Official Title: Randomized, Double-Blind, Vehicle-Controlled Pilot Study of the Efficacy and Safety of HylaCareTM in the Treatment of Acute Skin Changes in Patients Undergoing External Beam Radiotherapy for Tumors of the Breast.

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PROTOCOL NUMBER: STU 092012-058

PRINCIPAL INVESTIGATOR: Asal Shoushtari Rahimi M.D., M.S.
University of Texas Southwestern Medical Center
Department of Radiation Oncology

CO Investigators: Ann Spangler MD
Department of Radiation Oncology

Dan Garwood MD
Department of Radiation Oncology

Marilyn Leitch MD
Department of Surgery

Roshni Rao MD
Department of Surgery

Barbara Haley MD
Department of Medical Oncology

Chul Ahn, PhD
Professor
Department of Clinical Sciences
5323 Harry Hines Blvd
Dallas, TX 75390-9066
(214) 648-9418

NUMBER OF PATIENTS TO BE TREATED: 30

ESTIMATED START DATE: 2013

TEST ARTICLES: HylaCare™ (Test Serum)

Placebo (Control)
Vehicle

SPONSOR'S NAME AND ADDRESS: Hylaco, LLC
3401 Lee Parkway Suite 1504
Dallas, TX 75219

:

Version	Date
2	March 6, 2013
3	August 6, 2013
4	October 3, 2013
5	May 7, 2014

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1. INTRODUCTION AND PURPOSE

More than 50% of all patients with cancer receive some form of radiotherapy (RT), for curative or palliative purposes, during the course of their illness.

One of the dose-limiting effects of radiotherapy is the acute reaction that ionizing radiation induces in normal tissues. The severity of adverse events resulting from exposure to radiotherapy is, in general, related to age and general health as well as to treatment-related factors such as the area being treated, radiation dose per fraction, and the total dose administered.
Skin toxicity is the most common acute side effect of radiotherapy to the breast, occurring in more than 90% of patients.(1)

The specific purpose of this trial is to determine whether the hyaluronan components of HylaCare™ induce an effectiveness response significantly greater than use of a vehicle control which lacks those ingredients in the management of acute skin reactions to external beam radiotherapy.

2. BACKGROUND

Early-onset adverse events occur to tissues soon after treatment initiation with external beam radiation therapy begins. The emergence of such symptoms, when severe, can adversely affect the patient's quality of life, result in treatment interruptions, and can reduce patient compliance with the treatment regimen. Among the most common of these is skin toxicity, observed frequently in patients being treated for breast cancer. The onset of acute radio-epidermititis results in erythema, epilation, and epidermolysis, with the skin in the treated area becoming dry, pruritic, hypersensitive, easily irritated, and in the longer term, hyper-pigmented. With some forms of radiotherapy, treated skin may develop a moist reaction, resulting in severe soreness in the area of body folds. In addition, patients treated for breast tumors may develop changes in skin texture. Most skin reactions resolve within a few weeks after treatment is completed, although the skin may remain slightly darker than pretreatment.

The present management of radiation-associated skin toxicity includes instructions for care of the affected areas and the use of skin care products which can combat symptoms, without inducing further skin irritation.

Attention has recently been focused on the effects of hyaluronan (HA) for the management of radio-epithelitis and acute skin reactions. Liguori et al.(2) reported the effects of hyaluronan serum when applied to skin surfaces affected by radiation to head and neck, breast, and pelvic tumors. Compared to a matching placebo serum, patients treated with the HA serum showed a significant postponement in the first signs of acute radio-epithelitis and a reduction in the severity of skin reactions.

The present study will evaluate the effectiveness and safety of HylaCare™ in the management of acute skin reactions to extern albeam radiotherapy. HylaCare™ contains the patented HylaSponge® System, composed of small and large molecular weight hyaluronan (hyaluronic acid) and polymerized HylaSponges of infinite molecular weight. Due to its structure and preparation, the HylaSponge® System is designed to improve the controlled release and slow delivery of various ingredients. A Repeated Insult Patch Test (RIPT) with HylaCare™ in 30 volunteer subjects demonstrated no potential for eliciting either dermal irritation or sensitization(3).

Themajorpropertieswhichmakethisbiopolymeruniqueandvaluableforskincareare:

- Itsabilitytobeloadedwith,andthenslowlyrelease,waterandavarietyofactive ingredients
- Extremelyhighwaterretention
- Thequalityofactingasa“secondskin”,whichishydrated,protective,and biocompatible

HylaCare™,formulatedasatopicalproduct,hassuper-hydratingproperties.Itcontainsskin moisturizerssuchaspurelowandhighmolecularweighthyaluronan,the HylaSponge®System,andsqualane.ThesecharacteristicsmakeHylaCare ™anexcellent candidateforuseintheskincareofpatientswhomaydevelopacuteskintoxicityassociated withtheuseofexternalbeamradiotherapy.

2.1StudyObjectives

Theobjectiveofthiscontrolledstudywillbe todeterminetheeffectivenessandsafetyof HylaCare™inthemanagementofthesymptomsofacuteskintoxicityinducedbyexposureto externalbeamradiotherapyassociatedwiththetreatmentofbreastcancer.

Theprimarymeasuresofeffectivenesswillbe:

1. Physician'sFollow-UpEvaluation:assessingsignsandsymptomsateachirradiatedsiteat week5duringRTandat2weekspost-treatment:

2. Physician'sGlobalAssessment:assessingeachirradiatedsiteat5weeksofRTpriorto boostandat2weekspost-treatment

Asecondarymeasureofeffectivenesswillbe:

Thepatient'sindependentandseparateassessmentofthetolerancetoradiotherapyofeach treatedsiteatWeek5ofradiotherapyandat2weeksafteritscompletion.

AnadditionalmethodofevaluationwillbetheInvestigator’sassessment(diseaseorientedteam todoassessment)ofthebaselineandtreatmenttimelinephotos.

3.STUDYDESIGN

This will be a randomized, double blind, vehicl e-controlled evaluation of the effectiveness and safety of HylaCare ™. The study will employ the patient as her own control, a commonly used methodfortheevaluationoftopicaldermatologicagents.Eachpatientwillberandomizedblindly as to whether the study serum will be applied to the medial or lateral portion of the treated breast,usingthenippleasthedividingline(seeFigure1.below).Theproductandplacebowill alsobeappliedtothecontra-lateralbreastinthesamefashion,asafurthercontrol.Thestudy drug and placebo will be applied three (3) times daily, ***but not within 4 hours prior to radiation treatment***. Itisawellknownfactthatanycreamormoisturizerthatleavesafilmon thebreastpriortoradiationtreatmentcancauseaboluseffectwhichcanincreasessurfacedose tothebreastworseningdermatitis.Thus,notopicalagentshouldbeappliedtothebreast4hours beforeradiationtreatment.

Patientswillbeallocatedtothetreatmentusingarandomizedpermutedblock.Therewillbeno stratification.Patientswillberandomizedtoreceivetheinvestigationalproducttobeappliedto eitherthemedial(inside)orlateral(outside)portionofthebreast,aplaceboproductwillbeused ontheotherside.Patientsandclinicalinvestigatorswillbeblindedtothetreatmentassignments.

Patientswillalsocompletea dailylog,recordingdailyapplicationtimes.At,orpriorto,the firstradiotherapyvisit,thepatientwillbeprovidedwith3SetBagscontainingsufficient materialsfor3weeksoftreatment,orasneeded.PatientswillreceivemoreSetBagsat Week3andWeek5,orasneeded.Patientsan dinvestigatorswillnotknowwhichbottleof serumisstudyserumvs.placebo.Thebottleswillbelabeledwithanidentifyingcode showingthesubject'sinitialsplusapatientnumber,andanotherlabelindicatingwherethe serumistobeapplied(medialorlateralpartofthebreast).

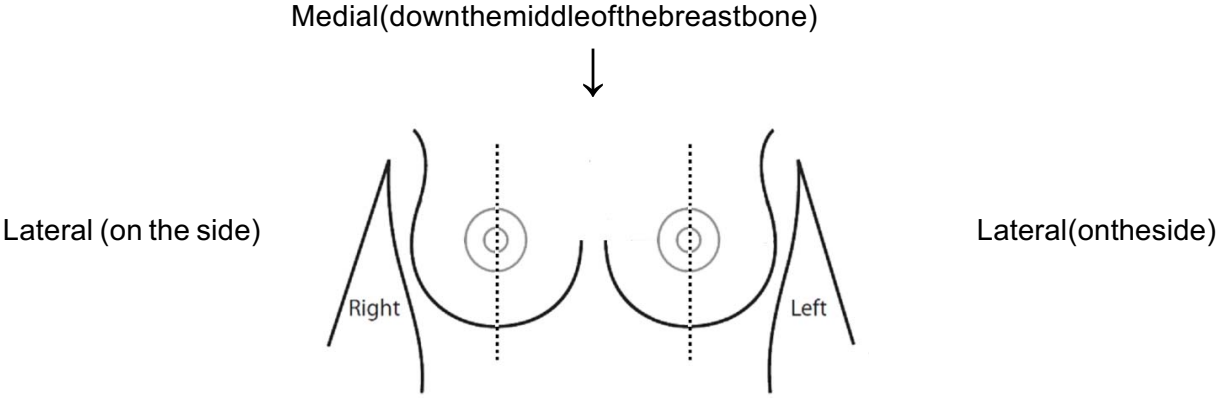


Figure1.Diagramshowingmedialandlateralportionsofbreaststobeaddressed.

