An Open Label, Dose Escalation Study to Evaluate the Safety and Efficacy of Intralesional Injection of STP705 in Adult Subjects with Facial Cutaneous Squamous Cell Carcinoma *in situ* (isSCC)

Protocol Number:	**SRN-705-011**
Version:	**1.0**
Date:	**18 April 2022**

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CONFIDENTIALITY STATEMENT

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APPROVAL PAGE

Protocol Number:	**SRN-705-011**
Version:	**1.0**
Date:	**18 April 2022**

We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

PROTOCOL APPROVAL FOR USE

Prepared by:

Nadia Sheibani, MPH Sirnaomics, Inc.	Date

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Marietta Radona, M.D. Therapeutics, Inc.	Date
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Approved by:	Michael Molyneaux, M.D., M.B.A. Chief Medical Officer Sirnaomics, Inc.	Date

SERIOUS ADVERSE EVENT REPORTING FOR SITES IN US

CONTACT THERAPEUTICS, INC. (TI) WITHIN 24 HOURS OF LEARNING OF ANY SERIOUS ADVERSE EVENT.

IF THE SERIOUS ADVERSE EVENT IS FATAL OR LIFE THREATENING, TI and SIRNAOMICS MUST BE INFORMED IMMEDIATELY.

Contact TI as described below and complete a Serious Adverse Event report form.

CALL, EMAIL, OR FAX SAE REPORT FORM TO*:	**Sirnaomics**
Attn.: Daniel J. Piacquadio, MD (Medical Monitor) **Phone:** (858) 571-1800 ext. 107 (office) (619) 889-7058 (cell) **Fax number**: (858) 571-1234 **Email:** danp@therapeuticsinc.com	**Attn.:** Michael Molyneaux, MD **Phone:** (949) 403-0828 **E-mail:** MichaelMolyneaux@sirnaomics.com

***NOTE: A copy of all SAE reports shall be provided to the project manager: Marietta Radona (mradona@therapeuticsinc.com) and your site monitor.**

For reporting of all serious adverse events, Investigators must fax all completed pages of the SAE report form within 24 hours to the following:

ATTENTION: Daniel J. Piacquadio, MD

FAX # / Email: (858) 571-1234 / danp@therapeuticsinc.com

To discuss SAE with the Medical Monitor, contact Daniel J. Piacquadio at the numbers provided above. Follow-up information to serious AEs must be provided to TI within 24 hours of investigator awareness.

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**SRN-705-011**
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I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with the applicable US Food and Drug Administration (FDA) regulations and Investigational Review Board (IRB) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

_____ _____

Principal Investigator's Signature Date

_____

Print Name

_____

Address

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Site Number

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PROTOCOL SYNOPSIS

Name of Sponsor/Company: Sirnaomics, Inc.	
Name of Study Product: STP705	
Protocol Number: **SRN-705-011**	**Indication:** Facial Cutaneous Squamous Cell Carcinoma *in situ*
Title of Study: An Open Label, Dose Escalation Study to Evaluate the Safety and Efficacy of Intralesional Injection of STP705 in Adult Subjects with Facial Cutaneous Squamous Cell Carcinoma *in situ* (isSCC).	
Study Center(s): Up to 3 centers in the United States	
Planned Number of Subjects: 30	**Study Development Phase:** Phase 1/2

Objectives:

The purpose of this trial is to evaluate the safety, tolerability, and efficacy of various doses of STP705 administered as intralesional injection in subjects with facial cutaneous squamous cell carcinoma *in situ* skin cancer (isSCC).

Goals:

- To determine the safe and effective recommended dose of STP705 for the treatment of facial isSCC.
- Analysis of biomarkers common to isSCC formation pathway including TGF-β1 and COX-2.

Endpoints Measures:

Primary Endpoint:

- Proportion of participants with histological clearance of treated facial isSCC lesion at the End of Treatment (EOT).

Histological clearance (HC) will be defined as the absence of detectable evidence of isSCC tumor cell nests as determined by central pathology review.

Secondary Endpoints:

- Change in size of the treated isSCC lesion over the pre-excision treatment period.

A baseline assessment of lesion size will be made by investigator at T1 (first visit).

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This is measured by widest width and longest length using a caliper or a ruler as deemed by the investigator judgement. The change in size will be assessed every visit until the surgical excision of isSCC at the End of Treatment (EOT) visit.

Safety Assessments:

- Incidence of adverse events (AEs) and serious adverse events (SAEs).
- Incidence of AEs and SAEs leading to discontinuation of trial medication.
- Incidence and severity of Local Skin Response (LSR), hypopigmentation and hyperpigmentation following treatment.
- Tolerability of repeated intralesional administration of STP705 as assessed by investigator evaluation of injection site reactions for all subjects and within each cohort.

In addition, safety measures will include clinically relevant changes or new abnormal findings in laboratory values, vital signs, electrocardiograms (ECGs), and physical examination.

Study Design:

This is an open label study designed to evaluate the safety and efficacy of various doses of STP705 administered as an intralesional injection in subjects with facial cutaneous *in situ* squamous cell carcinoma (isSCC).

Thirty subjects will be divided equally among 3 cohorts 30, 60, or 90 μg STP705 of 10 subjects each.

Enrolled subjects will receive an STP705 injection once weekly for 6 weeks. The lesion will be excised approximately 60 days after the last injection.

In the absence of dose limiting toxicities (DLT), the subsequent cohorts will receive increasing doses of STP705, following the same schedule of administration as the first cohort. Dose escalation will progress after ten subjects have been enrolled in the previous cohort, provided that none of the following SAEs or DLTs have occurred in any subject. The Investigator will be responsible for determining the relationship between an AE and the study treatment.

(1) Death in which the cause of death is determined to be possibly, probably, or definitely related to

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STP705

(2) The occurrence of an anaphylactic reaction to STP705

(3) The occurrence of a severe grade 3 local injection site reaction, which is not resolved or recurred; or a grade 4 local injection site reaction that precludes administration of consecutive doses

(4) The occurrence of a life-threatening SAE whose causal relationship to STP705 is determined to be probably or definitely related

(5) The occurrence of one or more non-life-threatening SAEs whose causal relationship to STP705 is determined to be definitely related

(6) The occurrence of grade 4 laboratory abnormalities, determined to be probably or definitely related to STP705

(7) The occurrence of hematologic and non-hematological adverse events, determined to be possibly, probably, or definitely related to STP705 and that are of CTCAE grade 3 or greater severity. Permissible exceptions to this rule include grade 3 fatigue of less than one week duration, and grade 3 nausea, vomiting, and diarrhea that resolve within 48 hours following institution of appropriate supportive care.

The study will have three phases: Screening Phase, Treatment Phase, and Follow-Up Phase.

Optional Pre-Screening Biopsy:
If a potential subject presents with a clinically suspicious facial isSCC lesion that was never biopsied, or cannot provide a confirmatory histopathology report, or that was biopsied more than 6 months prior to Screening, this lesion may be biopsied to determine eligibility (an optional pre-screening biopsy) by the investigator (or his/her qualified designee) as a consented procedure under this protocol prior to Screening.

Screening Phase (Visit 1) (-28 to -3 days prior to Baseline):
Screening assessments will commence after obtaining signed informed consent, and will include review of medical and medication history, isSCC lesion biopsy histopathology review, eligibility

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evaluation of facial cutaneous Squamous Cell Carcinoma *in situ (isSCC)*, physical examination, vital signs, height and weight, concomitant medications, electrocardiogram (ECG), chemistry, hematology, coagulation (if applicable), urinalysis, serum pregnancy (if applicable), baseline Local Skin Response (LSR Grading Scale), 2D photograph of lesion pre-marked with a surgical skin marker, manual measurement of longest diameter and area of lesion using a ruler or a caliper as deemed appropriate by the investigator. These assessments must be conducted within 28 days of the First Treatment Visit (Visit 2).

Treatment Phase (Visit 2 – Visit 9) (up to 14 weeks ± allowed windows):

Subjects who meet eligibility criteria will check-in to the clinic on the day the first treatment is scheduled. The following assessments will be performed prior to the first treatment: review of any changes in medical and medication history, vital signs, weight measurement, symptom-directed physical examination, concomitant medications, ECG, chemistry, hematology, urinalysis, urine pregnancy (if applicable), blood collected for Anti-Drug Antibody (ADA) analysis, creation of a pre-treatment lesion template along with measurement of longest diameter and area of the lesion using a ruler or a caliper, and 2D digital imaging of the lesion pre-marked with a surgical skin marker, baseline LSR Grading Scale assessment, baseline pigmentation, and Visual Analogue Scale (VAS) pain assessment at the site of lesion prior to dosing. The marking of the lesion using the skin marker should be repeated every visit.

Eligible subjects will be assigned to a cohort. All subjects who fail to meet eligibility criteria at Baseline/Treatment Visit (T1) are considered screen failures and are exited from the study without further evaluation.

The dosing regimen for each cohort is as follows:
Cohort A: STP705 30 μg dose, intralesional injection, given once a week for 6 weeks.
Cohort B: STP705 60 μg dose, intralesional injection, given once a week for 6 weeks.
Cohort C: STP705 90 μg dose, intralesional injection, given once a week for 6 weeks.

Schedule of Treatment Visits

- Visit 2 T1 (first treatment) – Within 4 weeks of the Screening Visit
- Visit 3 T2 (second treatment) – 7 days (±3 days) after T1

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- Visit 4 T3 (third treatment) – 7 days (±3 days) after T2
- Visit 5 T4 (fourth treatment) – 7 days (±3 days) after T3
- Visit 6 T5 (fifth treatment) – 7 days (±3 days) after T4
- Visit 7 T6 (sixth treatment) – 7 days (±3 days) after T5
- Visit 8 Observation Visit – 30 days (±3 days) after T6
- Visit 9 End of Treatment (EOT) Visit – 30 days (±3 days) after Observation Visit
    - Excision of tumor at EOT visit.

The study treatment STP705 will be administered by the licensed medical professional. All treatments for all dose cohorts are 0.6 mL administered as an intralesional injection. Post-treatment, LSRs and pain assessment at the site of the lesion using VAS will be evaluated within 15 minutes (±5 min) of the STP705 administration. At T1, 2D digital imaging of the lesion post-dose will also be taken.

An ECG will be performed at pre-dosing at the T1 Visit and at the EOT visit (before excision).

Vital signs will be assessed before the injection, and within 15 minutes (±5 min) after the injection at each treatment visit. At T1, vital signs will also be taken within 30 min (±5 min) and within 1 hour (±15 min) post-dose.

The Observation Visit (Visit 8) will be performed 30 (±3) days after the T6 visit. The following assessments will be performed: vital signs, symptom-directed physical examination, concomitant medications, blood collected for Anti-Drug Antibody (ADA) analysis, measurement of longest diameter and area of the lesion using a ruler or a caliper, 2D photography of the lesion pre-marked with a surgical skin marker, LSR Grading Scale assessment, and pigmentation assessment.

The End of Treatment (EOT) visit (Visit 9) will be performed 30 (±3) days after the Observation Visit (Visit 8). The following assessments will be performed at EOT (Visit 9): vital signs, weight measurement, symptom-directed physical examination, concomitant medications, ECG, chemistry, hematology, urinalysis, serum pregnancy (if applicable), blood collected for Anti-Drug Antibody (ADA) analysis, measurement of longest diameter and area of the lesion using a ruler or a caliper, 2D photography of the lesion pre-marked with a surgical skin marker, final LSR Grading Scale

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assessment, and pigmentation assessment. The surgical excision at the site of treated isSCC lesion will be performed at the EOT visit using the pre-treatment template for reference, and the resulting excision wound may be sutured, per site standard of care. The excised specimens will be assessed for histological clearance of the lesion.

Adverse events and medications will be monitored throughout the study.

Follow Up Phase

There will be Follow Up Visits at 7 days (±3 days) (Visit 10/FU1) and 21 days (±3 days) (Visit 11/FU2) after the lesion was excised at EOT (Visit 9). The following assessments will be performed at FU1 and FU2 Visits: removal of excision site sutures (FU1 only), review of adverse events and concomitant medications, symptom-directed physical examination, vital signs, 2D digital imaging of lesion/surgical site, pigmentation assessment, blood collection for Anti-drug antibody (ADA) assay (FU1 only) and blood collection for chemistry, hematology, and urine laboratory assessments (FU2 only).

Duration of Treatment:

- **Screening Period:** Up to 4 Weeks
- **Treatment Period:** Up to 14 Weeks (± allowed windows) including EOT excision
- **Follow-Up Phase:** Up to 3 Weeks (± allowed windows)

Total Study Duration: Up to 21 Weeks

INCLUSION CRITERIA

Inclusion Criteria: Subjects are required to meet all of the following criteria for enrollment into the study:

1. Male or female adult ≥ 18 years of age.
2. Primary, histologically confirmed facial isSCC lesion suitable for excision with a minimum diameter of 0.5 cm and with a maximum diameter of 2.0 cm.
3. Histological diagnosis of a qualified isSCC skin lesion (evidenced by a confirmatory histopathology report) made no more than 6 months prior to the screening visit.

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4. No other dermatological disease in the isSCC target lesion or surrounding area, which in the opinion of the investigator, could interfere with the study.
5. Willing to refrain from using non-approved lotions or creams on the target lesion and surrounding area during the treatment period (sunscreen and moisturizers allowed).
6. Willing to refrain from exposure to excessive direct sunlight or ultraviolet light and to avoid the use of tanning parlors for the duration of the study.
7. Laboratory values for the tests (listed in the Study Schedule) within the reference ranges as defined by the local laboratory, or "out of range" test results that are clinically acceptable to the investigator.
8. Ability to follow study instructions and likely to complete all study requirements.
9. Written informed consent obtained, including consent for tissue to be examined and stored by the Central Histology Lab.
10. Written consent to allow photographs of the target isSCC lesion to be used as part of the study data and documentation.
11. For female subjects of childbearing potential, a negative pregnancy test at screening and using an acceptable form of birth control (oral / implantable / injectable / transdermal contraceptives, intrauterine device, condom, diaphragm, abstinence, or a monogamous relationship with a partner who has had a vasectomy at least 6 months prior to screening).

EXCLUSION CRITERIA

1. Pregnant, lactating, or planning to become pregnant.
2. Presence of known or suspected systemic cancer.
3. Confirmatory histological report of the qualified isSCC lesion reveals evidence of severe squamous metaplasia, infiltrative, desmoplastic or micronodular growth patterns in the opinion of the investigator.
4. History of recurrence of the target isSCC lesion.
5. Concurrent disease or treatment that suppresses the immune system.

