN, lesion number, and photograph date.

All patient data and questionnaires will be accessed on the Health Information System (HIS) and Mirror Dermagraphix database, which are password protected with user level access. All the data will be entered and maintained in MSK Medidata.

Estimated time of accrual: 6 months
Accrual Rate: 4 patients per month
Time to complete study: 15 months

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

16.3 Quality Assurance

Study personnel will generate monthly registration reports to monitor patient accrual and completeness of registration data. Routine data quality reports will be generated to access missing data and inconsistencies. Accrual rates, extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Data quality and protocol compliance audits will be conducted by the study team on a regular basis throughout the study period.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecyle until there

are no participatns under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

17.0 REFERENCES

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18.0 APPENDICES

Appendix I: Modified CTCAE v5.0

Appendix IIA: RISRAS for MD

Appendix IIB: RISRAS for Patient

Appendix III: PRO-CTCAE

Appendix IV: Patient Information/Instructions Sheet

Appendix V: Application Diary

Appendix VI: Canfield 3D Imaging System Photo Documentation Manual