Applicationsthree(3)timesperdaywillcontinuethroughoutthecourseofradiotherapyandfor 24weeksafteritscompletion(endofstudy).Onanytreatmentday,therewillbeanapplication oftestandcontrolproductsimmediatelyaftertheradiotherapy.Noapplicationwillbemade withinfour(4)hourspriortoradiotherapy.

HylaCare™andamatching(inappearance,consistencyandodor)vehiclecontrolproductwill besuppliedinidenticallyappearingopaquebottles anddispensedaccordingtoarandomized codelistpreparedbytheStatistician.

Thispilotstudywillbeinitiallyconductedatonecenterwith30patientsundergoingstandard fractionationexternalbeamradiotherapy.

Patientsenrolledinthisstudywillbethosewhoaretoundergocurativeorpalliative radiotherapyfortumorsofthebreast.Treatmentprescriptionwillbe50.4Gyin28fractionswith tangentialbeams,followedbya10Gyin5fr actionelectronorphotonboost.Thosewhomeetall selectioncriteriawillhaveahistorytaken, undergoaphysicalexamination,andabaseline evaluationbytheInvestigator.Thisevaluationwilldescribethetumorlocationandsymptoms, aswellastheintendedradiotherapytreatmentplan,dose,anddurationoftreatment.The radiationtreatmentprotocolforeachpatientwillbedeterminedbytheRadiationOncologist.

Afterthecommencementofradiotherapy,patientswillbeevaluatedatWeek5,andat 2weekspost-treatment,byoneoftheradiationoncology investigatorswhowillexamine andgradethebreastforacuteskintoxicitychangesusingtheNCIC-CTCversion4.0scale.A secondInvestigatorGradingScalewillalsobeusedforevaluation.Evaluationofthe changeswill alsoincludeexaminationandquestioningforeryt hema,pruritis,pain,dryness,exfoliation, epilation,hyperesthesia,orothersigns/symptomsateachsite.Asupra-clavicularfieldmay beirradiatedandmayalsobetreatedwithProductsAandB,butwillnotbeassessedfor dermatitis.

Atstudycompletion,boththeInvestigatorandpatientwill,independentlyandseparately, assesstheoveralldermatitisoftheirradiatedbreastandthecontralateral(non-irradiated) breast.

1. GradingScale:NCIC-CTC

Adverse Event	1	2	3	4	5
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; desquamation patchy moist desquamation, mostly confined to skin folds and creases moderate edema	Moist desquamation in areas other than skin folds and creases bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing					

2. InvestigatorGradingScale:

Gradethestatusofthemedialandlateralsidesoftheirradiatedskinas:
0=normalskin
1=lightepidermalirritation,consistingoftheonsetoferythema,possiblyassociatedwithslight edema
2=erythemawithdrydesquamation
3=wetdesquamation</=2cm
4=wetdesquamationfrom2.1–5cm
5=wetdesquamationfrom5.1-9cm
6=wetdesquamation>9.1cm

4.STUDYPROCEDURES

4.1SubjectSelectionCriteria

PatientswillberecruitedbytheInvestigatorfromhis/heravailablepatientpopulation,orby referral.SelectedpatientsmustmeettheInclusionandExclusioncriteria:

InclusionCriteria

- Female,age18orolder
- Diagnosisofbreastcancer
- Intactbreast(notsurgicallyabsent)
- Plannedfractionatedexternalbeamradiotherapytobedeliveredbyopposing, tangentialbeamsto50.4Gyin28fractionswithaplannedphotonorelectronboost of10Gyin5fractions(foratotalof33fractions)
- Abilitytounderstandandcomplywiththerequirementsofthisstudy
- AbilitytogiveInformedConsent
- Forsexuallyactivefemales,patientagreestouseacceptablemethodof birthcontrol

ExclusionCriteria

- Womenwhoarepregnantorlactating
- Useofconcomitantskincarepreparationsatanyofthetreatedorcontrolportalareas tobeobserved
- Any infection or unhealed wound of the radiotherapy portal areas, or generalized dermatitis
- Severerenalfailure(serumcreatinine >3.0mg/dL)within6monthsofstudy registration

- Allergichistory,includinganaphylaxisorsevereallergiestoproductsinstudyserum orplacebo
- Plannedrelocationwhichwouldmakefollow-upvisitsimpossibleduringthecourseof thestudy
- CollagenvasculardiseasesuchasLupus,orscleroderma

4.2 StudyDuration

Patientsselectedforthisstudywillbeundergoingradiotherapyforcurativeorpalliativetreatment withfractionatedexternalbeamradiotherapy tobedeliveredbyopposing,tangentialbeamsto 50.4Gyin28fractionswithaplannedphotonorelectronboostof10Gyin5fractions(totalof 33fractions).Patientswillbefollowedfor2weeksafterradiotherapyhasfinished,withafollow-upvisitsat2weekspost-treatment.

4.3DataCollection

Datawillbecollected(typewritten,orhandwrittenlegiblyinblackink)ontheappropriatecase reportformssuppliedbytheSponsor.

4.4 ConcomitantMedications

Patients will be asked about changes in their medications (prescription, nonprescription, or herbals) during their participation including name of the drug, indication for use, dosage, date startedanddatestopped.Changesinmedicationswillberecorded.

4.5GeneralPlan

Thepatient'soveralltreatmentplanwillbeguidedbyhertumortype.Ingeneral,itsplanning stepswillinclude:

1. Specialradiologicstudiesmaybeorderedtohelpplantheradiationtreatments
2. Devices(e.g.,breastboards,vaclok)maybefabricatedtomaintainproper positioningduringtreatment pertheradiationoncologist
3. Simulationx-rayswillbeperformedto ensureaccurateplanningofthesizeand directionoftheradiationtreatmentfieldsonaweeklybasis
4. Tattoosorothermarkerswillbeappliedtoensurethepropersetupfordailytreatment
5. Custom-madeblocksmaybefabricated,basedonCTsimulation,toshieldnormal structures
6. Duringasetupsession,thefieldar rangementsandblockswillbecheckedforproper alignment
7. Ingeneral,thebordersofthefieldare:
    i. Superior:inferiortotheclavicle
    ii. Lateral:mid-axillaryline
    iii. Inferior:2cminferiortotheinfra-mammaryfold
    iv. Medial:Mid-sternum

4.6TestArticleBlindingandAdministration

At,orpriorto,thefirstradiotherapyvisit,the patientwillbeprovidedwith3SetBagscontaining sufficientmaterialsfor3weeksoftreatment,orasneeded.PatientswillreceivemoreSetBags atWeek3andWeek5,orasneeded.EachSetBagwillcontaintwo(2)60mLbottlesof HylaCare™,andtwo(2)i denticallyappearingbottlesofPlacebo(ControlVehicle).Both containerswillbelabeledwiththepatient'sinitials,studynumber,andlocationofskintobe covered(ie.rightlateralbreast,leftmedialbreast,etc.)Additionally,thepatientwillbe instructedastotheproperapplicationoftheserums,includingamount,location,coverage,

andhandwashing. ***See "Patient Instructions", Form 8***

Thecontentsofeachbottle(HylaCare ™orPlacebo)willhavebeendeterminedbya computerizedrandomassignmentscheme,thecodefo rwhichwillbekeptatthestudysiteina sealedenvelope.

The radiotherapy nurse, research team or physician will instruct the patient as to the proper application method and ensure that the patient understands which container contents are to be applied to which site (see Figure 1 and Patient Instructions, Form 8). The patient will apply a sufficient amount of either HylaCare or plac ebo (as prescribed in the experimental randomized design) to cover the entire marked surface of their irradiated skin area IMMEDIATELY AT THE END OF THE TREATMENT SESSION. At this time the same treatment will be applied to the contralateral (non-irradiated) breast. The patient will make two other applications during the day to ensure a total of three (3) daily applications of both HylaCare ™ and the vehicle control. **No applications will be made within 4 hours before radiotherapy.** The three (3) daily applications will continue throughout the course of radiotherapy and for 2 weeks after its completion. A drawn dashed line on both treated and untreated breast, as seen in Figure 1 will determine areas for use of study serum and placebo.

Thepatientwillalsobeinstructed:

1. Toapplyproductonlytotheareasidentifiedonbothbreasts **immediately**afterthe radiotherapysession,andthentwomoretimesthatday.
2. Onnon-treatmentdays,toapplytheproductthree(3)timesdaily
3. Nottouseotherskincareproductsonanyoftheradiotherapy-exposedskinareas
4. Toreportanygeneralizedreactionsoranylocalizedreactionsintreatmentareatothe investigatoratthenextdailysession,ormoresevereреactionsbytelephone(See Section8).
5. todiscontinueuseoftopicalagentsiftheydevelop>/=grade3dermatitis.

Suggestionsforpersonalcareoftheirradiatedtreatmentsitesmayinclude:

1. Avoidirritatingtheskin
2. Whenwashing,useonlylukewarmwaterandmildsoap,pattingthesurface dry
3. Avoidtheuseoftightclothing
4. Donotrub,scruborscratchtheskin
5. Avoidtheuseofheatingpadsoricepacks
6. Donotusepowders,creams,perfumes,deod orants,bodyoils,ointments,orlotions ontheirradiatedsurfaces
7. Avoiddirectsunexposure;ifnecessary,wearprotectiveclothing

5.SOURCEOFRESEARCHMATERIAL

5.1 HylaCare™(TestSerum)andPlace bo(VehicleControl)

HylaCare™(TestSerum)andPlacebo(VehicleControl)willbesuppliedinidenticallyappearing opaque60mLbottles.