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6. Subjects with baseline QT corrected interval QTc > 480 msec using Fridericia's formula.
7. Chronic medical condition that in the judgment of the investigator(s) would interfere with the performance of the study or would place the patient at undue risk.
8. Known sensitivity to any of the ingredients in the study medication including an allergy to trehalose.
9. Use of a tanning bed or other excessive or prolonged exposure to ultraviolet light or direct sunlight during the study.
10. Treatment with systemic chemotherapeutic agents within the 6 months prior to the screening visit.
11. Use of systemic retinoids within the 6 months prior to the screening period.
12. Treatment with systemic immunomodulators or immunosuppressants within the 6 months prior to the screening period.
13. Use of topical immunomodulators within 2 cm of the target isSCC lesion within the 4 weeks prior to the screening period.
14. Treatment with the following topical agents within 2 cm of the target isSCC lesion within the 4 weeks prior to the screening visit: aminolevulinic acid, 5-fluorouracil, corticosteroids, retinoids, diclofenac, ingenol mebutate, tirbanibulin, or imiquimod.
15. Treatment with liquid nitrogen, surgical excision, or curettage within 2 cm of the target isSCC lesion during the 4 weeks prior to the screening visit.
16. Evidence of current chronic alcohol or drug abuse that, in the opinion of the investigator, would impair the subject's ability to comply with study schedule.
17. Current enrollment in an investigational drug or device study or participation in such a study within 4 weeks of the screening visit.
18. In the investigator's opinion, evidence of unwillingness, or inability to follow the restrictions and requirements of the protocol and complete the study.

Statistical Considerations:

<u>Sample Size Determination and Rationale:</u>

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A total of 30 eligible subjects (10 subjects/cohort) will receive treatment with 30 μg, 60 μg, or 90 μg STP705. No statistical power calculation is used to establish the sample size.

Analysis Populations:

Intent-to-Treat (ITT) population
The ITT population is defined as all enrolled subjects. The ITT population will be the primary population for the analysis of primary and secondary outcome measures.

Safety Population
The Safety Population will include all subjects who received at least one dose of study medication (any dose of STP705). This population will be used for the analysis of safety parameters.

Missing Data:

Every effort will be made to obtain required data at each scheduled evaluation for all subjects who have been treated to minimize missing data. For the primary efficacy end point of histological clearance of treated isSCC lesion at EOT, missing due to early termination or other reasons will be imputed as histological clearance = No.

Statistical Methods
All collected study data will be presented in subject data listings. Statistical analysis will be performed using SAS®. A detailed description of the statistical Analysis methods and data conversions that will be used in the study will be presented in the Statistical Analysis Plan (SAP). Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for continuous variables. Frequencies and percentages will be presented for categorical variables. Summaries will be provided for each treatment group and will include 95% confidence interval where appropriate and as designated in the SAP.

Safety Summaries and Analysis:

<u>Adverse Events</u>

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Adverse events (AEs) will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) at study start. Treatment Emergent AEs (TEAE) are defined as events with an onset on or after the first treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- Overall (i.e., regardless of severity or relationship to treatment).
- By intensity (mild, moderate, severe, life threatening or death).
- By causality (definitely, probably, possibly, unlikely, or unrelated).
- By impact on study treatment (dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown).

In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

Other Safety Data

- Local Skin Response (LSR)

Local skin response grades will be summarized by frequency counts and descriptive statistics per cohort and visit for each of the individual LSRs: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration.

- Clinical Laboratory Data

All laboratory values will be listed. Laboratory measurements will also be summarized and presented by treatment group and time point.

- Electrocardiogram (ECG)

All ECG values will be listed. ECG measurements will also be summarized and presented by treatment group and time point.

- Vital signs

All vital sign results will be listed and/or summarized.

- Physical Examination

All clinically significant physical examination findings will be listed as Medical History (from Visit 1 or

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Visit 2 prior to treatment) or Adverse Events (all events as of treatment at Baseline or thereafter).	

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
COX-2	Cyclooxygenase-2
CRO	Contract Research Organization
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End of Treatment
FDA	Food and Drug Administration
FUV	Follow-up Visit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HEENT	Head, Ears, Eyes, Nose, and Throat
HIPAA	Health Insurance Portability Accountability Act
HKP	Histidine-Lysine Polypeptide
IA	Interim Analysis
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization

Abbreviation	Term
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
iRECIST	Immune-modified RECIST
isSCC	In-situ Squamous Cell Carcinoma
LAR	Legally Authorized Representative
LSR	Local Skin Response
nBCC	Nodular Basal Cell Carcinoma
NMSC	Non-Melanoma Skin Cancer
PI	Principal Investigator
QTc	Q-T Corrected Interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sBCC	Superficial Basal Cell Carcinoma
SCC	Squamous Cell Carcinoma
SOP	Standard Operating Procedure
SV	Screening Visit
TGF-β1	Transforming Growth Factor Beta
TEAE	Treatment Emergent Adverse Event
TV	Treatment Visit
VAS	Visual Analogue Scale

1. INTRODUCTION AND BACKGROUND

1.1 STATEMENT OF INTENT

The design, conduct, and reporting of this study will be in compliance with the protocol, International Conference on Harmonization/Good Clinical Practice (ICH/GCP), and all appropriate regulatory requirements. Investigator(s) participating in this study will have documented training in GCP. Independent monitoring of the trial will be accomplished utilizing a Contract Research Organization (CRO).

1.2 BACKGROUND OF THE DISEASE

Non-melanoma skin cancer (NMSC) is a growing public problem due to its increasing incidence and medical care costs (Feehan and Shantz, 2016). There are an estimated 3.5 million people in the United States who have been diagnosed with NMSC making it the most common form of cancer in the country (American Cancer Society, 2015). NMSC consists of two major subtypes: (i) basal cell carcinoma (BCC) and (ii) squamous cell carcinoma (SCC).

Squamous cell carcinoma of the skin (cutaneous squamous cell carcinoma, or SCC) is characterized by the occurrence of precursor lesions called actinic keratosis that most commonly result from exposure to UV light. The incidence of actinic keratosis increases with advancing age (Christenson et al, 2005) (Ley, 1993). Individuals with a suppressed immune system are also at increased risk for SCCs (Athar et al, 2011). Development of SCC is linked closely to genomic perturbations, genetic mutations (e.g., p53 gene mutation), and altered expression of key molecules (e.g., overexpression of TGF-β1 and COX-2) that impacts squamous cell lineage commitment and terminal differentiation (Howell and Ramsey, 2018) (Dotto and Rustgi, 2016).

The most common areas for SCC to occur are the face, neck, bald scalp, extensor forearms, dorsal hands, and shins. The SCC lesions can be flat, nodular, and even plaque-like in some cases with significant induration and or subcutaneous spread noticeable on palpation. Histopathologically, SCC is notable for irregular nests, cords and sheets of neoplastic keratinocytes invading the dermis (Howell and Ramsey, 2018). A distinguishing feature of SCCs is their high degree of cellular heterogeneity that makes them particularly difficult to target with monotherapeutic approaches (Dotto and Rustgi, 2016).

SCCs exist on a continuum of neoplastic growths that may progress from actinic keratosis to intraepidermal carcinoma (also known as cutaneous squamous cell carcinoma *in situ*, isSCC), to early cutaneous squamous cell carcinoma. Distinguishing each step in the progression of the lesion is made difficult by the high degree of variability in clinical appearance, and the lack of

distinguishing features (Wheller and Soyor, 2015). Many consider actinic keratosis and isSCC to be SCC that is still confined to the epidermis (Feldman and Fleischer, 2011).

1.3 CURRENT TREATMENT OPTIONS

The gold standard of treatment for high-risk NMSC is Mohs micrographic surgery (MMS) or radiotherapy. Some of the non-surgical treatment options are pharmacotherapy, cryotherapy, photodynamic therapy, laser, and radiotherapy (Lv and Sun, 2017). Though these treatments provide non-invasive options for the patients, there is evidence in the literature that demonstrate that non-surgical treatments are not as effective for curing NMSC (Gracia-Cazana and Gonzalez, 2016) (Gracia-Cazana et al, 2016).

1.4 ROLE OF TGF-β1 IN NMSC

TGF-β1 has been identified as a major factor that promotes epithelial cell proliferation and is a critical regulator of NMSC development and progression in humans (de Caestecker et al, 2000). TGF-β1 has been linked with stromal alterations that play a primary role not only in the progression, but also in the initiation of SCC (Dotto and Rustgi, 2016). The cell surface receptor for TGF-β1 is a complex of TGF-β1 type I and type II transmembrane receptors (TβRI and TβRII), both of which are serine threonine kinases. Binding of TGF-β1 to TβRII recruits TβRI into a heterotetrametric complex resulting in phosphorylation and activation of the cytoplasmic domain of TβRI by TβRII kinase (Ikushima and Miyazono, 2010). This activates the kinase activity of the TβRI towards its substrates the R-(receptor activated) Smads, which for TGF-β1 are Smad2 and Smad3. Once phosphorylated, Smad2 or Smad3 form a complex with the co-Smad, Smad4, and translocate to the nucleus to regulate TGF-β responsive genes, through either specific Smad-binding element, other suppressive elements, or through interaction with other transcription factors (Massagué and Gomis, 2006). TGF-βs can also activate members of the mitogen-activated protein (MAP) kinase signaling molecules including JNK, p38, ERKs, and the PI3 K/AKT pathway (Ikushima and Miyazono, 2010).

Studies have shown that an increase in TGF-β1 expression is reported in human cutaneous SCC tissues (Han et al, 2005). TGF-β1 overexpression promotes tumor progression, metastasis, and epithelial-mesenchymal transition at the later stages of skin carcinogenesis (Li et al, 2005). The tumor promotion role is associated with its effect on the loss of epithelial cell adhesion, extracellular matrix remodeling, and enhanced angiogenesis (Weeks et al, 2001). Additionally, current data suggests, that TGF-β1 overexpression may have a tumor promoting effect even at the early stages of skin carcinogenesis if overexpressed in proliferative cells of the epidermis/tumor epithelia (Li et al, 2005). A study analyzing BCC tissues samples from 24 patients reported that the lesioned skin of BCC patients had significant mRNA overexpression of

TGF-β1 and Smad3 as compared to non- lesional skin thus suggesting a possible role of TGF-β1/Smad signaling in the pathogenesis of BCC (Gambichler et al, 2007) In-vitro studies have demonstrated that TGF-β1modulates the response of keratinocytes to ultraviolet radiation and acts as a potential mediator of the cellular stress response in keratinocytes that could lead to the development of NMSC (Merryman et al, 1998). In vivo studies demonstrated Smad3 knockout mice were resistant to skin chemical carcinogenesis and suggested that this was due to abrogation of endogenous TGF-β1 activity (Li et al, 2005). Studies have also demonstrated overexpression of TGF-β1 by SCC cells enhances matrix degrading enzymes (MMP-13 and MMP-1) expression that plays a major role in disruption of the skin tissue architecture and promotes the invasion of SCC cells in turn promoting tumor growth (Leivonen et al, 2006). Given the critical role of TGF-β1 in tumor progression, it has been acknowledged as an attractive target for preventive and therapeutic approaches against NMSC development (Dotto and Rustgi, 2016).

1.5 ROLE OF COX-2 IN NMSC

Cyclooxygenase (COX), also known as prostaglandin-endoperoxide synthase (PTGS), is an enzyme that is responsible for the formation of prostanoids, including thromboxane and prostaglandins such as prostacyclin. COX-2 is one of the members of the PTGS family (Shujio et al, 2016). The exact molecular mechanism of COX-2 is still under investigation, however, there are multiple possible mechanisms of COX-2 that could play a role in the development of skin cancer. COX-2 can act as a proliferative factor for malignant cells by promoting the synthesis of prostaglandin E2 (PGE2) (Elmets et al, 2010). COX-2 also mediates antiapoptotic effects on BCC cells through induction of Mcl-1 and Bcl-2 expression. Bcl-2 is a known antiapoptotic factor and Mcl-1 upregulation is involved in c-Myc and IL-6 mediated antiapoptotic effects (Tjiu et al, 2006). COX-2 is also required by the myeloid suppressor cells to produce immunosuppressive molecule arginase-1 that promotes the invasion and angiogenesis of human BCC cells (Elmets et al, 2010). Additionally, studies have reported that COX-2 could promote epithelial-mesenchymal transition (weakens intercellular adhesions) that enhances the motility of BCC and SCC cells to penetrate surrounding tissues and metastasize (Elmets et al, 2010).

Several published studies have reported a positive correlation between COX-2 overexpression and development of skin cancer. A meta-analysis study was conducted using multiple databases to evaluate the correlation between COX-2 expression and skin cancer. The analysis included 10 studies with 518 skin cancer patients and 195 healthy controls. The results showed a significant correlation between COX-2 expression and skin cancer (both SCC and BCC); COX-2 expression was significantly higher in patients with skin cancer compared to healthy controls (Shujio et al, 2016). Clinical and pre-clinical studies have demonstrated that COX-2 inhibitor (celecoxib) has

been highly effective in preventing NMSC in subjects who were at high risk of developing skin cancers (that is, subjects with large number of actinic keratoses, or had already developed one or more skin cancers) (Elmets et al, 2010). There is also evidence from epidemiological studies that COX-inhibitors are associated with decreased risk of cutaneous SCCs (Butler et al, 2005) (Grau et al, 2006). In-vivo studies have demonstrated that COX-2 expression is increased in murine skin neoplasms after chronic exposure to carcinogenic doses of ultraviolet radiation. Acute ultraviolet radiation resulted in increased COX-2 expression that continued to increase in developing papillomata and SCC (An et al, 2002). In-vitro studies have reported that COX-2 overexpression induces resistance to apoptosis in human BCC cells. In vivo studies have demonstrated that COX- 2 overexpression results in induction of angiogenesis and has a strong correlation with increased levels of VEGF-A expression (Tjiuet al, 2006). Overall, the positive correlation with COX-2 overexpression and NMSC renders it as an attractive therapeutic target.

1.6 Name and Description of the Investigational Product

The active investigational product in the study is STP705. This is shown in Table 1-1.