HylaCare™containsthefollowingingredients:
HylaSponge®System
Water
Xanthangum
Hydroxyethylcellulose

Squalane
EMTPolymer (Hydroxyethylacrylate,Sodiumacryloyldimethyl,Tauratecopolymer)
Benzylalcohol-DHA(benzylalcohol,(dihydroaceticacid)

TheVehicleControlcontainstheabove- notedingredientsexceptforHylaSponge ®System

5.2 ProperHandlingandStorage

1.Storetestarticlecontainersatroomtemperature
2.Donotfreeze

6.EVALUATIONSANDCONSENT

Patients who meet all selection criteria will be enrolled in numerical sequence. The assigned numberwillcorrespondtotheorderinwhichtheyareenrolled.Thefollowingvisitswilloccur:

Visit#	Title	Time
BL*	BaselineEvaluation(s)	0(Priortotreatment)orWeek1visit
1	Radiotherapy (RT)	Initiation
2	Follow-UpEvaluation	At5Weekspriortoboost
3	FinalEvaluation	2weeksafterRTends

*BaselineEvaluationmayrequiremorethanonevisit.

6.1BaselineProcedures(Visit#BL)

AttheBaselineEvaluation,allenrolledpatientswillundergohistory,physical examination,andbaselinelaboratory/radi ologicalassessmentsdictatedbythe planoftreatmentforthetumortoundergoradiotherapy.

TheResearchTeamortreatingPhysicianwillcompletetheseformsandactions:

- (Form1)InformedConsent(Form1)
- (Form2a/2b)Inclusion/ExclusionCriteria(Forms2A/2B)
- (Form3)PhysicianFollow-UpAssessmentForm3
- (Form4)DemographicsandHistoryForm4
- (Form5)GeneralPhysicalExaminationForm5
- (Form6)RadiotherapyTreatment
- (Form7)PatientDailyLog
- (Form8)PatientInstructions

6.2TableofBaselineandSubsequentAssessments

Assessment of all radiation-exposed skin areas will occur as directec in the table below followingtheinitiationofradiotherapyandat2and4weeksafterthecompletionofradiotherapy. Theseformsandactivitieswillbecompletedorreviewedateachassessment:

FORM/ACTION	Base Line	Week 1	Week 2	Week 3	Week 4	Week 5 Priorto boost	Week 6	Week 7	2 weeks post
InformedConsent	V								
Photography	V					V			V
Inclusion/ ExclusionCriteria	V								
PhysicianFollow-UpAssessment						V**			V
Demographics andHistory	V								
GeneralPhysical Examination	V								
Concomitant Medication	V	review	review	review	review	review	review	review	review
Baseline Assessment	V								
UrinePregnancy Test	V***								
Radiotherapy Treatment		****							
PatientDailyLog		V	V	V collect log page	V	V collect logpage	V	V	V collect logpage
AdverseEvent	If needed	If needed	If needed	If needed	If needed	If needed	If needed	If needed	Ifneeded
PatientOverall Evaluation						V*****			V
PhysicianGlobal Assessment						V			V
Patient Completion									V

*Photographsofpatient'sbreastspriortoradiationtherapy:Thebaselinephotoshouldbea close-upencompassingonlythebreasttobetreatedata45degreeobliqueanglewitharms elevatedoverthepatient'shead.Otherphotosshouldbeastraightfrontalviewofbothbreasts takenineitherastandingorseatedpositionwiththepatient'shandsonherhips,excludingher face.Boostareawillbelabeledpriortoweek5photoandaphotowillbetakenshowingtheboost area. Labeleachslideorphotographwiththedateandthepatientcasenumber.Thelabeled photographswillbestoredelectronicallyunderstudyspecificpatientfolders.

**Separatephotowithboostdrawnonskin.
***IfPatientisofchild-bear ingageandsexuallyactive
****PriortofirstRadiationTherapy

*****Evaluationshouldbecompletedpriortoboo st,butPatientwillnotberemovedfromthe studyisthisiscompletedaftertheboost.

6.3 FinalVisit

Thiswilloccurat2weeksafterthecompletionofradiotherapy.Theseformsandactionswillbe completed:

- Physician'sFollow-UpAssessmentForm3
  Describestheradiotherapytreatmentandprovidesatimelinetocompare irradiatedandnon-irradiatedbreastindications
- Physician'sGlobalAssessmentForm9

TobecompletedatWeek5priortoboostandalso2weekspostradiation

- PatientOverallEvaluationForm10
  Usedtoelicitpatientevaluationofprophylaxis
- PatientCompletionForm11
  Finalcompilationofpatientdatauponstudycompletionordiscontinuation

6.4InformedConsent

Writtenconsentwillbeobtainedfromeachpatientpriortoenteringthistrialandwillbecome partofthepatient'spermanentstudyrecord.Eachpatientwillbeassuredthatstudy participationisvoluntaryandthatshemaywithdrawatanytime.Atthetimeofobtaining writtenconsent,theInvestigatorwilladvisepatientsoftheexperimentalnatureofHylaCare™, thedurationofthetrial,alternatemodesofprophylaxis,andprevalentadverseeventsthat mightoccuranddiscusswilling nesstohavephotographstaken.

7.EFFICACYPARAMETERS

Theprimarymeasuresofeffectivenesswillbe:

- Physician'sFollow-UpEvaluation(Form3):assessingsignsandsymptomsateach irradiatedsiteWeek5duringRTandat2weekspost-treatment

- Physician'sGlobalAssessment:assessingeachirradiatedsiteatWeek5RTpriortoboost andat2weekspost-treatment

Asecondarymeasureofeffectivenesswillbethepatient'sindependentandseparateassessment ofthetolerancetoradiotherapyofeachtreatedsiteatthecompletionofradiotherapyandat2 weeksafteritscompletion.

AnadditionalmethodofevaluationwillbetheInvestigator'sassessment(diseaseorientedteam todoassessment)ofthebaselineandtimelinephotos.

Inaddition,otherlocal(irradiatedareas)symptoms/signs(e.g.,pain,tenderness,pruritus, dryness,epilation,hyperesthesia)andanygene ralizedadverseeventswillbeevaluatedonthe basisofNCICtoxicitycriteria http://ctep.cancer.gov/reporting/ctc.html .

Week5ofradiotherapyandatthe finalevaluation(2weekspost-treatment),theInvestigatorwill makeanoverallglobalassessmentofeffectivenessofradiationtoleranceofthetreatedbreast (medialandlateralbreastwillbescoredindividua lly).Thisassessmentwillbebaseduponthe Investigator'sexperience,comparingtheskinappearanceandsymptomatologyofthesitewith thenormallyexpecteddegreeofradiationdamageforsimilarbodysites.Theoverallresultwill begradedas:

0=poor(worsethantypicalexpectations)
1=fair(equalto,orslightlybetterthantypicalexpectations)
2=good(moderatelybetterthantypicalexpectations)
3=excellent(markedlybetterthantypicalexpectations)

TheInvestigatorwillalsojudgewhichofthepairedsites(medial,lateral))tolerated radiotherapybetter,intermsof:(1)symptomsexperiencedbythepatientand(2)overallskin appearance.Ifinvestigatorfeelsmedialandlateralbreastsymptomatologyequivalent,then thiswillbereportedassuch.

IndependentoftheInvestigator,thepatientwillalsoassesswhichofthepairedsitesfared betterintermsof:(1)symptomsexperiencedand(2)overallskinappearance,atthecompletion ofradiotherapyand2weekspost-treatment.

8. PotentialRisks

InvestigationalProduct:

InprevioususeofHylaCareasacommercialproduct,noadverseeventshavebeen identified.

PsychologicalStress:

Questionnaireswillbegiventothepatientasapartofthisstudy,whichmaymakethemfeel uncomfortable.Patientcanrefusetoansweranyofthequestions,takeabreakorstop participatinginthisstudyatanytime.

LossofConfidentiality:

Anytimeinformationiscollected;thereisapotentialriskforlossofconfidentiality.Every effortwillbemadetokeepthepatientsinformationconfidential;however,thiscannotbe guaranteed.

Photographs:

Patientcouldfeelslightlyuncomfortableduringthephotographicsessionswhenaskedto positionthebodytotakethephotographofthebreastarea.Patientscouldbeuncomfortable withstandingstillforanextendedperiodoftimeorfromturningtheirbodyinvarious positions.Theycouldbesensitivetothebrightandrepeatingflashesfromthecamera,which cansometimescauseheadaches,irritationoftheeyes,discomfort,aftereffectssuchas seeingspots,andinrarecases,couldstimulateamigraineheadacheorepilepticseizure.

Photographsincludeariskofidentification.Patientsprivacywillbeprotectedtothegreatest extentpossible.Photoswillbetakentoexcludefacesoranyotheridentifyingmarks.Photos willonlybeidentifiedbyauniquesubjectidentificationnumberthatcontainsnopersonal identifyinginformation.Forresearchpurposes,photosmaybeusedinscientificpublications.