Table 1-1: Description of Investigational Product

COMPONENT	CONCENTRATION (MG/VIAL)	FUNCTION
siRNA TGF-β1	0.16 mg	Drug Substance
siRNA COX-2	0.16 mg	Drug Substance
HKP peptide	0.8 mg	Excipient for generation of nanoparticles
Trehalose dihydrate	64 mg	Excipient for lyophilization

The drug substance is composed of two siRNA oligonucleotides, targeting TGF-β1 and COX-2 mRNA respectively. The two siRNA strands are formulated in nanoparticles with histidine-lysine- polypeptide (HKP) at a ratio of 1:2.5 in mass weight (siRNA: peptide), which is further formulated into a lyophilized powder drug product. The administration route will be intralesional injection.

1.7 Pre-Clinical Studies

1.7.1 Effect of STP705 on Human Cutaneous Squamous Carcinoma Cell Viability in Vitro

An In vitro study (Study Report: Assessment of down regulation on cell proliferation) was conducted to evaluate the effects of STP705 on HSC-1 (human cutaneous squamous carcinoma cells) cell viability. HSC-1 cells were transfected with STP705 or siRNAs/Lipofectamine 2000 complexes and 72-hours post-transfection cell viability was measured using CellTiter-Glo Luminescent cell viability assay (Promega). Values from untreated cells (Blank) were set as 100%, and test values were expressed relative to this control value. All values in Figure 1-1 represent the mean ± standard deviation. The cells transfected with siRNA for TGF-β1 had an average cell viability of 53% (at 200nM) and cells transfected with siRNA for COX-2 had an average cell viability of 59% (at 200nM). However, cells transfected with STP705 (consisting of both TGF-β1 siRNA and COX-2 siRNA delivered using HKP branched polypeptide nanoparticle) showed a dose-dependent reduction in cell viability with 1376nM concentration and showed 32% cell viability. Figure 1-2 demonstrates that HSC-1 cells transfected with STP705 at 72 hours post-transfection, had an IC50 of 1275nM. In other words, STP705 at 1275nM can inhibit HSC-1 cell viability by 50%.

FIGURE 1-1: PERCENT CELL VIABILITY OF HSC-1 CELLS AT 72 HOURS POST-TRANSFECTION WITH STP705

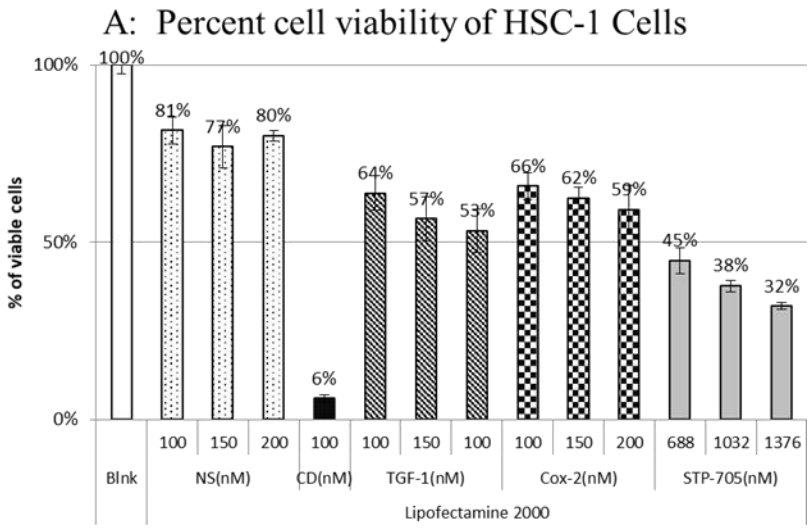


Figure 1-1 demonstrates percent cell viability of HSC-1 cells at 72 hours post transfection with CellTiter-Glo assay. Values are presented as percentage of non-transfected control ± standard deviation of four replicates. NS = non-silencing siRNA (QIAGEN); CD = Cell Death siRNA (QIAGEN).

FIGURE 1-2: DOSE-DEPENDENT PERCENT CELL VIABILITY

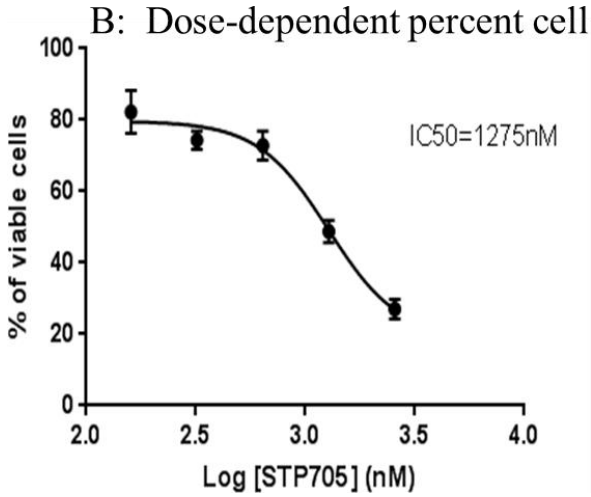


Figure 1-2 illustrates the IC50 of STP705 on cell viability of HSC-1 cells at 72 hours post-transfection.

1.7.2 EVALUATION OF STP705 ON TUMOR GROWTH IN AN A431 XENOGRAFT MOUSE-TUMOR MODEL

The objective of the study was to demonstrate the efficacy of STP705 on tumor suppression in an A431 xenograft mouse tumor model. A431 is a human squamous carcinoma cell line that has been widely used to evaluate the anti-cancer effect of various therapeutic compounds.

Thirty-two (32) female athymic nude mice (BALB/c nu/nu, SPF, 5-weeks old) bearing subcutaneous xenograft tumors of A431 were randomized into four groups (8 animals/group) see Table 1-2 below.

TABLE 1-2: A431 XENOGRAFT TUMOR IN NUDE MICE STUDY DESIGN (15-DAYS)

Group	Tumor	Dose	Mouse*	Administration** Route & Volume
Control	A431	D5W	8	Intratumoral Injection-70µl
STP705-H	A431	40µg	8	Intratumoral Injection-70µl
STP705-L	A431	20µg	8	Intratumoral Injection-70µl
DDP	A431	0.5mg/kg***	8	Intratumoral Injection-70µl

*Mouse: BALB/c nu/nu, 5weeks old, female.

** Intratumoral injection every two days; total injection: 7 times.

*** The dose of DDP changed to 1mg/kg from day-9 post-treatment.

STP705 solution was administered by direct injection into the A431 tumor every two days (total 7 administrations). DDP (also known as Cisplatin, Platinol) is a chemotherapy treatment option for non-melanoma skin cancers (NMSC). DDP was chosen as an active comparator and positive control in this study. The intratumoral route of administration was utilized since the goal of the study was to evaluate the effect of STP705 on A431 (human squamous cell carcinoma) tumor growth.

Clinical observations were conducted daily on all animals during the treatment. The body weights and tumor measurements were conducted every two days (before test article administration). At the end of the study (day 15 post-treatment), animals were sacrificed, tumors were collected, and tumor weight was measured.

Body Weight Measurements: no loss of body weight or changes between the STP705-treated animals and control groups were observed. However, there was loss of weight in the DDP-treated group at 11-, 13- and 15-days post-treatment compared with STP705-treated and control groups.

FIGURE 1-3: BODY WEIGHT CURVE

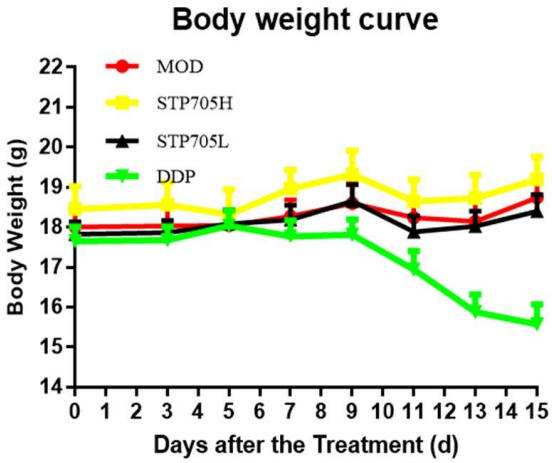


Figure 1-3 demonstrates the mean body weight of animals in control group, STP705-high dose, STP705-low dose and DDP groups. There was no difference in body weight of animals between control (MOD) and STP705-treated groups. DDP group showed a drop in body weight at 11-, 13- and 15-days post-treatment.

Clinical Observations: No major clinical observations were observed in STP705-treated animals. All animals completed their respective survival period.

Tumor Volume was measured every other day using microcalipers. Table 1-3 highlights the *p*-values of control compared to the STP705-high, STP705-low, and DDP-treated groups. The results demonstrated that low dose of STP705 (STP705-L) treated animals showed significant reduction in tumor volume at 9-, 11-, 13- and 15-days post-treatment as compared to the control animals. STP705-H treated animals showed significant reduction in tumor volume at 13- and 15-days post- treatment as compared to the control animals. DDP-treated animals also showed significant reduction in tumor volume at 11-, 13- and 15-days post-treatment as compared to the control animals. Overall, at all time-points STP705- and DDP-treated animals showed lower values of tumor volume than control animals.

TABLE 1-3: TUMOR VOLUME (*P*-VALUES)

	Days Post-Treatment							
$P_{control}$ vs	**0**	**3**	**5**	**7**	**9**	**11**	**13**	**15**
STP705-H	0.991	0.874	0.185	0.354	0.243	0.100	0.042	0.036
STP705-L	0.999	0.462	0.156	0.191	0.046	0.025	0.015	0.027
DDP	0.404	0.586	0.172	0.418	0.255	0.030	0.027	0.024

Table 1-4 demonstrates that at 11-days post-treatment, the low dose of STP705 (STP705-L) treated animal group achieved comparable tumor growth inhibition index and ratio of tumor volume achieved by the DDP-treated animal group at 15-days post-treatment.

TABLE 1-4: SUMMARY OF TUMOR GROWTH INHIBITION INDEX AND RATIO OF TUMOR VOLUME (T/C) AT 11-, 13- AND 15-DAYS POST-TREATMENT

	STP705-H	STP705-L	DDP
Tumor Growth Inhibition Index			
11-days Post-Treatment	23.32	35.58	26.89
13-days Post-Treatment	29.39	38.88	32.04
15-days Post-Treatment	33.58	36.38	35.94
Ratio of Tumor Volume (T/C)			
11-days Post-Treatment	0.77	0.64	0.73
13-days Post-Treatment	0.71	0.61	0.68
15-days Post-Treatment	0.66	0.64	0.64

Tumor Weight was measured at the end of the study post-euthanasia (at day-15 post-treatment).

Average tumor weight. STP705-H (p=0.004), STP705-L (p=0.012) and DDP-treated (p=0.026) groups showed significantly lower tumor weight as compared to the control group. This indicates that STP705-treatment inhibits tumor growth.

FIGURE 1-4: TUMOR WEIGHT

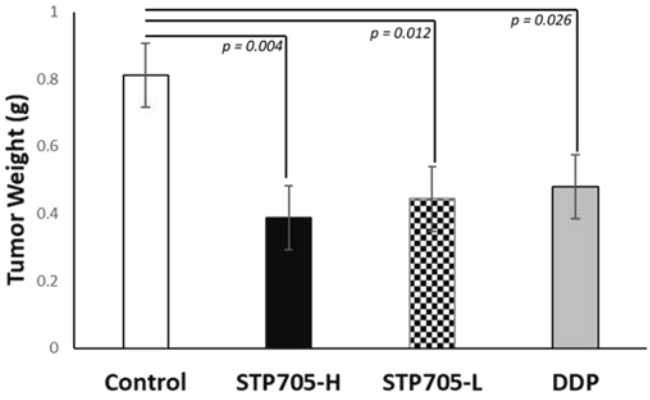


Figure 1-4 demonstrates the mean tumor weight (± standard error) of STP705-H, STP705-L, DDP, and control animal groups at day-15 post-treatment in A431 xenograft mouse tumor model. Animals treated with STP705 and DDP showed significantly lower tumor weights (indicative of reduced tumor growth) as compared to the control animal group.

Conclusion: Intratumoral doses of STP705 were able to significantly suppress tumor growth of human squamous carcinoma in an A431 xenograft mouse tumor model. The data showed that intratumoral injection of STP705 was able to significantly inhibit tumor growth at 13- and 15-days post-treatment in the low and high ST705 groups. STP705-treatment demonstrated inhibitory effect on tumor growth starting from day-5 post-treatment and sustained it through the entire study. This was also supported by significantly lower slope value and reduction in tumor weight reported in the STP705-treatment group as compared to the control group.

In-life observations and body weights data it is suggested that all STP705-treated animals tolerated treatments well, and the animals that survived to their scheduled endpoints showed no signs of acute toxicity that were due to the treatment. On the other hand, DDP-treated animals showed drop in body weight starting from 11-days post-treatment and continued to lose weight for the duration of the study.

The study suggested that STP705-treatment potentially has the benefit of accelerated inhibition of tumor growth without major clinical side effects as compared to the DDP-treatment. Overall,

the study indicated that STP705 treatment, by inhibiting TGF-β1 and COX-2 expression, promotes human squamous carcinoma tumor suppression in a xenograft mouse model.

1.8 Overview of Clinical Experience

SRN-705-001 Study: A randomized, double-blind, within-subject placebo-controlled study was designed to evaluate the safety and efficacy of various doses of STP705 administered as intradermal (i.e., intralesional) injection in subjects with linear hypertrophic scar.