RiskstoEmbryo,FetusorBreast-fedInfant:

Females:Forpatientswhoarepregnantorbreast-feedinganinfant,itispossiblethatthey mayexposetheunbornchildorinfanttorisks. Forthatreason,pregnantandbreast-feeding femalescannotparticipateinthestudy.Forpatientwhoareparticipatinginthisstudyand areofchildbearingageandsexuallyactive,resultsofaurinepregnancytestwillbe obtained,anditmustbenegativebeforeparticipatinginthestudy.Patienttakingpartinthis studyandwhoaresexuallyactive,mustusemedically-acceptablebirthcontrol (contraceptives)duringthestudy.Medically-acceptablebirthcontrol(contraceptives) includes:

(1)Surgicalsterilization(suchas hysterectomyor“tubestied”),

(2)Approvedhormonalcontraceptives(suchasbirthcontrolpills,patchorring;Depo-Provera,Depo-Lupron,Implanon),

(3)Barriermethods(suchascondomordiaphragm)usedwithaspermicide(asubstance thatkillssperm),or

(4)Anintrauterinedevice(IUD).

Patientwhobecomepregnantduringthisstudy,mustnotifytheresearchersimmediately.

OtherRisks

Theremaypossiblybeothersideeffectsthatareunknownatthistime.

Radiationexposuretoawoman’sreproductiveorgansmayharmanembryoorfetus.Also,if radioactivematerialsareusedforcertaintypesofscans,harmmaycometoanembryo, fetus,oraninfantwhoisbreastfeeding.

Pregnancytestsperformedduringtheearlystagesofpregnancydonotalwaysreveal pregnancy.Therefore,radiationexposurethatincludesthereproductiveorganswillbe limitedtothefirsttendaysafterawomanwhocanbecomepregnanthasbegunhermost recentmenstrualperiod.Thisisstandardpolicyinclinicsandhospitalswithin UT Southwestern.Thispolicyappliesunlessthereisanimportantmedicalreasonrequiring radiationoutsidethistimeframe.

RisksofRadiation–RadiationTherapy:
Theradiationtherapyusedinthisresearchisthestandardradiationtherapy,therefore,the riskofharminvolvedisthesame.

High-doseradiationtreatmentstoorneararaman'stesticlesorawoman'sovariesmay produceharmfulchangesthatcouldbepassedontochildrenthroughaspermoranegg.

Women:Femalesabletohavechildrenshouldavoidbecomingpregnantuntilafterthey havehadthreemenstrualperiodsaftertheendofallradiationtherapy.Afterthree menstrualperiods,thereisalmostnoriskofharmfulchangestoanegg.

Possiblesideeffectsofradiationtherapytothebreastinclude:

Likely(thesesideeffectsoccurin10%ormoreofpatients):

- Reddeningoftheskinduringtreatmentandforseveralweeksfollowing treatment
- Tanningoftheskinlastingmonthsandmaybepermanent
- Slightlysmallerbreastsizeorchangeinthewaythebreastlooks
- Tirednessandweaknessduringtreatmentandforseveralweeksfollowing treatment
- Swellingofthebreast
- Peelingoftheskininthearea treatedwithradiation
- Mildpainatthesiteofradiationtreatmentrequiringoverthecounterpain Relievers.

LessLikely(thesesideeffectsoccurin3-9%ofpatients):

- Sorenessortightnessinmusclesofthechestwallunderthetreated breast
- Severepainatthesiteofradiationrequiringprescriptionpainrelievers

RarebutSerious(thesesideeffectsoccurinlessthan3%ofpatients):

- Cough
- Difficultybreathing
- Inflammationoftheheartmuscle
- Ribfracture
- Slightincreaseinriskforheartdiseaseforpatientswithcancerintheleftbreast
- Riskofdevelopinganothercancer

Ateachfollow-upassessment,patientswillbeevaluatedforanyadverseeffects.Thesewillbe groupedasfollows:

1.Localizedreactionsattheirradiatedsites
2.Otheradverseevents

TheInvestigatorwillenterdetailsofanyoftheseeventsontheAdverseEventForm.The

duration,intensity,andanyactiontakenwillberecorded.

8.1DefinitionofAdverseEvent

Anadverseevent(AE)isanyuntowardmedicalo ccurrenceinapatientreceivingstudytreatment andwhichdoesnotnecessarilyhaveacausalrelationshipwiththistreatment.AnAEcan thereforebeanyunfavorableandunintendedsign(includinganabnormallaboratoryfinding), symptom,ordiseasetemporallyassociatedwiththeuseofanexperimentalintervention,whether ornotrelatedtotheintervention.

8.2SeverityofAdverseEvents

Allnon-hematologicadverseeventswillbegraded accordingtotheNCICommonTerminology CriteriaforAdverseEvents(CTCAE)version4.0.TheCTCAEv4isavailableat http://ctep.cancer.gov/reporting/ctc.html

IfnoCTCAEgradingisavailable,theseverityofanAEisgradedasfollows:

Mild(grade1):theeventcausesdiscomfortwithoutdisruptionofnormaldailyactivities.
Moderate(grade2):theeventcausesdiscomfortthataffectsnormaldailyactivities.
Severe(grade3):theeventmakesthepatientunabletoperformnormaldailyactivitiesor significantlyaffectshis/herclinicalstatus.
Life-threatening(grade4):thepatientwasatriskofdeathatthetimeoftheevent.
Fatal(grade5):theeventcauseddeath.

8.3StepstoDetermineIfanAdverseEventRequiresExpeditedReporting

Step1:Identify the type of adverse event using the NCI Common Terminology CriteriaforAdverseEvents(CTCAEv4).

Step2:GradetheadverseeventusingtheNCICTCAEv4.

Step3:Determinewhethertheadverseeventisrelatedtotheprotocoltherapy Attributioncategoriesareasfollows:

- Definite–TheAE *is clearly related*tothestudytreatment.
- Probable–TheAE*is likely related* tothestudytreatment.
- Possible–TheAE *may be related*tothestudytreatment.
- Unrelated–TheAE *is clearly NOT related*tothestudytreatment.

Note:Thisincludesalleventsthatoccurwithin30daysofthelastdoseofprotocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must alsobereportedaccordingly.

Step4:Determinethepriorexperienceoftheadverseevent. Expectedeventsarethosethathavebeenprev iouslyidentifiedasresultingfrom administrationoftheagent.Anadverse eventisconsideredunexpected,for expeditedreportingpurposesonly,wheneitherthetypeofeventortheseverityof theeventisnotlistedin:

- thecurrentknownadverseevents listedintheAgentInformation Sectionofthisprotocol;
- thedrugpackageinsert;
- thecurrentInvestigator'sBrochure

Theintensityofadverseeventswillbegradedasmild,moderate,orseveretodescribe

these observations regardless of whether they are medical events, symptoms, or physical findings. For purposes of consistency, the following definitions of intensity are provided:

Mild: Easily tolerated, causes minimal discomfort and does not interfere with everyday activities
Moderate: Causes sufficient discomfort to interfere with normal everyday activities
Severe: Incapacitating and prevents normal everyday activities

A Serious Adverse Event is any experience that suggests a significant hazard, contraindication, side effect or precaution, and includes any experience which:

- is fatal or life-threatening
- is permanently disabling (i.e., incapacitating or interfering with the ability to resume usual life patterns
- requires in-patient hospitalization or prolongation of hospitalization
- is a secondary cancer, or an overdose

For HylaCare ™, potential adverse events might include an allergic reaction. Although this has not been observed in other clinical trials of hyaluronan-based agents, this product is hyaluronan derived from a biological source; hence, the Investigator should be aware of the possibility that the material theoretically could cause an allergic reaction.

Any Serious Adverse Event Forms should be faxed, then emailed immediately to Hylaco (Janet L. Denlinger PhD, Chief Scientific Officer 2018861643/jdenlinger@hylaco.com) and Jean Wu (214-645-8913/jean.wu@utsouthwestern.edu). Any death or serious or unusual reaction is to be reported promptly (within 24 hours) by telephone to Dr. Denlinger (2018861562) or, in her absence, to Morgan Hare (214559 6125), even though it may not appear to be related to HylaCare ™.
All adverse events will be reviewed at the monthly radiation oncology research meeting which includes radiation oncologist not adhering to the protocol.

Any preliminary telephone report of a serious adverse event is to be followed by a detailed written report summary within three working days and must include copies of hospital/office records and other documents when applicable. An additional follow-up written report summary is to be forwarded to Hylaco within 10 days of the adverse event. The Investigator will also notify his/her Institutional Review Board (IRB) of any deaths, serious or unexpected reactions.

Follow-up of all adverse events will be continued until the overall clinical outcome has been ascertained. All deaths, serious and non-serious adverse events will be summarized in the report prepared for Hylaco after the conclusion of the study.

<u>UTSW IRB:</u> SAEs will be collected from the time consent is given, throughout the treatment period, and until subject's participation in the trial has ended or participants death.

Investigators and other site personnel must inform the UTSW IRB, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to UTSW IRB. It is the responsibility of the investigator to compile all necessary information.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to UTSW IRB..

All SAEs have to be reported to UTSW IRB, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Non-serious adverse events will be collected from the time consent is given, throughout the treatment period and up to and including the *30 day follow-up* period. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for *30 calendar days after the last dose of trial drug and/or until event resolution.* All new AEs occurring during that period must be recorded (if SAEs they must be reported to the UTSW IRB). All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

All serious adverse events must be reported to the UT Southwestern TELEPHONE LINE: (214) 633-1753 within 24 hours of the investigator's awareness of the occurrence of the event. All safety reports shall be faxed to (214) 645-8913 or e-mail to the attention of the project manager.

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.

9. DATA MONITORING

9.1 Statistical and Analytical Methods

Thirty patients will be recruited in this pilot st udy. Descriptive statistics will be computed to estimate the sample size needed for a future larger study if the study results looks promising.

Descriptive statistics will be obtained for baseline demographic, medical history,

physicalexamination,radiationtherapytreatment/dosimetrydata.
Patientswillbeallocatedtothetreatmentusingarandomizedpermutedblock.Therewillbeno stratification.Patientswillberandomizedtoreceivetheinvestigationalproducttobeappliedto eitherthemedial(inside)orlateral(outside)portionofthebreast,aplaceboproductwillbeused ontheotherside.Patientsandclinicalinvestigatorswillbeblindedtothetreatmentassignments. Theprimaryefficacyvariablesarethe Physici an'sFollow-UpEvaluation,tobeperformedat eachvisit,andthePhysician'sGlobalAssessment,tobeperformedattheendofradiotherapy and2(two)weeksafterthecompletionofradiotherapy.The *key* componentofthePhysician's Follow-UpEvaluationisthegrading,onanordinalscale(0to5)NCIC-CTC,aswellasthe InvestigatorGradingScaleoftheirradiatedareaofthebreast.Thedatacollectedfromthe Physician'sFollow-UpEvaluationwillbegroupedintotwoparts,thosedatacollecteddurin radiotherapyandthosedatacollectedfollowingthecompletionofradiotherapy.Foreach patient,thedifferencebetweentheHylaCare ™treatedsideandthecontrolsidewillbe determinedateachvisitduringradiotherapy.Thesedifferenceswillthenbeaveragedforeach patient.Thesignificanceofthemeandifferenceamongthepatientswillthenbedetermined usingapairedt-testorWilcox onsigned-ranktest.Thedataobta inedduringtheperiodfollowing radiotherapywillbeanalyzedinthismanner.TheanalysisofthePhysician'sGlobal Assessmentwillalsobeperformedseparatelyatthecompletionofradiotherapyandattheend ofthefollow-upperiod.Thecomparisonofthegroupswillbebasedonapairedt-testor Wilcoxonsigned-ranktest.Asecondaryanalysiswillbeperformedtoexaminethepossible influenceofbodyhabitus(BMI-breastsize)andradi ationhotspotsontheeffectivenessofthe HylaCare™prophylaxis.Allefficacyanalyseswillbebasedonamodifiedintent-to-treatpatient population.Thispopulationwillbedefinedas allpatientswhocommenceradiotherapyandwho haveatleastoneon-treatmentvisit.

Thesecondaryefficacymeasureisthepatient's assessmentofthetolerancetoradiotherapy. Thesedatawillbecollectedattheendofradiotherapyandattheendofthefollow-upperiod.At eachtimepointthepatientwillbeaskedthreequestionsandwillrespondtoeachquestionby indicatingwhichproductwaspreferredorifthepatienthadnopreference.Foreachquestionthe analysiswillcompare,amongthosepatientswhohaveapreference,thepercentwhoprefer HylaCare™tothepercentwhoprefertheControl.Thecomparisonwillbebasedonanexact BinomialtestofthehypothesisthatthepercentwhopreferHylaCare ™is50%,thepercentthat correspondstothepatienthavingnopreferencebetweenHylaCare ™ andthecontrol.

Theevaluationofphotostakenduringthecourse ofradiotherapyrepresentsthethirdefficacy measure.Thesewillbeevaluatedinablinde dmannerbythedisease orientedteam(which mayconsistofbreastsurgeons,plasticsurgeons,ormedicaloncologists)afterthelastpatient completespost-treatmentweek2follow-upandphoto

Safetywillbeassessedthroughtherecordingofresponsesandotheradverseevents.All patientswhoundergoprophylaxiswillbeincludedintheanalyses.Theadverseeventswillbe classifiedusingtheNCIC-CTCversion4.0.
AllcomputationswillbeperformedusingStatisticalAnalysisSystem(SAS)software.

Grading NCIC-CTC

Adverse Event	1	2	3	4	5
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; desquamation patchy moist desquamation, mostly confined to skin folds and creases moderate	Moist desquamation in areas other than skin folds and creases bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin	Death

		edema		graft indicated	
Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing					

InvestigatorGradingScale:
0=normalskin
1=lightepidermalirritation,consistingoftheonsetoferythema,possiblyassociatedwithslight edema
2=erythemawithdrydesquamation
3=wetdesquamation</=2cm
4=wetdesquamationfrom2.1--5cm
5=wetdesquamationfrom5.1-9cm
6=wetdesquamation>9.1cm

9.2SubjectSafety
Safety will be assessed through the recording of responses and other adverse events. All patients who undergo prophylaxis will be included in the analyses. The adverse events will be classifiedusingtheNC IC-CTCscale4.0.

9.3MonitoringProcedures
Throughoutthestudy,themonitororadesignateddeputywillmonitorcompletionoftheforms, discuss questions regarding adverse events, removal of patients from the trial, study conduct, ortheuseofthetestarticles.

The monitor will pay site visits to review each patient's Case Report Forms to help ensure completenessandaccuracyofdataentryspecified inthe Protocol.AsrequiredbyGoodClinical Practices guidelines, clinical records will be reviewed to confirm that: (1) the case report forms areconsistentwiththeInvestigator'sclinicalrecords;(2)backgroundclinicalandlaboratorydata and concomitant medications are recorded on the case report forms; (3) there is an accurate account of test and control article use; and (4) there is timely, appropriate reporting of any adverseevents.
Patientswillbeinstructedto discontinueuseoftopicalagentsiftheydevelop>/=grade3 dermatitis.

ThedataandsafetyMonitoringBoard/Committeeare:

- InternalDSMB/DSMC
- UTSWRadiationOnclolgyInvestigators
- ExternalDSMB/DSMC
- SimmonsCancerCenter

9.4HandlingofDropoutsorPatientsLosttoFollow-Up
Allpatientswhomeettheselectioncriteriawillbeconsideredevaluableforefficacyandsafety. Every attempt will be made to ensure that all patients complete the required follow-up visits. Those not appearing will be telephoned and/or contacted by mail to ensure that they complete their visit schedule. The reason for all dropouts is to be specified by the Investigator on the PatientCompletionForm.

9.5DiscontinuationofPatientsFromStudy
Participationinthisstudymaybediscontinuedforanyofthefollowingreasons:

- adverseevents
- severeinter-currentillness

- administrativereasons
- patient'svoluntarydecisiontodiscontinueparticipation
- Investigator'sopinionthatitisnotinthepatient'sbestinteresttocontinue

Any patient discontinued because of an adverse event will be followed for at least 4 weeks, or until the adverse event is resolved, or as otherwis e medically indicated. It is important that the reason and the date of discontinuation be reported on the Patient Completion Form. If at all possible, an assessment should be done at the time of withdrawal.
Patients who failed to apply the test and control products as directed for more than 5 days during radiation will be removed fr om the study for noncompliance.

10. PROCEDURES TO MAINTAIN CONFIDENTIALITY

Confidentiality of each patient's identity will be maintained. A subject number consisting of the patient's initials and a random number will be assigned to each patient upon study entry and that number will be used to identify that patient for the duration of the st udy. Only the patient's initials and numbers will be used on case report forms as well as any study-related correspondence.

11. PROTOCOL ADMINISTRATION

11.1 Discontinuation of the Study

Hylaco reserves the right to discontinue any study for administrative reasons at any time such as, but not limited to, a decision to discontinue further clinical investigation with the test article, improper conduct of the study by the Investigator, or inability to obtai n the number of patients required by the Protocol. Reimbursements for re asonable expenses will be made if such action is necessary.

11.2 Changes in the Protocol

Any changes that may affect the scientific soundness of the investigation or the rights, safety, or welfare of the subjects must receive appropri ate IRB approval prior to implementation. Any changes in this Protocol will require the express written consent of Hylaco.

11.3 Institutional Review Board

Prior to implementation of this study, the Protocol and Patient Consent Form must be reviewed and approved by a properly constitut ed Institutional Review Board (IRB). No ch anges that relate to the safety or welfare of patients may be made to the consent form unless they are approved by the IRB and Hylaco. All major amendments to the Protocol and case r eport forms must also be approved by the IRB and by Hylaco.

11.4 Reporting of Data

All information required by the Protocol is to be provided, or an explanation given for omissions. All case report forms (CRFs) must be made available as soon as they are completed in order that the Study Monitor may verify the validity and completeness of those forms and permit transmittal of the data to the Sponsor.

All data and information on these CRFs are to be neatly recorded in type or legibly written in black ink for ease of duplication, interpretation and analysis before submission to Hylaco. All corrections on the CRFs should be crossed out neatly with a single line, and the new entry initialed and dated by the member of the Investigator's staff making tile correction. Prior to forwarding the CRFs to Hylaco, they should be reviewed for completeness, accuracy, and legibility by the Principal Investigator and the Study Monitor. He/she will indicate by

signature on the appropriate forms that he/she has reviewed the data at each evaluation period.

12.0 REFERENCES

(1) Reference: **Topical Hyaluronic Acid vs. Standard of Care for the Prevention of Radiation Dermatitis After Adjuvant Radiotherapy for Breast Cancer: Single-Blind Randomized Phase III Clinical Trial . International Journal of Radiation Oncology*Biology*Physics** Volume 83, Issue 4, 15 July 2012, Pages 1089–1094 Chelsea Pinnix, M.D., Ph.D.−, George H. Perkins, M.D., M.P.H.−, Eric A. Strom, M.D.−, Wendy Woodward, M.D., Ph.D.−,

(2) Liguori, V., Guillemin, C., Pesce, G.F., Mirimanoff, R.O., and Bernier, J. (1997). Double-blind, randomized clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy. Radiotherapy and Oncology 42, 155-161.