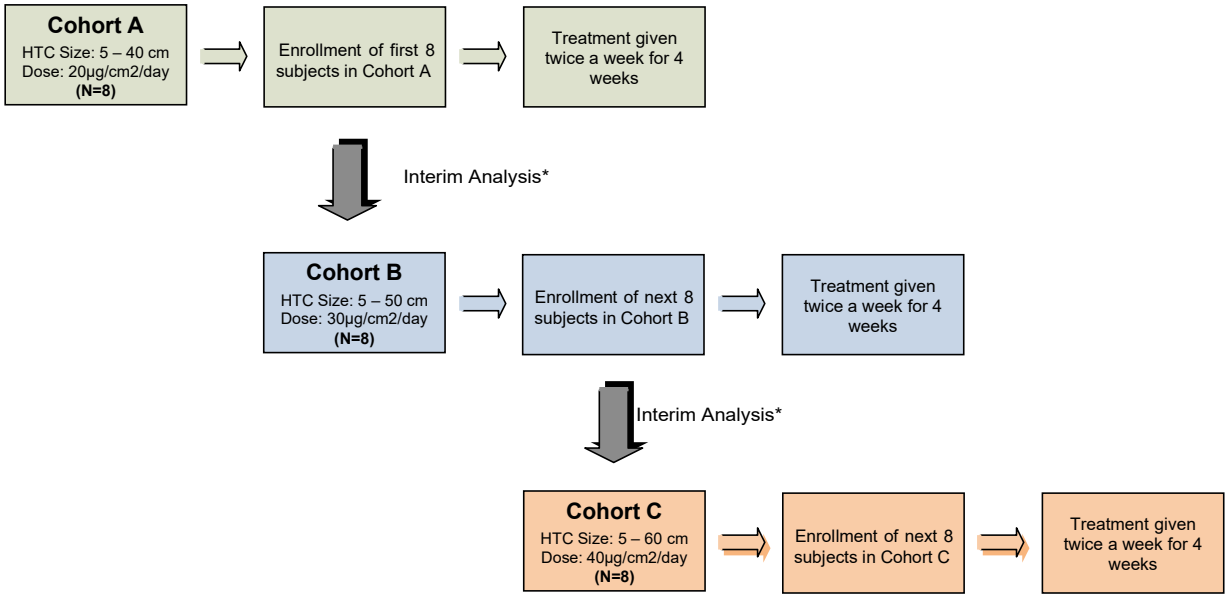
Twenty-four subjects were enrolled in this study; divided equally among 3 cohorts (20, 30 and 40 μg/cm^2/day dose level) of 8 subjects each. Each subject received both active (STP705) and control (placebo) treatment twice a week for a total of 4 weeks. The total length of linear hypertrophic scar was divided equally for treatment with STP705 and placebo. STP705 and Placebo were injected intradermally (intralesionally) every 1 cm length on the hypertrophic scar.

The study entry criteria required subjects to have had a hypertrophic scar that met all of the following criteria:

- linear scar, ≥5 to ≤40 cm in length (Cohort A), ≥5 to ≤50 cm in length (Cohort B), ≥5 to ≤60 cm in length (Cohort C)
- present for minimum 6 months and no greater than 24 months
- located anywhere in the body except on the face or front of neck
- resulting from surgical or traumatic injury

Refer to Figure 1-5 below for illustration of the cohort escalation approach.

FIGURE 1-5: COHORT ESCALATION SCHEMATIC



* If any of the pre-defined SAEs or dose limiting toxicities are present, the Data Safety Monitoring Board (DSMB) will conduct independent review of the data and will make a final decision for dose escalation to the next cohort.

Under Cohort A, eight subjects were enrolled into the study, seven of which were female. The average age was 42.8 years with a range from 31 to 58 years. Four subjects were reported as Black or African American (50%) and four as White (50%). All eight subjects were randomized and received at least one treatment with the study medication.

There have been no deaths, serious adverse events (SAEs), or dose limiting toxicities (DLTs) reported in the study. All subjects experienced adverse events (AEs), the majority of which were associated with injection site reactions (pain, tenderness, and erythema). The injection site reactions were typically mild or moderate in severity and did not require further action. Additionally, there were no clinically significant findings reported in physical examination or electrocardiogram results.

An independent review was performed by the Data Safety Monitoring Board (DSMB) after the enrollment of the first 8 subjects in Cohort A (STP705 20 µg/cm^2/day, intradermal (intralesional) injection, given twice a week for 4 weeks). Based on the review of available subject data, DSMB recommended that Sirnaomics consider increasing the interval between injections and/or to reduce the dose of IP to mitigate injection site reactions reported in Cohort A subjects.

Based on DSMB recommendations, Sirnaomics decided to initiate a new protocol SRN-705-002 titled *"A Dose Escalation Study to Evaluate the Safety and Tolerability of STP705 Administered as Intrascar Injection in subjects with Hypertrophic Scar"* with reduced STP705 doses and an increased interval between injections. This study will assess the safety and tolerability of STP705 at the following dose regimens:

- Cohort A: STP705 5 μg/cm^2/day, intrascar injection, given once a week for 4 weeks.
- Cohort B: STP705 10 μg/cm^2/day, intrascar injection, given once a week for 4 weeks.
- Cohort C: STP705 15 μg/cm^2/day, intrascar injection, given once a week for 4 weeks.

This new protocol SRN-705-002 has not yet initiated.

SRN-705-004 Study: This was a Phase 1/2 open label, dose escalation study designed to evaluate the safety and efficacy of various doses of STP705 administered as an intralesional injection in subjects with cutaneous *in situ* squamous cell carcinoma (isSCC). Twenty-five subjects were divided equally among 5 cohorts (10, 20, 30, 60 and 120 μg dose level) of 5 subjects each.

The dosing regimen for each cohort is listed below:

- Cohort A: STP705 10 μg dose, intralesional injection, given once a week for up to 6 weeks.
- Cohort B: STP705 20 μg dose, intralesional injection, given once a week for up to 6 weeks.
- Cohort C: STP705 30 μg dose, intralesional injection, given once a week for up to 6 weeks.
- Cohort D: STP705 60 μg dose, intralesional injection, given once a week for up to 6 weeks.
- Cohort E: STP705 120 μg dose, intralesional injection, given once a week for up to 6 weeks.

The primary efficacy endpoint was the proportion of subjects achieving histological clearance of the isSCC lesion by the End of Treatment (EOT). This was summarized descriptively by cohort group. Overall, 19 out of 25 subjects achieved histological clearance of the lesion by EOT. This included 3/5 subjects in the 10-μg dose group, 3/5 subjects in the 20-μg dose group, 4/5 subjects in the 30-μg dose group, 5/5 subjects in the 60-μg dose group, and 4/5 subjects in the 120-μg dose group.

Treatment was completed for all five planned cohorts with no reported dose limiting toxicities (DLT). The Sponsor's Medical Monitor reviewed the available safety data (and discussed the data with the CRO's Medical Monitor and PI), prior to the dose escalation for each cohort.

There were no serious adverse events or deaths reported in this study. LSR were measured in each group and there were no significant LSR associated with the administration of STP705.

1.9 RISK / BENEFITS ASSESSMENT

To ensure that STP705 is safe as a human therapeutic agent, the following nonclinical safety studies were conducted:

- Single dose acute toxicity studies on 60 mice and 8 cynomolgus monkeys with STP705 administered IV with one bolus injection.
- Repeat dose toxicity studies on 300 mouse and 40 cynomolgus monkeys with STP705 administered subcutaneously.
- Skin Sensitization using Guinea pig intact skin model.
- Bioavailability (BA) and Biodistribution (BD) using miniature pigs.
- Irritations at Injection Site using a monkey model.
- Genotoxicity studies: Ames with the Bacteria, Micronucleus with ICR mice, and chromosomal abnormality with mouse lung fibroblast cells.
- Toxicokinetic studies using a monkey model.

All these study results indicate that STP705 should be safe for the clinical application Sirnaomics has proposed. In addition to the above, the *in vitro* and *in vivo* efficacy model for STP705 showed the following:

***In Vivo* Results**

The objective of the study was to demonstrate the efficacy of STP705 on tumor suppression in an A431 xenograft mouse tumor model. A431 is a human squamous carcinoma cell line that has been widely used to evaluate the anti-cancer effect of various therapeutic compounds.

1. Intratumoral doses of STP705 were able to significantly suppress tumor growth of human squamous carcinoma in an A431 xenograft mouse tumor model.
2. The data demonstrated that STP705-low and high doses used in animal groups were able to significantly inhibit tumor growth at 13- and 15-days post-treatment.
3. STP705-treatment demonstrated an inhibitory effect on tumor growth starting from day- 5 post-treatment and sustained it through the entire study. This was also supported by significantly lower slope value and reduction in tumor weight reported by STP705- treated animal group as compared to the control group.

4. In-life observations and body weights data suggested that all STP705-treated animals tolerated treatments well, and the animals that survived to their scheduled endpoints showed no signs of acute toxicity that were due to the treatment. On the other hand, DDP-treated animals reported drop in body weight starting from 11-days post-treatment and continued to lose weight for the duration of the study.

Therefore, we concluded that the synergistic effect of simultaneous silencing of TGF-β1 and COX- 2 may act to eliminate isSCCs through down regulation of immunosuppression and increased apoptosis.

1.9.1 Risks/Discomfort to Subjects and Precautions to Minimize Risks

1.9.1.1 Intralesional injection for STP705 Administration

Intralesional injection for STP705 administration carries a risk of local injection site reaction (pain, tenderness, erythema/redness, induration/swelling), discomfort, the possibility of bruising at the site of the injection, and the possibility of infection at the site of injection. A use of local block anesthesia to the skin surrounding the lesion prior to intralesional STP705 administration is allowed as per discretion of the Investigator.

Additional care to local site reaction may include cold packs applied to the area for 15 minutes and up to 3 times daily. The Investigator may prescribe ibuprofen 600mg for local pain and inflammation up to 4 times daily and suggest 24-hour clinic follow up, if needed, to monitor for local reactions. Dosing should be interrupted if a local reaction was deemed moderate or severe by the PI. For subjects who develop severe reaction (grade 3) following study drug injection, the subject should be reevaluated closely until the AE returns to base line grade 1, 2 or less, at which time study treatment may be reintroduced at the discretion of the site investigator.

1.9.1.2 Local Skin Response

STP705 injection can be associated with local skin responses such as pain at the site of injection, rash and itching. These events are usually of short duration if they occur at all.

1.9.1.3 Allergic Reaction

Severe allergic reactions, or anaphylaxis, can be life-threatening. Although anaphylaxis has not been observed previously with STP705, injection of any study material carries with it the theoretical risk for allergic reaction. Accordingly, whenever STP705 is initially administered to subjects, site specific procedures to manage allergic reactions should be in place.

1.9.1.4 Pregnancy

Risks to unborn babies are unknown at this time; pregnant females will be excluded from this study. Female subjects of childbearing potential must have a negative pregnancy test prior to enrollment. Both male and female subjects and their partners of childbearing potential must agree to use appropriate birth control methods throughout the study duration (excluding female partners who are not of childbearing potential and male partners who have been sterilized).

1.9.1.5 Venipuncture for blood sampling

Venipuncture for blood sample collection carries a minimal risk of minor discomfort and the possibility of minor bruising at the site of the needle puncture and, rarely, the possibility of infection at the needle puncture site.

1.9.1.6 Unknown Risks

As with all research there is the remote possibility of risks that are unknown or that cannot be foreseen based on current information.

1.10 Treatment Rationale for this Study

STP705 drug substance is composed of two siRNA oligonucleotides, targeting the expression of TGF-β1 and COX-2 mRNA respectively, that have been well characterized in playing a major role in the progression of NMSC (both basal cell carcinomas and SCCs).

STP705 is formulated in nanoparticles with histidine-lysine polypeptide (HKP) at a ratio of 1:25 in mass weight (siRNA: peptide). The HKP-enhanced delivery of TGF-β1 and COX-2 specific siRNA combination is expected to down regulate TGF-β1 and COX-2 expression resulting in the inhibition of tumor growth and provide an alternative non-invasive approach for the treatment of cutaneous squamous cell carcinoma *in situ*.

The proposed mode of action of the STP705 in anti-tumor activities is shown in Figure 1-6.

Multiple preclinical in vivo animal studies have demonstrated the efficacy of STP705 on tumor suppression.

Sirnaomics has recently completed a phase I/II study [An Open Label, Dose Escalation Study to Evaluate the Safety and Efficacy of Intralesional Injection of STP705 in Adult Patients with Cutaneous Squamous Cell Carcinoma *in situ* (isSCC)], protocol ID: SRN-705-004, which

demonstrated a potentially safe and effective way of treating isSCC compared to the standard of care.

The primary efficacy endpoint was the proportion of subjects achieving histological clearance of the isSCC lesion by the End of Treatment (EOT). All subjects underwent surgical excision at the end of 6 weeks treatment.

Twenty-five eligible subjects were enrolled in the study. Overall, 19 out of 25 subjects achieved histological clearance of the lesion by EOT. This included 3/5 subjects in the 10µg dose group, 3/5 subjects in the 20µg dose group, 4/5 subjects in the 30µg dose group, 5/5 subjects in the 60µg dose group, and 4/5 subjects in the 120µg dose group.

In addition to the efficacy and safety profiles of the STP705, the injection itself was well-tolerated with majority of subjects experiencing no or low-grade local skin responses (LSRs).

Based on the preclinical and clinical studies of the STP705 and the potential benefit of STP705 for patients with isSCC, Sirnaomics is initiating a larger, double-blinded, randomized study to further evaluate the safety and efficacy of the STP705.

FIGURE 1-6: PROPOSED MODE OF ACTION – HYPOTHESIS FOR STP705-MEDIATED ANTI-TUMOR ACTIVITIES

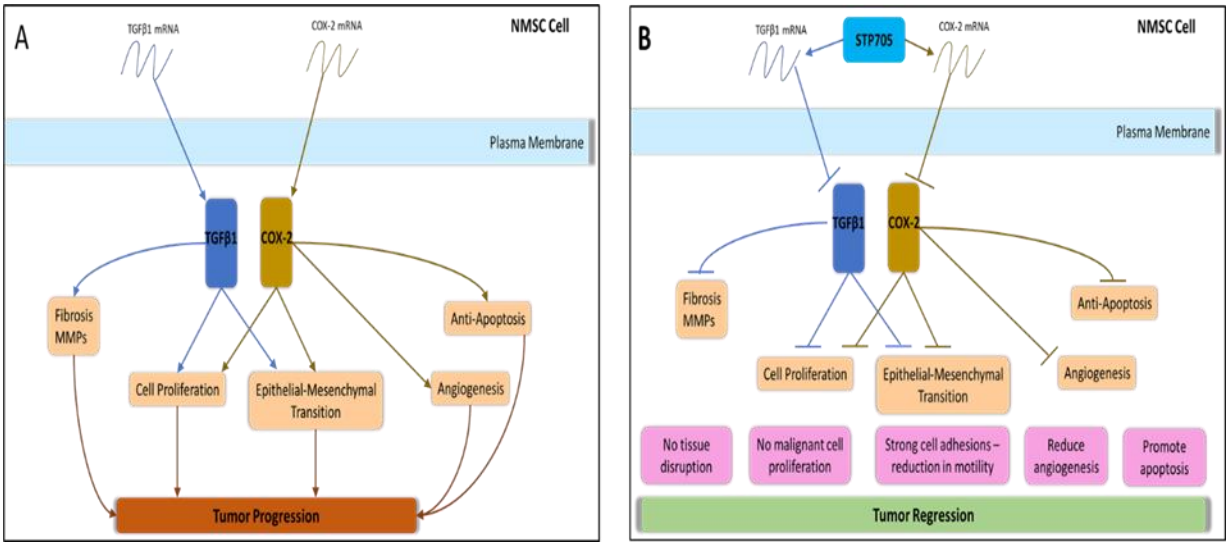


Figure 1-6 demonstrates the hypothesized mode of action of STP705, a combination therapy containing siRNA TGF-β1 and COX-2. (A) Outlines the proposed mechanism of TGF-β1 and

COX-2, in NMSC cells, that induces tumor progression by promoting tissue disruption, cell proliferation, epithelial-mesenchymal transition, angiogenesis, and anti-apoptosis. (B) Outlines the proposed mechanism of STP705-mediated inhibition of TGF-β1 and COX-2, in NMSC cells, that suppresses tumor progression by: (i) inhibiting tissue disruption, cell proliferation, and angiogenesis; (ii) maintaining cellular integrity of healthy cells; and (iii) promoting apoptosis of NMSC cells. Overall, the figure demonstrates that STP705 treatment, by inhibiting TGF-β1 and COX-2 expression, would promote BCC and SCC tumor suppression.

In addition to the biological activity of STP705, delivery is the key for a successful siRNA therapeutic candidate. The histidine-lysine- polypeptide (HKP) represents a unique biodegradable carrier with a broad clinical potential use and very different from the lipid nanoparticles and polymer nanoparticles used by others (e.g., Alnylam Pharmaceutical, Arbutus Biopharma, Dicerna Pharmaceutical and Arrowhead Pharmaceutical companies). Sirnaomics has demonstrated through xenograft models with the human squamous cell carcinoma cell line, A431, that intratumoral injection of STP705 is effective in suppressing tumor growth, and that STP705 had no obvious side effects in the mouse model. These studies have resulted in sustained siRNA release, substantial knockdown of target genes, and significant therapeutic benefits.

1.10.1 Rationale for Dose Selection

A phase I/II open-label dose-escalation study was completed in October 2020 [An Open Label, Dose Escalation Study to Evaluate the Safety and Efficacy of Intralesional Injection of STP705 in Adult Patients with Cutaneous Squamous Cell Carcinoma *in situ* (isSCC)], protocol ID: SRN- 705-004.

Participants in the first cohort were to attend the study center once weekly for an injection of STP705 into the isSCC lesion. The participants were to receive injections of STP705 once a week for up to 6 weeks. The clinician was to evaluate the tumor for clinical changes and reduction in size at each treatment visit for up to 6 weeks. If during the 6 weeks of treatment there was complete clinical clearance of the tumor, the treatments were to end. At the End of Treatment visit, the residual tumor, or former tumor location was to be excised for analysis.

In the absence of dose limiting toxicities (DLT), the subsequent cohorts were to receive increasing doses of STP705, following the same schedule of administration as the first cohort. Dose cohorts included 10, 20, 30, 60, and 120 μg doses of STP705. The total duration of the study was 14 weeks per dose group.

Efficacy results showed that STP705 was effective in treating isSCC lesions. The majority of subjects in each dose group and the majority of subjects overall in the study (76%, 19/25) achieved histological clearance of lesion by EOT (six weeks), which was the primary efficacy endpoint of the study. Safety results from the study demonstrate that STP705 is generally a safe treatment option for isSCC patients. No Treatment Emergent Adverse Events (TEAEs) led to death, treatment discontinuation, or treatment interruption. There were also no SAEs reported in the study.

Based on review of safety profile for 10 µg, 20 µg, 30 µg, 60 µg, and 120 µg dose levels of STP705 in the Phase I/II isSCC study, Sirnaomics has developed the Phase I/II, An Open Label, Dose Escalation Study to Evaluate the Safety and Efficacy of Intralesional Injection of STP705 in Adult Patients with Facial Cutaneous Squamous Cell Carcinoma *in situ* (isSCC) with proposed dose levels of STP705 30 µg, 60 µg, and 90 µg to further evaluate the safety and efficacy of the intralesional injection in isSCC subjects.

2. STUDY OBJECTIVES

The purpose of this trial is to evaluate the safety, tolerability, and efficacy of various doses of STP705 administered as intralesional injection in subjects with facial cutaneous squamous cell carcinoma *in situ* skin cancer (isSCC).

GOALS:

- To determine the safe and effective recommended dose of STP705 for the treatment of facial isSCC.
- Analysis of biomarkers common to isSCC formation pathway including TGF-β1 and COX-2.

3. STUDY DESIGN

This is an open-label study designed to evaluate the safety and efficacy of various doses of STP705 administered as an intralesional injection in subjects with facial cutaneous *in situ* squamous cell carcinoma (isSCC). A total of 30 eligible subjects will be divided equally (10 subjects/cohort) among 3 cohorts to receive 30 µg, 60 µg, or 90 µg STP705.

Enrolled subjects will receive an STP705 injection once weekly for 6 weeks. Thirty days (± acceptable window) after Observation Visit, the lesion will be excised.

In the absence of dose limiting toxicities (DLT), the subsequent cohorts will receive increasing

doses of STP705, following the same schedule of administration as the first cohort. Dose escalation will progress after ten subjects have been enrolled in the previous cohort, provided that none of the following SAEs or DLTs have occurred in any subject. The Investigator will be responsible for determining the relationship between an AE and the study treatment.

(1) Death in which the cause of death is determined to be possibly, probably, or definitely related to STP705

(2) The occurrence of an anaphylactic reaction to STP705

(3) The occurrence of a severe grade 3 local injection site reaction, which is not resolved or recurred; or a grade 4 local injection site reaction that precludes administration of consecutive doses.

(4) The occurrence of a life-threatening SAE whose causal relationship to STP705 is determined to be probably or definitely related

(5) The occurrence of one or more non-life-threatening SAEs whose causal relationship to STP705 is determined to be definitely related

(6) The occurrence of grade 4 laboratory abnormalities, determined to be probably or definitely related to STP705

(7) The occurrence of hematologic and non-hematological adverse events, determined to be possibly, probably, or definitely related to STP705 and that are of CTCAE grade 3 or greater severity. Permissible exceptions to this rule include grade 3 fatigue of less than one week duration, and grade 3 nausea, vomiting, and diarrhea that resolve within 48 hours following institution of appropriate supportive care.

The study will have three phases: Screening Phase, Treatment Phase, and Follow-Up Phase.

Optional Pre-Screening Biopsy:

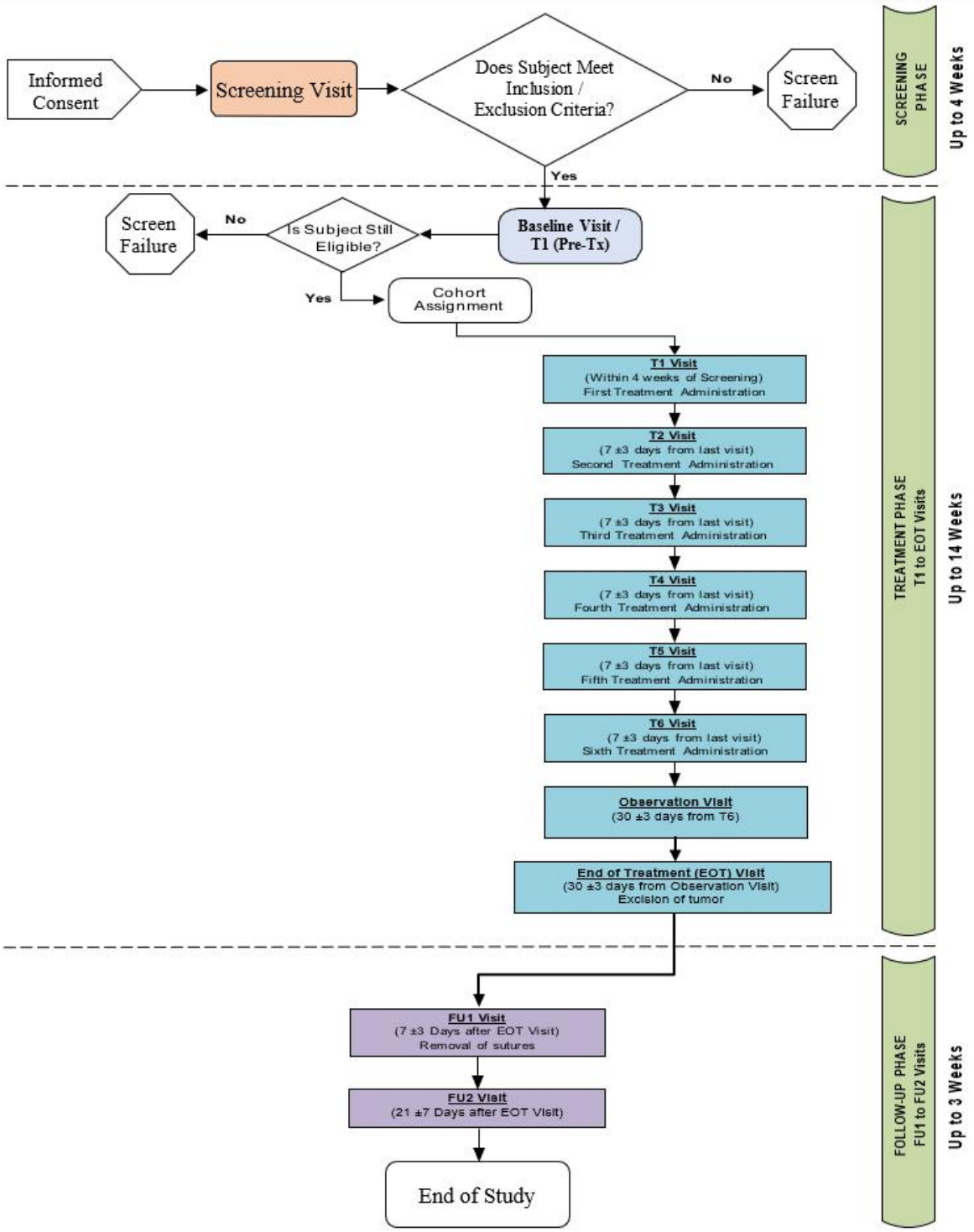
If a potential subject presents with a clinically suspicious facial isSCC lesion that was never biopsied, or cannot provide a confirmatory histopathology report, or that was biopsied more than 6 months prior to Screening, this lesion may be biopsied to determine eligibility (an optional pre-screening biopsy) by the investigator (or his/her qualified designee) as a consented procedure under this protocol prior to Screening.

Phases of the Study

The study will have three phases: Screening Phase, Treatment Phase, and Follow-Up Phase.

A study flow diagram is shown in Figure 3-1.

FIGURE 3-1: STUDY FLOW DIAGRAM



3.1 STUDY CENTER

Up to 3 centers in the United States.

3.2 STUDY POPULATION

A total of 30 adult subjects with facial Cutaneous Squamous Cell Carcinoma *in situ* (isSCC) will be enrolled in this study.

Ten subjects treated in each cohort will receive six weeks of treatment with 30 μg, 60 μg, or 90 μg STP705.

3.3 ELIGIBILITY CRITERIA

3.3.1 INCLUSION CRITERIA

Potential subjects are required to meet all of the following criteria for enrollment into the study:

1. Male or female adult ≥ 18 years of age.
2. Primary, histologically confirmed facial isSCC lesion suitable for excision with a minimum diameter of 0.5 cm and with a maximum diameter of 2.0 cm.
3. Histological diagnosis of a qualified isSCC skin lesion (evidenced by a confirmatory histopathology report) made no more than 6 months prior to the screening visit.
4. No other dermatological disease in the isSCC target lesion or surrounding area, which in the opinion of the investigator, could interfere with the study.
5. Willing to refrain from using non-approved lotions or creams on the target lesion and surrounding area during the treatment period (sunscreen and moisturizer allowed).
6. Willing to refrain from exposure to excessive direct sunlight or ultraviolet light and to avoid the use of tanning parlors for the duration of the study.
7. Laboratory values for the tests (listed in the Study Schedule) within the reference ranges as defined by the local laboratory, or “out of range” test results that is clinically acceptable to the investigator.
8. Ability to follow study instructions and likely to complete all study requirements.
9. Written informed consent obtained, including consent for tissue to be examined and stored by the Central Histology Lab.
10. Written consent to allow photographs of the target isSCC lesion to be used as part of

the study data and documentation.

11. For female subjects of childbearing potential, a negative pregnancy test at screening and using an acceptable form of birth control (oral / implantable / injectable / transdermal contraceptives, intrauterine device, condom, diaphragm, abstinence, or a monogamous relationship with a partner who has had a vasectomy at least 6 months prior to screening).

3.3.2 Exclusion Criteria

Potential subjects meeting any of the following criteria will be excluded from enrollment:

1. Pregnant, lactating, or planning to become pregnant.
2. Presence of known or suspected systemic cancer.
3. Confirmatory histological report of the qualifying isSCC lesion reveals evidence of severe squamous metaplasia, infiltrative, desmoplastic or micronodular growth patterns in the opinion of the investigator.
4. History of recurrence of the target isSCC lesion.
5. Concurrent disease or treatment that suppresses the immune system.
6. Subjects with baseline QTc > 480 msec using Fridericia's formula.
7. Chronic medical condition that in the judgment of the investigator(s) would interfere with the performance of the study or would place the patient at undue risk.
8. Known sensitivity to any of the ingredients in the study medication including an allergy to trehalose.
9. Use of a tanning bed or other excessive or prolonged exposure to ultraviolet light or direct sunlight during the study.
10. Treatment with systemic chemotherapeutic agents within the 6 months prior to the screening visit.
11. Use of systemic retinoids within the 6 months prior to the screening period.
12. Treatment with systemic immunomodulators or immunosuppressants within the 6 months prior to the screening period.
13. Use of topical immunomodulators within 2cm of the target isSCC lesion within the 4 weeks prior to the screening period.
14. Treatment with the following topical agents within 2cm of the target isSCC lesion within the 4 weeks prior to the screening visit: aminolevulinic acid, 5-fluorouracil,

corticosteroids, retinoids, diclofenac, ingenol mebutate, tirbanibulin, or imiquimod.