(3) Final Report: Repeated Insult Patch Test for HylaCare™ Batch code lot # 34905R020711. Lab and 2-7-11.

APPENDIX A

EVALUATIONS and ACTIONS

BaselineVisit

AttheBaselineEvaluation,allenrolledpatientswillundergohistory,physical examination,andbaselinelaboratory/radi ologicalassessmentsdictatedbythe planoftreatmentforthetumortoundergoradiotherapy.

TheResearchTeamortreatingPhysicianwillcompletetheseformsandactions:

- (Form1)InformedConsent
- (Form2a/2b)Inclusion/ExclusionCriteria
- (Form3)PhysicianFollow-UpAssessment
- (Form4)DemographicsandHistory
- (Form5)GeneralPhysicalExamination
- ((Form6)RadiotherapyTreatment
- (Form7)PatientDailyLog
- (Form8)PatientInstructions

6.2TableofBaselineandSubsequentAssessments

Assessment of all radiation-exposed skin areas will occur as described in the table below following the initiation of radiotherapy and at 2 weeks after the completion of radiotherapy. Theseformsandactivitieswillbecompletedorreviewedateachassessment:

FORM/ACTION	Base Line	Week 1	Week 2	Week 3	Week 4	Week 5 Prior to boost	Week 6	Week 7	2 weeks post
InformedConsent	V								
Photography	V					V			V
Inclusion/ ExclusionCriteria	V								
PhysicianFollow-UpAssessment						V**			V
Demographics andHistory	V								
GeneralPhysical Examination	V								
Concomitant Medication	V	review	review	review	review	review	review	review	review
Baseline Assessment	V								
UrinePregnancy Test	V***								
Radiotherapy Treatment		****							
PatientDailyLog		V	V	V collect log page	V	V collect log page	V	V	V collect log page
AdverseEvent	If needed	If needed	If needed	If needed	If needed	If needed	If needed	If needed	If needed
PatientOverall Evaluation						V*****			V
PhysicianGlobal Assessment						V			V
Patient Completion									V

Photographsofpatient'sbreastspriortoradiationtherapy:Thebaselinephotoshouldbea close-upencompassingonlythebreasttobetreatedata45degreeobliqueanglewitharms

elevatedoverthepatient'shead.Otherphotosshouldbeastraightfrontalviewofbothbreasts takenineitherastandingorseatedpositionwiththepatient'shandsonherhips,excludingher face.Boostareawillbelabeledpriortoweek5photoandaphotowillbetakenshowingthe boostarea. Labeleachslideorphotographwiththedateandthepatientcasenumber.The labeledphotographswillbestoredelectronicallyunderstudyspecificpatientfolders.

**Separatephotowithboostdrawnonskin.

***IfPatientisofchild-bear ingageandsexuallyactive

****PriortofirstRadiationTherapy

*****Evaluationshouldbecompletedpriortoboo st,butPatientwillnotberemovedfromthe studyisthisiscompletedaftertheboost.

FinalVisit
Thiswilloccurat2weeksafterthecompletionofradiotherapy.Theseformsandactionswillbe completed:

- PhysicianFo llow-UpAssessmentForm3
  Describestheradiotherapytreatmentandprovidesatimelinetocompare irradiatedandnon-irradiatedbreastindications
- Physician'sGlobalAssessmentForm9
  TobecompletedatWeek5priortoboostandalso2weekspostradiation
  - PatientOverallEvaluationForm10
    Usedtoelicitpatientevaluationofprophylaxis
- PatientCompletionForm11
  Finalcompilationofpatientdatauponstudycompletionordiscontinuation

APPENDIXB

FORMS

FORM 1

CONSENT TO PARTICIPATE IN RESEARCH TEMPLATE

Instructions

Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?

The study is being done to provide information about the effectiveness and safety of a product containing the patented HylaSponge®System and whether the use of this product reduces the tissue damage that results from radiotherapy treatment.

Why is this considered research?

This is a research study because the HylaSponge®System is being compared to placebo when applied to the breast which is undergoing radiotherapy as part of treatment for cancer.

The following definitions may help you understand this study:

- Double-blind means neither you nor the researchers will know which product you are receiving.
- Randomization means the products will be assigned by chance for application to either side of your breast.
- Standard medical care means the regular care you would receive from your personal doctor if you choose not to participate in this research.
- Researchers means the study doctor and research personnel at the University of Texas Southwestern Medical Center

Why am I being asked to take part in this research study?

You are being asked to take part in this study because you are going to be receiving radiotherapy as part of your treatment for breast cancer.

Do I have to take part in this research study?"

No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time.

If you decide not to take part in this research study it will not change your legal rights or the quality of health care that you receive at this center.

How many people will take part in this study?

We plan to have approximately 30 people participate in this study here at UT Southwestern.

What is involved in the study?
If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures. Some of the procedures may be part of your standard medical care, but others are being done solely for the purpose of this study.

Screening Procedures
To help decide if you qualify to be in this study, the researchers may ask you questions about your health, including medications you take and any surgical procedures you have had.

You may also have to fill out certain forms or have the following exams, tests or procedures:

Visit 1:

- Demographic information (age, gender, race, ethnic origin, and skin type);
- Eligibility assessment and an explanation of study purposes and procedures;
- Complete medical history including vital signs (temperature, pulse, respirations, blood pressure), height, weight, physical exam, allergies;
- Record current medications, vitamins, or herbs that you are taking;
- Photographs of breast. At your first visit, and at Week 5, and 2 weeks post-radiation treatment, photographs will be taken. Photos will be taken to exclude faces or any other identifying marks. Photos will only be identified by a unique subject identification number that contains no personal identifying information. These photographs are part of the research. **You will not be able to participate in the research if you do not want to have photographs taken**.
- You will be randomized to receive the investigational product to be applied to either the medial (inside) or lateral (outside) portion of your breast, a placebo product will be used on the other side.
- You will be given a supply of the investigational product and placebo and instruction/demonstration for application.
- During participation, you will be asked to do the following:
- No application of any skin care product besides the study products
- No use of skin products that may affect the color of your skin, such as sunless tanning lotions;

Study Medication/Intervention
You will be provided with the study products to apply three times a day to each side as designated according to your random assignment. Please be sure to wash your hands before and between each application of product/cream. The creams/products will be labeled with your Subject Number.
Products will be supplied by the sponsor. This part of the study will be blinded, that is, both products will be packaged identically by the sponsor and labeled product A and product B so that neither you, nor the investigator, nor the research team will be able to distinguish which Product is applied to areas of radiation exposure..

Procedures and Evaluations during the Research

Study Visits

- Every week during your radiation treatment you will be assessed by an Investigator.
- The Investigator will evaluate the status of your skin, comparing the medial (inside) to the lateral (outside), and determining an overall assessment of your skin's tolerance to the radiotherapy.
- At your first visit, and during Week 5, and 2weeks post-radiation treatment, photographs will be taken.
- On your last day of radiation, both you and your radiation oncologist will be asked to complete an assessment of your skin, giving you an opportunity to report how you felt the creams worked, and if the skin on one side of your breast fared better than the other side

Study Visit 9: (2 weeks after last radiotherapy)

- The physician will examine your skin
- Photographs of your breast
- You will return of any unused investigational product, as well as empty containers
-
- We will ask you about your current medications and any changes in your medications
- We will ask you about any adverse events (side effects or medical problems) that you are having
- We will ask you to complete another patient assessment, giving you another opportunity to report how you felt the creams worked, and if the skin on one side of your breast fared better than the other side.

- Additionally, during the entire duration of this study, we will ask you to maintain a log describing when you applied the products/creams.

- **Restricted Therapies**
    - Drugs, procedures, and/or treatments restricted during the course of this study include:
    - Use of any skin products on the bilateral breast, unless directed by physician
    - Application of any additional skin care products besides the study products.

Please ask your doctor if you have any questions about the medications that you are taking.

The photographs, assessments, and measurements in this study are designed for research, not for medical purposes. They are not useful for finding problems or diseases. Even though the researchers are not looking at this information to find or treat a medical problem, you will be told if they notice something unusual. You and your regular doctor can decide together whether to follow up with more tests or treatment.

How long can I expect to be in this study?
Your participation in this study will last about 11 weeks.
You can choose to stop participating for any reason at any time.

What are the risks of the study?
Study Procedure/Intervention
Because of your participation in this study, you are subject to the following risks: You should discuss these with the researchers and your regular health care provider.

Investigational Product
In previous use of *HylaCare*™, no adverse events have been identified.

Psychological Stress
Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions, take a break or stop your participation in this study at any time.

Loss of Confidentiality
Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Photographs
You could be slightly uncomfortable during the photographic sessions when asked to position your body to take the photograph of your breast area. You may be uncomfortable with standing still for an extended period of time or from turning your body in various positions. You may be sensitive to the bright and repeating flashes from the camera, which can sometimes cause headaches, irritation of the eyes, discomfort, after effects such as seeing spots, and in rare cases, could stimulate a migraine headache or epileptic seizure.

Photographs include a risk of identification. Your privacy will be protected to the greatest extent possible. Photos will be taken to exclude faces or any other identifying marks. Photos will only be identified by a unique subject identification number that contains no personal identifying information. For research purposes your photos may be used in scientific publications.