15. Treatment with liquid nitrogen, surgical excision, or curettage within 2cm of the target isSCC lesion during the 4 weeks prior to the screening visit.
16. Evidence of current chronic alcohol or drug abuse that, in the opinion of the investigator, would impair the subject's ability to comply with study schedule.
17. Current enrollment in an investigational drug or device study or participation in such a study within 4 weeks of the screening visit.
18. In the investigator's opinion, evidence of unwillingness, or inability to follow the restrictions and requirements of the protocol and complete the study.

4. STUDY SCHEDULE

The study is divided into three phases: Screening Phase, Treatment Phase, and Follow-Up Phase.

If a potential subject presents with a clinically suspicious isSCC lesion that was never biopsied, or cannot provide a confirmatory histopathology report, or that was biopsied more than 6 months period to Screening, this lesion may be biopsied (**an optional pre-screening biopsy**) to determine subject eligibility. In this case, after the subject has been consented, the biopsy shall be performed by the investigator (or his/her qualified designee) under this protocol prior to Screening. Only those subjects with a qualifying lesion and histopathology consistent with an isSCC lesion may advance to the Screening Phase.

Screening Phase (Visit 1) (-28 to -3 days prior to Baseline):
Screening assessments will commence after obtaining signed informed consent, and will include review of medical and medication history, isSCC lesion biopsy histopathology review, eligibility evaluation of facial cutaneous isSCC, physical examination, vital signs, height and weight, concomitant medications, electrocardiogram (ECG), chemistry, hematology, coagulation (if applicable), urinalysis, serum pregnancy (if applicable), baseline Local Skin Response (LSR Grading Scale), 2D photograph of lesion pre-marked with a surgical skin marker, manual measurement of longest diameter and area of lesion using a ruler or a caliper as deemed appropriate by the investigator. These assessments must be conducted within 28 days of the First Treatment Visit (Visit 2).

Treatment Phase (Visit 2 – Visit 9) (up to 14 weeks ± allowed windows):
Subjects who meet eligibility criteria will check-in to the clinic on the day of the first treatment. The following assessments will be performed prior to first treatment: review of any changes in medical and medication history, vital signs, weight measurement, symptom-directed physical

examination, concomitant medications, ECG, chemistry, hematology and urinalysis, urine pregnancy (if applicable), blood collected for Anti-Drug Antibody (ADA) analysis, creation of a pre-treatment lesion template along with manual measurement of longest diameter and area of the lesion using a ruler or a caliper, and 2D digital imaging of the lesion pre-marked with a surgical skin marker, baseline LSR Grading Scale assessment, baseline pigmentation, and Visual Analogue Scale (VAS) pain assessment at the site of lesion prior to dosing. The marking of the lesion using the skin marker should be repeated every visit.

Eligible subjects will be assigned to a cohort. All subjects who fail to meet eligibility criteria at Baseline/Treatment Visit (T1) are considered screen failures and are exited from the study without further evaluation.

The dosing regimen for each cohort is as follows:
Cohort A: STP705 30 μg dose, intralesional injection, given once a week for 6 weeks.
Cohort B: STP705 60 μg dose, intralesional injection, given once a week for 6 weeks.
Cohort C: STP705 90 μg dose, intralesional injection, given once a week for 6 weeks.

SCHEDULE OF TREATMENT VISITS

- Visit 2 T1 (first treatment) – Within 4 weeks of the Screening Visit
- Visit 3 T2 (second treatment) – 7 days (±3 days) after T1
- Visit 4 T3 (third treatment) – 7 days (±3 days) after T2
- Visit 5 T4 (fourth treatment) – 7 days (±3 days) after T3
- Visit 6 T5 (fifth treatment) – 7 days (±3 days) after T4
- Visit 7 T6 (sixth treatment) – 7 days (±3 days) after T5
- Visit 8 Observation Visit – 30 days (±3 days) after T6
- Visit 9 End of Treatment (EOT) Visit – 30 days (±3 days) after Observation Visit
  - Excision of tumor at EOT visit.

The study treatment STP705 will be administered by the licensed medical professional. All treatments for all dose cohorts are 0.6 mL administered as an intralesional injection. Post-treatment LSRs and pain assessment at the site of lesion using VAS will be evaluated within 15 minutes (±5 min) of the STP705 administration. At T1, 2D digital imaging of the lesion post-dose will also be taken.

An ECG will be performed at pre-dosing, at the T1 Visit and at the EOT visit (before excision).

Vital signs will be assessed before the injection, and within 15 minutes (±5 min) after the injection at each treatment visit. At T1, vital signs will also be taken within 30 min (±5 min) and within 1 hour (±15 min) post-dose. Adverse events will be assessed.

For Visits 3-7 (T2-T6) the following assessments will be performed prior to dosing: vital signs, weight measurement, symptom-directed physical examination, review of adverse events and concomitant medications, blood collected for Anti-Drug Antibody (ADA) analysis, measurement of longest diameter and area of the lesion using a ruler or a caliper, 2D photography of the lesion pre-marked with a surgical skin marker, LSR Grading Scale assessment, pigmentation assessment, and Visual Analogue Scale (VAS) pain assessment at the site of lesion prior to dosing.

The Observation Visit (Visit 8) will be performed 30 (±3) days after T6 (Visit 7). The following assessments will be performed: vital signs, symptom-directed physical examination, review of adverse events and concomitant medications, blood collected for Anti-Drug Antibody (ADA) analysis, measurement of longest diameter and area of the lesion using a ruler or a caliper, 2D photography of the lesion pre-marked with a surgical skin marker, LSR Grading Scale assessment, and pigmentation assessment.

The End of Treatment (EOT) visit (Visit 9) will be performed 30 (±3) days after the Observation visit (Visit 8). The following assessments will be performed at EOT (Visit 9): vital signs, weight measurement, symptom-directed physical examination, review of adverse events and concomitant medications, ECG, chemistry, hematology, urinalysis, serum pregnancy (if applicable), blood collected for Anti-Drug Antibody (ADA) analysis, measurement of longest diameter and area of the lesion using a ruler or a caliper, 2D photography of the lesion pre-marked with a surgical skin marker, final LSR Grading Scale assessment, and pigmentation assessment. The surgical excision at the site of treated isSCC lesion will be performed at the EOT visit using the pre-treatment template for reference, and the resulting excision wound may be sutured, per site standard of care. The excised specimens will be assessed for histological clearance of the lesion.

Adverse events and medications will be monitored throughout the study.

Follow Up Phase

There will be Follow Up Visits at 7 days (±3 days) (Visit 10/FU1) and 21 days (±3 days) (Visit 11/FU2) after the lesion was excised at EOT (Visit 9). The following assessments will be performed at FU1 (Visit 10) and FU2 (Visit 11) Visits: removal of excision site sutures (FU1 Visit 10 only), review of adverse events and concomitant medications, symptom-directed

physical examination, vital signs, 2D digital imaging of lesion/surgical site, pigmentation assessment, blood collection for Anti-drug antibody (ADA) assay (FU1 Visit 10 only) and blood collection for chemistry, hematology, and urine laboratory assessments (FU2 Visit 11 only).

The study Schedule of Assessments in presented in Table 4-1.

TABLE 4-1: SCHEDULE OF ASSESSMENTS

	Screening Phase	Treatment Phase								Follow-Up Phase	
Visit Number	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Study Visits	**SV**	**Baseline / T1** (Pre-Tx)	**Baseline / T1** (Post-Tx)	**T2**	**T3**	**T4**	**T5**	**T6**	**Observation Visit**	**EOT**	**FU1**	**FU2**
Days		**Day 1**		**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 66**	**Day 96**	**Day 103**	**Day 117**
Window Period	-28 to -3 Days prior to the Baseline visit	3 to 28 Days from Screening Visit		7 (±3) Days from T1 visit	7 (±3) Days from T2 visit	7 (±3) Days from T3 visit	7 (±3) Days from T4visit	7 (±3) Days from T5 visit	30 (±3) Days from T6 visit	30 (±3) Days from Observation visit	7 (±3) Days from EOT	21 (±3) Days from EOT
Informed Consent [1]	X											
Medical and Medication History [2]	X	X										
Biopsy [3]	Completed prior to Screening											
Vital Signs, Height, Weight [4]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam [5]	X	X		X	X	X	X	X	X	X	X	X
Electrocardiogram, 12-lead [6]	X	X								X		
Chemistry, Hematology, Coagulation (if applicable), Routine Urinalysis [7]	X	X								X		X
Serum pregnancy test [8]	X									X		
Urine pregnancy test [8]		X										
Eligibility Assessment	X	X										
Blood collection: Anti-Drug Antibody (ADA) Analysis		X		X	X	X	X	X	X	X	X	
Study Drug Administration [9]		X		X	X	X	X	X				

	Screening Phase	Treatment Phase								Follow-Up Phase	
Visit Number	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Study Visits	**SV**	**Baseline / T1** (Pre-Tx)	**Baseline / T1** (Post-Tx)	**T2**	**T3**	**T4**	**T5**	**T6**	**Observation Visit**	**EOT**	**FU1**	**FU2**
Days		**Day 1**		**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 66**	**Day 96**	**Day 103**	**Day 117**
Window Period	-28 to -3 Days prior to the Baseline visit	3 to 28 Days from Screening Visit		7 (±3) Days from T1 visit	7 (±3) Days from T2 visit	7 (±3) Days from T3 visit	7 (±3) Days from T4visit	7 (±3) Days from T5 visit	30 (±3) Days from T6 visit	30 (±3) Days from Observation visit	7 (±3) Days from EOT	21 (±3) Days from EOT
Adverse events [10]			X	X	X	X	X	X	X	X	X	X
Concomitant medications assessment	X	X	X	X	X	X	X	X	X	X	X	X
Local Skin Response (LSR Grading Scale) [11]	X	X	X	X	X	X	X	X	X	X		
Injection Site Pain Assessment (Visual Analogue Scale) [12]		X	X	X	X	X	X	X	X			
2D Photography of lesion [13]	X	X	X	X	X	X	X	X	X	X	X	X
Longest diameter and Area Measurement of lesion [14]	X	X		X	X	X	X	X	X	X		
Pigmentation assessment [15]		X		X	X	X	X	X	X	X	X	X
Surgical excision of tumor [16]										X		
Suture removal [17]											X	
Assess. of Histological Clearance of lesion [18]										X		
Immunohistochemistry analysis [19]										X		

1. Informed Consent must be obtained prior to patient participation in any protocol-related activities that are not part of routine care.
2. Medical and Medication History will be recorded.
3. Biopsy: A pathology report of a biopsy performed within 6 months of Screening of the target isSCC lesion is required for review by investigator for histological confirmation that the isSCC lesion meets all I/E criteria. In the event such a biopsy is not available for any reason, an optional pre-screening biopsy of the target isSCC lesion may be performed per protocol (see Section 4).
4. Vital Signs including heart rate, respiratory rate, blood pressure and body temperature will be monitored pre-dose and within 15 minutes (±5 min), within 30 min (±5 min) and within 1 hour (±15 min) post- administration at T1; pre-dose and within 15 minutes (±5 min) post-administration at T2-T6. Height will be measured only at screening visit. Weight will be measured pre-dose at T1-T6.
5. Physical exams: Complete physical exam at screening, abbreviated symptom directed physical examination T1 and thereafter (see Section 7.5)
6. Electrocardiogram, 12-lead will be performed at screening visit, before treatment at T1, and EOT visit (before excision).
7. Hematology (CBC with Automated Differential): Hemoglobin, Hematocrit, MCV, MCHC, MCH, RBC count, WBC count, RDW, platelets,

   Differential # and %: Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils

   Coagulation: aPTT, PT, and INR (only for subjects receiving anticoagulation therapy, performed at Screening Visit only)
   Chemistry: Albumin, Alkaline Phosphatase, ALT, AST, Total Bilirubin, Glucose, Total Protein, Creatinine, Urea (BUN), Sodium, Potassium, Calcium, Chloride, CO_2

   Urinalysis: pH, Appearance, Color, Specific gravity, Ketones, Bilirubin, Blood, Glucose, Protein, Nitrites, Leukocyte Esterase

8. Serum/Urine pregnancy test: For female subjects of childbearing potential.
9. Study drug administration: STP705 will be injected intralesional. The study treatment (STP705 injections) will be administered by the licensed medical professional. A use of local block anesthesia to the skin surrounding the lesion prior to intralesional STP705 administration is allowed as per discretion of the Investigator**.**
10. Adverse events: The AE reporting will begin from the application of the first dose of the IP at T1 visit.
11. Local Skin Response (LSR) Assessment made using the LSR Grading Scale table provided pre-dose and within 15 minutes (±5 min) post-dose at each visit where treatment is administered at T1-T6, at Observation visit, and at EOT. See Section 7.13 for LSR Grading scale assessment.
12. VAS: Injection site pain evaluation via Visual Analogue Scale. This assessment will be performed pre-dose and within 15 minutes (±5 min) of the STP-705 administration to assess the severity of pain at the site of lesion during the injection at T1-T6, and during the Observation Visit. See Section 7.12 for details. Note: Use of pain block anesthesia would also be documented on the Pain Assessment Sheet as well as a concomitant medication log.
13. 2D photography of lesion: See Section 7.14 for details of digital imaging/2D photography of lesion. Photographs will be taken at T1-T6 pre-treatment, at Observation Visit, EOT, FU1 and FU2 visits. At T1 only photographs will be taken post treatment.
14. Lesion measurement: The longest diameter will be measured using a caliper or ruler, as appropriate, based on the location of the lesion. The area will be measured as the product of the longest and perpendicular diameters at T1-T6 before administration, at observation visit, and at EOT.
15. Pigmentation assessment: Presence and severity of hyperpigmentation and hypopigmentation will be assessed and quantified as 0-3 (None, Mild, Moderate, Severe) at all visits except Screening. Note this assessment shall be completed: (i) prior to the treatment being administered at the T1 to T6 visits and (ii) prior to performing the excision at the EOT visit.
16. Surgical excision of tumor: Post-treatment excisions should be performed around the target lesion. The surgery will be performed by a licensed medical professional.
17. Suture removal: per standard of care at FU1 visit.

18. Assessment of histological clearance: The microscopic sections (stained with hematoxylin and eosin) per case should be examined to ensure that the specimens are thoroughly evaluated for residual isSCC. Post-treatment excision specimens are to be examined by the primary dermatopathologist, independent of the clinician's assessment of the presence or absence of isSCC. See Section 7.18.

19. Immunohistochemistry analysis: Residual tissue from the excision, if available, will be used for analysis of biomarker expression common to the isSCC tumor formation pathway such as TGF-β1, COX-2.

4.1 SCREENING PHASE

Screening Phase is designed to determine whether subjects are eligible to proceed to the Treatment Phase of the study. This phase consists of a series of screening assessments designed to determine eligibility. A written informed consent from the subject will be obtained by the Investigator or suitably qualified designee before the performance of any other protocol-specific procedure.

NOTE: Prior to Screening, if a potential subject presents with a clinically suspicious isSCC lesion that was never biopsied or that was biopsied more than 6 months period to Screening, this lesion may be biopsied to determine subject eligibility (**an optional pre-screening biopsy**). In this case, after the subject has been consented, the biopsy shall be performed by the investigator (or his/her qualified designee) under this protocol prior to Screening. Only those subjects with a qualifying lesion and histopathology consistent with an isSCC lesion may advance to the Screening Phase.

4.1.1 SCREENING VISITS (SV)

The Screening Visit (SV) will take place within the 28 days (4 weeks) to 3 days prior to first dose.

The subject will sign and date the informed consent form (ICF) and Health Insurance Portability Accountability Act (HIPAA) authorization (according to site practices) prior to any study-related procedures. A unique identification number (subject number) will be assigned to each subject who has provided written informed consent. The subject number will incorporate a two-digit Study Center number (e.g., 01) and a three-digit numeric ID assigned in successive order of entering the study after signing the ICF at each center, beginning with 001 at each site (e.g., 01-001, 01-002).

Subject Screening #:	**XX**	**-**	**YYY**
	XX=Study Center		YYY=Subject Numeric ID

Study center will be instructed to maintain the study-specific screening and enrollment logs at their sites. If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented, and the same subject number will be used at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of once and may be enrolled if they are found to meet all inclusion and no exclusion criteria when re-screened.

Once the ICF has been signed, screening procedures and information will be obtained to confirm subject eligibility, including:

- Demographic information (see Section 7.3)
- Detailed medical and medication history (see Section 7.4)
- Concomitant medications assessment (see Section 7.8)
- Vital Signs (see Section 7.6)
- Body Weight & Height measurements (see Section 7.7)
- Complete physical examination (excluding rectal, breast and genital examinations unless medically necessary) (see Section 7.5)
- Supine 12-lead safety Electrocardiogram (see Section 7.10)
- Clinical laboratory assessments (see Section 7.11)
    - Safety laboratory tests (serum chemistry, hematology, coagulation (if needed), and urinalysis)
    - Serum pregnancy test (HCG) for female subjects of childbearing potential (a positive result will exclude the subject from the study).
        - Childbearing potential is defined as someone who is not surgically sterile (Hysterectomy, bilateral tubal ligation (at least 6 months prior to initiation of treatment), or bilateral oophorectomy) or is not more than one year past complete cessation of menstrual cycles in women 50 years of age and older.
- Local Skin Response (LSR Grading Scale) (see Section 7.13)
- 2D photography of lesion (see Section 7.14)
- Longest diameter and area measurement of lesion (see Section 7.15)

If, in the opinion of the PI or designee, the subject has any clinically significant abnormality or risk factor which will add considerable risk to participation or make it unlikely that he/she will complete the study, he/she will be excluded from the study.

All screening information will be fully documented in the subject's medical records (i.e., source documents).

- For subjects consented who do not meet eligibility criteria, a Screen Failure electronic Case Report Form (eCRF) will be completed. The Screen Failure eCRF will contain the following details:

The subject's identification number, the date of ICF signature, demographic information (see Section 7.3), and the reason for screen failure. No additional information will be required for subjects who fail screening.

- For consented subjects who meet eligibility criteria, all required information will be recorded into the appropriate page of the eCRF.

4.2 TREATMENT PHASE

Subjects who meet eligibility criteria will check-in to the clinic on the day the first treatment is scheduled, and the following assessments will be performed prior to the first treatment: review of any changes in medical and medication history, vital signs, weight measurement, symptom-directed physical examination, concomitant medications, ECG, chemistry, hematology, and urinalysis, urine pregnancy (if applicable), blood collected for Anti-Drug Antibody analysis (ADA), creation of pre-treatment lesion template along with measurement of longest diameter and area of the lesion, and 2D digital imaging of the lesion, baseline Local Skin Response (LSR) Grading Scale assessment, baseline pigmentation, and pain assessment at the site of lesion (Visual Analogue Scale) prior to dosing.

Eligible subjects will be enrolled to the cohort. All subjects who fail to meet eligibility criteria at Baseline/Treatment Visit (T1) are considered screen failures and are exited from the study without further evaluation.

4.2.1 TREATMENT VISIT 1

4.2.1.1 Treatment Visit 1 Pre-Dose

The patient's eligibility will be reconfirmed by a review of inclusion/exclusion criteria and the following procedures and assessments will be completed:

- Assessment of any changes in medical history or concomitant medications (see Section 7.4 and 7.8)
- Vital Signs including heart rate, respiratory rate, blood pressure and body temperature will be monitored prior to dosing (see Section 7.6)
- Weight measurement (see Section 7.7)
- An abbreviated symptom directed physical examination (see Section 7.5)
- Supine 12-lead safety Electrocardiogram on admission (see Section 7.10)
- Clinical laboratory assessments (see Section 7.11)

- Urine pregnancy test prior to dosing (*for female subjects of childbearing potential*)
- Safety laboratory tests (serum chemistry, hematology, and urinalysis)
- Blood draws for anti-drug antibody (ADA) analysis just prior to dosing

- 2D Photography of Lesion (see Section 7.14)
- Create template of the lesion prior to treatment using anatomical landmarks and markings with surgical pen around the lesion to facilitate identification of the target lesion location at follow up visits. (see Target Lesion Identification, Measurement & Photography Guide) provided
- Longest diameter and Area Measurement of Lesion (see Section 7.15)
- Pigmentation assessment (see Section 7.16)
- Local Skin Response Grading Scale assessment (LSR) (see Section 7.13)
- Injection Site Pain Assessment (Visual Analogue Scale) prior to dosing (see Section 7.12)

Eligible subjects will be enrolled and assigned to the cohort. All subjects who fail to meet eligibility criteria at Treatment Visit (T1) are considered screen failures and are exited from the study without further evaluation.

4.2.1.2 Treatment Visit 1 Dosing

The study treatment (STP705 injections) will be administered intralesional by a licensed medical professional. Subjects will be instructed by study staff to not rub or scratch the injection site area for approximately 1 hour after injection(s). Please refer to the Pharmacy Manual provided for further details.

4.2.1.3 Treatment Visit 1 Post-Dosing

Subjects will remain confined to the clinic for up to 1.5 hours post-dosing. The following procedures will be performed after the administration of the study medication:

- Vital signs including heart rate, respiratory rate, blood pressure and body temperature will be monitored within 15 minutes (±5 min), within 30 min (±5 min), and within 1 hour (±15 min) post- administration at T1. (see Section 7.6)
- Injection Site Pain Assessment (Visual Analogue Scale) within 15 minutes (±5 min) post-dosing (see Section 7.12)

- Subjects will be monitored for any Adverse Events (see Section 9)
- Concomitant medication assessment (see Section 7.8)
- Local Skin Response (LSR Grading Scale) within 15 minutes (±5 min) post-dosing (see Section 7.13)
- 2D Photography of Lesion (see Section 7.14)

4.2.2 Treatment Visit 2 Through 6 (T2-T6)

The following procedures will be performed from the second through sixth treatment visit unless stated otherwise:

- Assessment of any adverse events and changes in concomitant medications (see Section 9 and 7.8)
- Vital signs (pre- and post-study drug administration): post-treatment vital signs will be assessed within 15 minutes (±5 min) following study treatment administration) (see Section 7.6)
- Weight measurement (see Section 7.7)
- An abbreviated symptom directed physical examination (see Section 7.5)
- Blood collection for Anti-drug antibody analysis prior to treatment administration. (see Section 7.11)
- Injection Site Pain Assessment (Visual Analogue Scale) pre-dosing and within 15 minutes (±5 min) post-dosing (see Section 7.12)
- Local Skin Response (LSR Grading Scale) pre-dosing and within 15 minutes (±5 min) post-dosing (see Section 7.13)
- Study drug administration (see Section 6.4)
- 2D Photography of Lesion pre- dosing (see Section 7.14)
- Pigmentation assessment pre-dosing (see Section 7.16)
- Longest diameter and Area Measurement of Lesion pre-dosing (see Section 7.15)

4.2.3 Observation Visit

The following procedures will be performed at the Observation Visit:

- Assessment of any adverse events and changes in concomitant medications (see

Section 9 and 7.8)

- Vital Signs (see Section 7.6)
- An abbreviated symptom directed physical examination (see Section 7.5)
- Blood collection for Anti-drug antibody analysis prior to treatment administration. (see Section 7.11)
- Injection Site Pain Assessment (Visual Analogue Scale) (see Section 7.12)
- Local Skin Response (LSR Grading Scale) (see Section 7.13)
- 2D Photography of Lesion (see Section 7.14)
- Pigmentation assessment (see Section 7.16)
- Longest diameter and Area Measurement of Lesion (see Section 7.15)

4.2.4 End of Treatment Visit

The following procedures will be performed at the End of Treatment Visit:

- Assessment of any adverse events and changes in concomitant medications (see Section 9 and 7.8)
- Vital Signs (see Section 7.6)
- An abbreviated symptom directed physical examination (see Section 7.5)
- Supine 12-lead safety Electrocardiogram (see Section 7.10)
- Clinical laboratory assessments (see Section 7.11)
  - Safety laboratory tests (chemistry, hematology, urinalysis)
  - Blood draw for anti-drug antibody (ADA) analysis
  - Serum pregnancy test (HCG) for female subjects of childbearing potential
- Local Skin Response (LSR Grading Scale) (see Section 7.13)
- Longest diameter and Area Measurement of lesion (see Section 7.15)
- 2D Photography of lesion (see Section 7.14)
- Pigmentation assessment (see Section 7.16)
- Surgical excision of the lesion (see Section 7.17)

- Assessment of histological clearance of lesion (see Section 7.18) by the central pathology lab once excision is received and analyzed
- Lesion immunohistochemistry analysis (see Section 7.19) by the central vendor

4.2.5 Follow-Up Visit 1 and 2 (FU1 – FU2)

The following procedures and assessments will be completed at the first and second follow-up visit unless stated otherwise:

- Assessment of adverse events and concomitant medications (see Section 9 and 7.8)
- Abbreviated symptom-directed physical examination (see Section 7.5)
- Vital signs (see Section 7.6)
- 2D Photography of lesion/surgical site (see Section 7.14)
- Pigmentation Assessment (see Section 7.16)

FU1 Only

- Blood collection for Anti-Drug Antibody analysis (see Section 7.11)
- Suture removal: per site standard of care

FU2 Only

- Blood collection: chemistry, hematology, urinalysis (see Section 7.11)

4.2.6 Unscheduled Visits

In the event that the subject returns to clinic at a time other than a regularly scheduled study visit including checking the excision site if required by site's standard of care, the visit will be regarded as an unscheduled visit. Assessments at unscheduled visits are at the discretion of the Investigator. All pertinent findings, including adverse events or changes in medications, will be noted in the eCRF.

5. SUBJECT COMPLETION, WITHDRAWAL AND CRITERIA FOR STOPPING THE STUDY

A subject is considered to have completed his/her part of the study in which they are enrolled once all Post-Study (Follow-up) Visit assessments have been performed, or the subject withdraws from the study prematurely.

While subjects are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Reasonable effort will be made to determine why any subject withdraws from the study prematurely. This information will be recorded. If a subject withdraws prematurely during the Treatment Phase, all assessments at the EOT visit including surgical excision of the lesion per protocol will be performed and subjects will be monitored until they are stable for discharge from the study. If a subject withdraws prematurely after EOT, all data normally collected at the next scheduled Post-Study (Follow-up) Visit should be recorded at the time of premature discontinuation.

Subjects' participation may also be terminated prior to completing the study for any of the following reasons:

1. Adverse event

2. Protocol violation

3. Loss to follow-up

4. Subject's own request (withdrawal of consent)

5. Other

If a subject fails to return for the scheduled study visit or is discontinued from the study, an attempt will be made to determine the reason(s). If the subject is unreachable by telephone, a registered letter will be sent to the subject requesting that he/she contact the clinic.

All subjects with an ongoing SAE at the Post-Study (Follow-up) Visit (scheduled or premature) must be followed until the event is resolved (with or without sequelae) or deemed stable.

In the event that a subject is withdrawn from the study at any time due to an adverse event or SAE, safety procedures must be followed (see Section 9).

5.1 Replacement of Subjects

Subjects who withdraw consent or dropout from the study after first treatment will be replaced.

5.2 Screen Failures

A subject who has signed a consent form, has been assigned a subject number, but is not treated is classified as a screen failure. Subject number, demographics and reason for screen failure will be recorded.

If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented, and the same subject number will be used at the time of re-screening. Subjects who fail their first screening attempt may be re-screened again (i.e., up to two screenings) and may be enrolled if they are found to meet all inclusion and no exclusion criteria at the subsequent screening visit.

6. STUDY TREATMENT

6.1 DESCRIPTION OF INVESTIGATIONAL PRODUCT

The STP705 drug substance is composed of two siRNA oligonucleotides, targeting TGF-β1 and COX-2 mRNA respectively. STP705 is formulated in nanoparticles with histidine-lysine-polypeptide (HKP) at a ratio of 1:2.5 in mass weight (siRNA: peptide), which is further formulated into a lyophilized powder drug product. Following reconstitution with Water for Injection the administration route will be intralesional injection.

STP705 Injection is a sterile lyophilized white powder before reconstitution. After reconstitution, it is a colorless and transparent solution, free of particulates. Each investigational product vial will contain 0.32 mg (320μg) of STP705. The composition of the reconstituted product is provided in Table 6-1 below.

TABLE 6-1: COMPOSITION OF STP705 POWDER FOR INJECTION

COMPONENT	CONCENTRATION (MG/VIAL)	FUNCTION
RNA STP705-1 TGF- β1	0.16 mg	Drug Substance
RNA STP705-2 COX-2	0.16 mg	Drug Substance
HKP Peptide	0.8 mg	Excipient for generation of nanoparticles
Trehalose dihydrate	64 mg	Excipient for maintaining osmolarity of the drug product

6.2 INVESTIGATIONAL PRODUCT PACKAGING AND LABELING

6.2.1 STP705

STP705 study drug will be packaged, labeled, and shipped by Sirnaomics, Inc. (or designee). STP705 is supplied in a 6-mL glass vial (Schott 6R) with a stopper and crimp and flip-off seal.