Other Risks
There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?
You will be carefully screened prior to participation in this study to be sure that you do not have any conditions that would make it unsafe for you. You will be closely monitored during the study. You will be asked, at each visit, about how you are feeling and about any problems or changes in your health that you are having. If you have any adverse events (side effects) from the study products, your surgeon will discuss appropriate treatment with you.

What will my responsibilities be during the study?
While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Store study materials (containers of product) in a secure place at home away from anyone who is unable to read and understand labels, especially children.
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem or something purchased over the counter.
- Tell your regular doctor about your participation in this study.
- Report to the researchers any injury or illnesses while you are on study even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

What should I do if I think I am having problems?
If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area). Tell emergency personnel about any medications you are taking.

What are the possible benefits of this study?
If you agree to take part in this study, there may or may not be direct benefits to you. The researchers cannot guarantee that you will benefit from participation in this research. You may benefit from a reduction in skin irritation, decreased inflammation, and improved healing, but this cannot be guaranteed.

We hope the information learned from this study will may provide a better understanding of the effects of HylaCare™ on irradiated skin.

What options are available if I decide not to take part in this research study?
This is not a treatment study. You do not have to be part of it to get treatment for your elective procedure.

Will my insurance provider or I be charged for the costs of any part of this research study?
No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

However, the standard medical care for your condition (care you would have received whether or not you were in this study) is your responsibility (or the responsibility of your insurance provider or governmental program). You will be charged, in the standard manner, for any procedures performed for your standard medical care.

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas.

You retain your legal rights during your participation in this research

Can I stop taking part in this research study?
Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

Your doctor may be a research investigator in this study. S/he is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

If I agree to take part in this research study, can I be removed from the study without my consent?

Yes. The researchers may decide to take you off this study if:

- Your medical problem becomes worse.
- The researchers believe that participation in the research is no longer safe for you.
- The researchers believe that other treatment may be more helpful.
- The sponsor stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researchers' instructions.

Will my information be kept confidential?

Information about you that is collected for this research study will remain confidential unless you give your permission to share it with others, or if we are required by law to release it. You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Hylaco, LLC;
  Disease Oriented Breast Team- Surgical Oncologist, Medical Oncologist, Plastic surgeons
- Representatives of government agencies involved in keeping research safe for people; and
- The UT Southwestern Institutional Review Board.

Medical information collected during this study and the results of any test or procedure done may be included in your medical record and this information may be available to health care providers and authorized persons including your insurance company.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Are there procedures I should follow after stopping participation in this research?
If you, the researchers, or the sponsor stops your participation in the research, you may be asked to do the following:

- Let the researchers know immediately that you wish to withdraw from the research.
- Return to the research center for tests that may be needed for your safety.
- Return any unused study materials, including empty containers.
- Discuss your future medical care, if any, with the researchers and/or your personal doctor.

Whom do I call if I have questions or problems?
For questions about the study, Asal Rahimi MD 214 645-8525
For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told whom to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.
  You understand that a copy of this signed consent document, information about this study l the results of any test or procedure done may be included in your medical record and this ormation may be available to health care providers and authorized persons including your urance company.

_____

Participant's Name (printed)

_____ _____

Participant's Signature Date

_____

Name of person obtaining consent (printed)

_____ _____

Signature of person obtaining consent Date

FORM 2A

Test Article: HylaCare™
Study No.:
Investigator's Name:

INCLUSION CRITERIA

Patient No.:
Today's Date:

For the patient to be included in the study, all answers to the following questions 1-6 must be checked YES, AND at least the answer to one part of question 7 must be checked YES

	YES	NO
1. Is the patient 18 years or older?	☐	☐
2. Is there a diagnosis of cancer of the breast?	☐	☐
4. Will the planned radiotherapy be administered via tangential ports?	☐	☐
5. Has the patient provided a prior written Informed Consent form t?	☐	☐
6. Does the patient have the ability to understand ad comply with the requirements of this study?	☐	☐
7. For sexually active females, one of the answers provided below must be "YES"		
a. Has the patient agreed to use an acceptable method of birth control; or take oral contraceptives for at least one month prior to study and for the duration of the study?	☐	☐
b. Been sterile, infertile or otherwise incapable of becoming pregnant, or	☐	☐
c. been post-menopausal for at least one year?	☐	☐

Investigator's Signature: _____ Date: _____

FORM 2B

Test Article: HylaCare™
Study No.:
Investigator's Name:

EXCLUSION CRITERIA

Patient No.:
Today's Date:

For the patient to be included in the study, all answers to the following questions must be checked NO

	YES	NO
1. Is the patient either pregnant or lactating?	☐	☐
2. Is the patient using any medication that might interfere with the interpretation of the test article's effectiveness or safety?	☐	☐
3. Will the patient be using any concomitant skin care preparations on any of the irradiated areas?	☐	☐
4. Does the patient have any infection or unhealed wound in the intended radiotherapy skin port areas?	☐	☐
5. Does the patient have any form of generalized dermatosis?	☐	☐
6. Does the patient have any known disease to affect the skin healing process? (e.g. severe renal failure, etc.)?	☐	☐
7. Does the patient have a history of anaphylaxis or multiple severe allergies?	☐	☐
8. Does the patient have a history of allergy to avian-sourced protein products? (e.g., chicken, eggs)?	☐	☐
9. Does the patient plan to relocate during the course of the study, making scheduled visits impossible?	☐	☐
10. Does the patient have collagen vascular disease (Lupus, scleroderma)?	☐	☐

Investigator's Signature: _____ Date: _____

Test Article: HylaCare™	FORM 3 Physician's Follow-Up Assessment Form	Patient No.:
Study No.:		
Investigator's Name:		Today's Date:

DateRadiotherapyInitiated(mm/dd/yy):_____/_____/_____

NumberofweeksofRTcompleted:5___
2weekspost-treatment___
Check(X)signsorsymptomsreportedbythepatientattheirradiatedskinareas:

Indication	Rightbreast			LeftBreast			Whichsideof IRRADIATEDBREAST ONLYisworse? (M/L/equal)
	Medial	Lateral		Medial	Lateral		
Redness							
Pain							
Tenderness							
EasilyIrritated							
Burning							
Dryness							
Hypersensitive							
HairLoss							
Other (describe)							

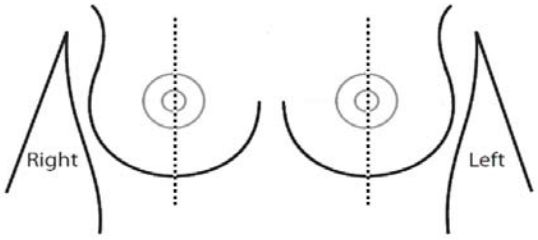
Comments:

[Form3,continued]

I. GradingNCIC-CTC

Adverse Event	1	2	3	4	5
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; desquamation patchy moist desquamation, mostly confined to skin folds and creases moderate edema	Moist desquamation in areas other than skin folds and creases bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation					

PleaseuseNCIC-CTCgradinganddiagrambelow:



II. Inaddition,usingtheInvestigatorGradingScal e,gradethestatusofthemedialandlateral sidesoftheirradiatedskinas:

0=normalskin
1=lightepidermalirritation,consistingoftheonsetoferythema,possiblyassociated withslightedema
2=erythemawithdrydesquamation
3= wetdesquamation</=2cm
4= wetdesquamationfrom2.1–5cm
5= wetdesquamationfrom5.1-9cm
6= wetdesquamation>9.1cm

Investigator's Signature: _____Date:_____

[Form3,continued]

If there is any skin desquamation, note minimal and maximal desquamation size:
Medial: _____ mm minimal x _____ mm maximal
Lateral: _____ mm minimal x _____ mm maximal

Most severe desquamation is dry___ or wet_____?

At 2-week Post-Radiation visit: Describe any treatment performed:
Skin cleansing:_____
Other (describe):_____

Please grade the current status of desquamation healing at 2-week Post-Radiation visit:
Right Breast
Medial: _____ **1 = no evidence of healing (or worsening)**
2 = Beginning of proliferation
3 = Tissue granulation
Lateral: _____ **4 = Re-epithelialization**

Left Breast
Medial: _____ **1 = no evidence of healing (or worsening)**
2 = Beginning of proliferation
3 = Tissue granulation
Lateral: _____ **4 = Re-epithelialization**

Has the patient started any concomitant medication(s) since the last visit, or has the medication dosage changed? If yes, please list below.

Medication	Dose	indication

Has the patient reported any adverse events since the last visit? Yes: _____ No: _____
If Yes, please list below and complete Adverse Event Form.

I

Investigator's Signature: _____Date:_____

Test Article: HylaCare™
Study No.:
Investigator's Name:

FORM 4
DEMOGRAPHICS
AND MEDICAL HISTORY

Patient No.:
Today's Date:

PATIENT DEMOGRAPHICS

Date of Birth (mm/dd/yy): _____ SEX: Female

Height (inches): _____ Weight (pounds): _____

Race: _____

1=White; 2=Black; 3=Hispanic; 4=Asian; 5=Other, specify

BMI: _____ Breast Cup Size: _____

MEDICAL HISTORY
(Check appropriate boxes)

System	Normal	Abnormal	If Abnormal, specify:
Allergies			
Drug Sensitivities			
Dermatologic			
HEENT			
Cardiovascular			
Pulmonary			
Gastrointestinal			
Renal			
Endocrine-metabolic			
GU Systems			
Musculoskeletal			
Peripheral Vascular			
Neurological			
Psychiatric			
Other			

Additional comments on Medical History findings (if any):_____

_____

Investigator's Signature: _____Date:_____

Test Article: HylaCare™
Study No.:
Investigator's Name:

FORM 5
GENERAL PHYSICAL EXAMINATION

Patient No.:
Today's Date:

PHYSICAL EXAMINATION	Normal	Abnormal	If Abnormal, specify:
Head and Neck			
Skin and Mucosa			
Eyes			
Lymph Nodes			
Cardiovascular			
Chest and Lungs			
Abdomen			
Musculoskeletal			
Other			

Additional Comments (if any):_____

_____

_____

_____

_____

Investigator's Signature: _____ Date:_____

Test Article: HylaCare™	**FORM 6 RADIOTHERAPY TREATMENT FORM**	Patient No.:
Study No.:		
Investigator's Name:		Today's Date:

Dateoffirstradiotherapysession(mm/dd/yy):_____/_____/_____

MaximumHotspot:

Circlewhether6MV15MV18MVorMIXEDPHOTONSareused.

Ifmixedphotonsareused,pleasenoteweightingofeachphotonenergy.

#cc'sreceivinggreaterthan107%prescriptiondose:_____

#cc'sreceivinggreaterthan110%prescriptiondose:_____

#ofcc'sofbreasttissueinthetangentialfield(breasttangentsincludingchestwallandribs)

Wholebreastradiationprescriptiondose:_____Maximumdose:_____

Whichbreastisbeingirradiated?Right____Left_____

Investigator'sSignature: _____Date: _____

Test Article: HylaCare™
Study No.:
Investigator's Name:

FORM 7
PATIENT DAILY LOG

Patient No.:
Today's Date:

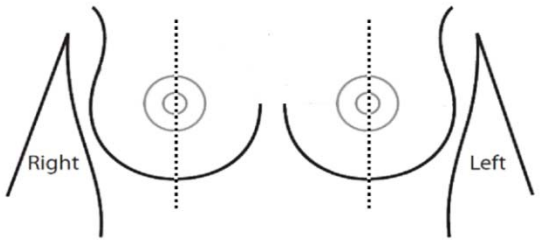
Day (Date)	Morning (time of application)	Afternoon (time of application)	Evening (time of application)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			
Day (Date)	Morning (time of application)	Afternoon (time of application)	Evening (time of application)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			
Day (Date)	Morning (time of application)	Afternoon (time of application)	Evening (time of application)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Test Article: HylaCare™	**FORM 8** **PATIENT INSTRUCTIONS FORM** **(to be given to the patient!)**	Patient No.:
Study No.:		Today's Date:
Investigator's Name:		

You have been given two nearly identical pump containers of serum to be applied to your irradiated skin three times a day. The label on each container will tell you on which side to apply the serum, either medial (inside) or lateral (outside). The picture below shows you which container should be used on which location.

At Baseline visit or first week of treatment, at Week 3, Week 5 and 2 weeks post-treatment you will be given sufficient Set Bags as needed to complete the study.

Please outline the areas of skin that will be subject to irradiation. Note areas to be included in study with a CIRCLE, and note areas outside study area with an X.



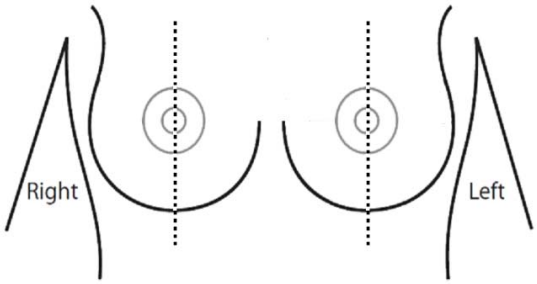
Use diagram to indicate which jar to use on which portion of breast.

Note:

(1) The above-outlined areas, within the circles to indicate inclusion in the study, are the ones to which the test article products are be applied.

(2) The patient will be instructed how, where, and how much product to apply to each irradiated skin area.

(3) The patient will also be instructed to apply these products only to the encircled areas, and not to apply any other skincare products to these sites.



Application Methods

Ensure that your hands are clean, then use the pump to dispense an adequate amount of serum. Apply enough serum to cover the entire area noted in the diagram. Wash your hands again, before switching to the other serum and applying to the other side. Do not use any other products on the treatment areas.

Additional Information

Apply serums three times a day, every day, but **ensure that you don't apply anything to your skin within 4 hours before your radiotherapy appointment.**

Ensure that you apply the serums IMMEDIATELY AFTER radiotherapy treatment.

Apply only to the area identified for prophylaxis.

Report any reactions (general or localized) to the investigator at the next daily session, or more severe reactions by telephone.

Suggestions for personal care of the irradiated skin

1. Avoid irritating the skin
2. When washing, use only lukewarm water and mild soap, patting the surface dry
3. Avoid the use of tight clothing
4. Do not rub, scrub or scratch the skin
5. Avoid the use of heating pads or ice packs
6. Do not use powders, creams , perfumes, deodorants, body oils, ointments or lotions on the irradiated surfaces
7. Avoid direct sun exposure, if necessary, wear protective clothing

Study No.:	**Form 9** **PHYSICIAN'S GLOBAL ASSESSMENT FORM**	Patient No.:
Investigator's Name:		Today's Date:

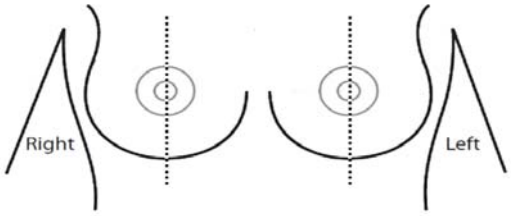
Note: ThisformshouldbecompletedatWeek5 priortoboostandattheendofstudy (2weeksaftercompletionofRT).
Pleasemakeanoverallglobal assessmentoftheeffect ivenessofradiationskin toleranceofbothsidesof theirradiatedbreasttissue.Basedonyourjudgmentand pastexperience,comparetheskinappearanceandpatient'sreportedsymptomatology foreachsideofthebreast,andforeachbreas t(testsubstance-treatedandvehicle control-treated)withthenormallyexpected degreeofradiationdamageforsimilarbody sites.Gradeyouroverallimpressionas:

0=poor(worsethantypicalexpectations)
1=fair(equalto,orslightly betterthantypicalexpectations)
2=good(moderatelybetterthantypicalexpectations)
3=excellent(markedlybette rthantypicalexpectations)

Pleasecomparethetwoirradiat edsites.Inyouropinion, whichskinsitefaredbetter, basedonsymptomsexperienc ebythepatientandoverallskinappearance?

RightBreast:
Medial:_____Lat eral:_____EqualTolerance:_____
LeftBreast
Medial:_____Later al:_____Equal Tolerance:_____

Comments:



_____
_____
_____
_____

Investigator's Signature: _____Date:_____

Test Article: HylaCare™	**FORM 10** **PATIENT'S OVERALL** **EVALUATION FORM**	Patient No.:
Study No.:		
Investigator's Name:		Today's Date:

Note: The patient should complete this questionnaire at Week 5 prior to boost and at the final visit (2 weeks after the completion of RT).

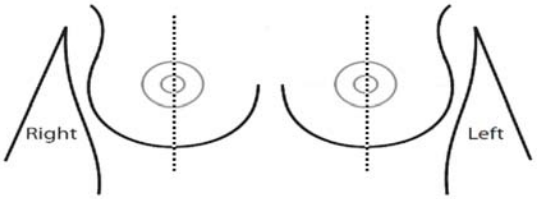
Instructions to the Patient

You have now completed your prescribed course of radiotherapy administrated to your breast.
Please compare the two sides (medial [inner] and lateral [outer]) of your irradiated breast which were exposed to radiation.

In terms of any localized skin reactions you have experiences throughout your radiotherapy (such as redness, soreness, itching, or others), which side of the irradiated breast do you believe fared better.
_____ Medial better than lateral (inner better than outer)
_____ Lateral better than medial (outer better than inner)
_____ No difference between medial (inner) and lateral (outer)

Which side of the irradiated breast has maintained an overall appearance closest to its appearance before radiotherapy began?
_____ Medial (inner)
_____ Lateral (outer)
_____ No difference between medial (inner) and lateral (outer)

Do you have any preferences between the serums applied to your skin?
_____ Prefer the product applied to medial side (inner)
_____ Prefer the product applied to lateral side (outer)
_____ No preference between the two products



If you did prefer one product over the other, please explain why:
_____
_____

Investigator's Signature: _____ Date: _____

Test Article: HylaCare™	**FORM 11 PATIENT COMPLETION FORM**	Patient No.:
Study No.:		
Investigator's Name:		Today's Date:

Note: To be completed at the final visit, or upon discontinuation from the study.

1.Subject Overview
Did the patient experience any side effects from the study agent? Yes: _____ No: _____

If yes, complete Adverse Event Form

2.Study Completion
Did the patient complete the entire study? Yes: _____ No: _____

If no, complete information below.

3.Discontinuation from Study
Date of withdrawal (mm/dd/yy): _____/_____/_____

Reason for withdrawal (check and explain)
_____Adverse Event:_____
_____Did not meet protocol criteria:_____
_____Unreliable:_____
_____Lost to follow-up/moved:_____
_____Subject requested discontinuation:_____
_____Other:_____

Explain (in detail, as needed)
_____
_____
_____

I have reviewed and evaluated the information provided in these case report forms and believe it accurate represents the patient's clinical progress in the study.

Investigator's Signature: _____Date:_____