STP705 vials will be labeled with information such as: study protocol number; fill volume; concentration; storage condition; a "use as per study protocol" statement; a cautionary statement; and the sponsor's name and address.

A representative sample of the Investigational Product STP705 container label is listed below:

FIGURE 6-1: STUDY DRUG CONTAINER LABEL

STP705 Lot number: 109-002-001 Protocol Number: SRN-705- ___ ___ __ Sponsor: Sirnaomics Inc 401 Professional Drive, Ste 280, Gaithersburg, MD 20879. Phone Number: 301-740-1730. Manufacturer: Berkshire Sterile Manufacturing, MD 01238. Dosage Form: Lyo Powder in 6R vial. Route of administration: Injection USE AS PER PROTOCOL. Storage condition: 2-8°C. Caution: New-Drug Limited by US Federal laws to investigational use

6.3 INVESTIGATIONAL PRODUCT STORAGE

STP705 study drug will be shipped refrigerated from the distribution center at a controlled temperature (2°C to 8°C) to the Investigator's site using insulated shipping containers. Each shipping container will contain STP705 and a TempTale Ultra Monitor which provides the temperature history for the shipment. Upon receipt at the site, the responsible site staff or pharmacist should verify the integrity of the vials. Study drug should be stored refrigerated at 2°C to 8°C. The known long-term stability is 36 months (from manufacturing date) at 2°C to 8°C. Access to study drug will be restricted to authorized personnel only.

The Investigator must maintain an accurate record of the shipment, storage, and dispensing of the study drug in a drug accountability log. An accurate record including the date and amount of study drug dispensed for each subject must be available for inspection at any time. An unblinded study CRA independent of the CRA assigned to monitor the investigational site will be responsible for reviewing all pharmacy records related to investigational product receipt and shipment, subject randomization, and investigational product preparation for injection and disposal of un-used solutions of STP705. Study drug will be accounted for on an ongoing basis during the study.

Refer to Pharmacy Manual for further details.

6.4 INVESTIGATION PRODUCT ADMINISTRATION

The STP705 study treatment will be reconstituted by the study pharmacist or designated staff and administered at the site of the lesion by a licensed medical professional. The volume of the IP to be administered is 0.6 mL for all treatment cohorts. Diluted IP should not be saved for future use and should be discarded after use as per facility standard procedures of drug waste disposal. Diluted STP705 IP is stable for no more than 24 hours refrigerated from the time of constitution. Refer to the product insert of normal saline for use and stability.

The dosing regimen for each cohort are as follows:

Cohort A: STP705 30 µg dose, intralesional injection, given once a week for 6 weeks.
Cohort B: STP705 60 µg dose, intralesional injection, given once a week for 6 weeks.
Cohort C: STP705 90 µg dose, intralesional injection, given once a week for 6 weeks.

TABLE 6-2: INVESTIGATIONAL PRODUCT PREPARATION AND DOSAGE

Lesion size	No of Injections	30 µg dose	60 µg dose	90 µg dose
0.5 to ≤ 2.0cm diameter	1	30 µg/0.6 mL	60 µg/0.6 mL	90 µg/0.6 mL
		STP705 preparation		
		1. 320 µg vial diluted with 6.4 mL of water for injection (WFI). 2. Withdraw 0.6 mL from 6.4 mL and inject into lesion	1. 320 µg vial diluted with 3.2 mL of water for injection (WFI). 2. Withdraw 0.6 mL from 3.2 mL and inject into lesion	1. 320 µg vial diluted with 2.1 mL of water for injection (WFI). 2. Withdraw 0.6 mL from 2.1 mL and inject into lesion
		Discard un-used solutions of STP705 and saline		

Refer to the Pharmacy Manual for further details.

6.4.1 INJECTION PROCEDURE AND POST-INJECTION MONITORING

Study treatment (IP Injection) will be administered intralesional by a licensed medical professional.

Post-Injection Monitoring

- **Applicable for all treatment administrations:**
  - Vital signs will be monitored within 15 minutes (±5 min) post-administration.
  - Subject will be observed at approximately 15 minutes post-injection or

longer, if necessary, on visits where treatment is administered for Local Skin Response (LSR) assessment.

- In addition, the tolerability of repeated intralesional administration of STP705 is evaluated based on assessment of subject-perceived injection site pain using the Visual Analogue Scale (VAS). This assessment will be performed within 15 minutes (±5 min) after each study treatment administration.

6.4.2 Treatment Modification

The dose interruption and permanent discontinuation for any toxicity are described below.

Dose interruption: Refer to Table 6-3 below. Recovery to acceptable levels of toxicity (base line grade 1 or 2 or less) must occur to allow STP705 continuation.

Permanent discontinuation of Treatment: If Grade 4 event is reported, study treatment will be permanently discontinued.

Table 6-3: Dose Modification and Management

CTCAE Grade	Treatment Modifications
Grade 1 or 2	No dose adjustment is required
Grade 3	Withhold treatment until symptoms resolve to: Grade 1 or less (if not considered a safety risk for the patient)
Grade 4	Study treatment will be permanently discontinued

6.5 Investigational Product Accountability

The Investigator or designee will verify the contents of each shipment against the shipping documents. Verification of IP receipt will be documented according to the Sponsor's requirements.

An accountability log will be provided to the site for use by the Investigator to maintain current and accurate inventory records (batch, expiry, and quantity) covering the dispensing and the destruction of the IP. An expiration memo will be sent with every IP shipment to the site.

The study treatment will be administered by trained, qualified, medical professionals. The total volume of study product administered will be recorded in source documents and the eCRF.

Study treatment packaging labels with a traceable unique identifier will be saved and available for inspection for Investigational Product accountability throughout the study.

At the conclusion of the study the Investigator must return or destroy all remaining IP as instructed by the Sponsor. Further details will be provided in the Pharmacy Manual.

7. DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

7.1 INFORMED CONSENT

A written informed consent will be obtained for this study by the Investigator or designee from all subjects prior to performance of any protocol-specific procedure. This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

The Investigator must comply with applicable regulatory requirements and must adhere to the Good Clinical Practice (GCP) in the process of obtaining and documenting the informed consent. The Investigator, or designee, must also inform subjects of all pertinent aspects of the study. Before written informed consent is obtained from the subject, the Investigator or a person designated by the Investigator, must provide the subject enough time and opportunity to inquire about the details of the study and to decide whether to participate in the trial. All questions raised by the subject about the study must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Authorization for release of protected health information must also be obtained, as per local policies.

7.2 ASSESSMENT OF ELIGIBILITY

During the Screening Phase and prior to first treatment dosing at T1, the Investigator must assess a subject's continued suitability and eligibility for the trial. The Inclusion and Exclusion criteria of this protocol are described in Sections 3.3.1 and 3.3.2. If the subject is not suitable or eligible for the trial, then the subject will be designated a screen failure. In the unlikely event the subject has more than one "qualified" facial isSCC lesion, only one lesion may be treated in this trial. In this case, the investigator may elect which lesion is to be treated. It is also important that the management of any other isSCC lesion(s) does not interfere with the per protocol assessment and management of the isSCC lesion designated for treatment in the study.

7.3 DEMOGRAPHIC INFORMATION

For the purposes of this study, demographic information will include:

- Dates of ICF signature
- Date of birth
- Gender
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, Caucasian, or other)
- Ethnicity (Hispanic/Latino or Not Hispanic/Latino)

7.4 MEDICAL HISTORY

A medical history will be recorded during the Screening Phase and prior to first treatment dosing at T1 and will include:

- All ongoing medical conditions
- Any prior medical conditions that have resolved within the last year.

Events that emerge prior to the first treatment (T1) will be recorded in the medical history and not as AEs. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration, and severity of any ongoing baseline medical conditions prior to the patient's receiving investigational product treatment.

Medical histories will be recorded using the body system categories outlined below:

- Cardiovascular
- Respiratory
- Gastrointestinal
- Renal
- Hepatic
- Neurological
- Endocrine
- Lymphatic
- Hematologic
- Immunologic
- Dermatologic
- Psychiatric
- Other

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of diagnosis
- History status (end date [e.g., date resolved] or ongoing)

7.5 PHYSICAL EXAMINATION

Complete physical exam to be done at screening only. Abbreviated symptom directed physical exam to be done at T1 and thereafter. The physical examination will include routine examinations for the following:

- General Appearance
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Lymph Nodes
- Heart/Cardiovascular abnormalities
- Respiratory
- Abdomen
- Musculoskeletal and Extremities
- Neurologic abnormalities
- Dermatologic abnormalities
- Any other body system for which an abnormality is noted and which, in the opinion of the Investigator, is relevant to the safety of the subject or could impact safety or efficacy results for the subject, i.e., the abnormality is clinically significant (CS).

Each abnormality will be recorded in the source, and the Investigator will record an assessment of its clinical significance. Any clinically significant findings at Screening or T1 (prior to dosing) will be recorded as medical history; any new or worsening clinically significant findings with or after the first dose will be recorded as adverse events.

7.6 VITAL SIGNS

The following vital signs will be collected:

- Blood pressure
- Heart rate
- Respiratory rate
- Temperature

Note: *Vitals will be taken pre- and post- study treatment administration.*

Note: *Vital signs will be monitored within 15 minutes (±5 min), within 30 min (±5 min), and within 1 hour (±15 min) post-administration on T1.*
Vital signs will be assessed before the injection, and within 15 minutes (±5 min) after the injection on Treatment Visits T2-T6.

7.7 Body Height and Weight Measurements

The following information will be collected:

- Height (only at Screening Visit 1)
- Weight
  - ***Note:*** *Only weight will be taken at T1-T6.*
- BMI (derived from the height and weight measurements) at Screening

7.8 Concomitant Medications

All medications and therapies administered or taken by the subject beginning 30 days prior to Screening Visit and throughout the study will be recorded in the source documents and, for enrolled subjects, on the appropriate page of the eCRFs. Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication and topical medication.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose).
  - **Note:** *Each new dose of medication should be recorded as a separate entry, apart from medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.*
- Route of dosing
- Indication for use
  - In the case of pain medication, the site of pain should be recorded.
- Start date
- Stop date (if medication/therapy is not ongoing)

7.9 PROHIBITED MEDICATIONS AND THERAPIES

The following medication or therapies should NOT be used during the study.

a) Immunosuppressants
b) Cytotoxic chemotherapy
c) Cytostatic therapy
d) Autoimmune disease therapy
e) Use of any investigational drug(s) or devices
f) Systemic corticosteroids
g) Any topical (within 2 cm of the target lesion) prescription drug or OTC topical steroids. Note: other OTC medications may be used with the consent of the investigator on a case-by-case basis.
h) Any therapies (within 2 cm of the target lesion) including but not limited to liquid nitrogen, laser, or other energy-based devices, micro-needling, surgical excision, and curettage.

7.10 ELECTROCARDIOGRAM (ECG)

A resting supine 12-lead ECG will be conducted at the Screening Visit (SV), prior to the first study treatment, and at the End of Treatment visit. The results will be evaluated by the Investigator. The following parameters will be measured: ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), QTc interval (msec). Additionally, the central ECG vendor will provide an overall interpretation of the ECG reading as either normal or abnormal, and the Investigator will review the ECG results and designate all abnormal ECGs as either not clinically significant or clinically significant. If abnormalities are observed, each will be provided by the central ECG vendor in the data transfer along with all ECG results.

The Investigator must receive and review the ECG report from the central ECG vendor of the Screening ECG prior to enrollment. Only those subjects who have normal or not-clinically significant results at the Screening Visit (SV) will be enrolled in this study.

7.11 CLINICAL LABORATORY ASSESSMENTS

Samples will be collected for analysis for the following parameters described in Table 7-1 and Table 7-2:

- Hematology Parameters (Blood Sample): SV, T1, EOT, and FU2
- Serum Chemistry Parameters (Blood Sample): SV, T1, EOT, and FU2

- Coagulation Parameters (Blood Sample): SV (only for subjects receiving anticoagulation therapy)
- Serum pregnancy test (for female subjects of childbearing potential): SV and EOT
- Urinalysis (Urine Sample) SV, T1, EOT, and FU2
- Urine pregnancy test (for female subjects of childbearing potential): T1*
- Anti-Drug Antibody (ADA) Analysis (Blood Sample): T1-FU1, see Table 7-2 for details

*In the United States, the site must be registered and conform to Clinical Laboratory Improvement Amendments (CLIA) requirements and possess a current valid CLIA Certificate of Waiver or higher.

All urine and blood samples should be submitted to the local laboratory on the day of collection. All laboratory reports will be reviewed by the Investigator.

Post-treatment, new, or worsening abnormal results that are considered by the Investigator to be clinically significant will be recorded as adverse events. If the Investigator judges it necessary, testing may be repeated to make the determination of clinical significance.

TABLE 7-1: LAB PARAMETERS

Hematology (CBC with Automated Differential)	Chemistry	Urinalysis
WBC, RBC, Platelets, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW Differential # and %: Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils	Albumin, Alkaline Phosphatase, ALT, AST, Total Bilirubin, Glucose, Total Protein, Urea, Nitrogen, Creatinine, Sodium, Potassium, Chloride, Calcium, CO2	Color, appearance, Bilirubin, Blood, Glucose, Ketones, Leukocyte Esterase, Nitrite, pH, Protein, and Specific gravity
Coagulation Parameters*		
aPTT, PT, INR *for subjects receiving anticoagulation therapy, performed at SV only		
Miscellaneous		
Serum pregnancy test Urine pregnancy test (for female subjects of childbearing potential) ADA		

Samples for evaluation of anti-drug antibodies (ADA) will be collected prior to dosing on Day 1 of every week for the 6 weeks cycles, at Observation Visit, at the End of Treatment (EOT) Visit prior to surgical excision, and at Follow-Up Visit 1. A laboratory manual will be provided with instructions for collecting and processing of the samples.

TABLE 7-2: SAMPLE COLLECTION TIME POINTS FOR ANTI-DRUG ANTIBODY ASSESSMENTS

Visit Day	ADA Sample Collection Time Points (Blood Serum)
T1	Prior to first study drug administration at Treatment Visit 1
T2	Prior to second study drug administration at Treatment Visit 2
T3	Prior to third study drug administration at Treatment Visit 3
T4	Prior to fourth study drug administration at Treatment Visit 4
T5	Prior to fifth study drug administration at Treatment Visit 5
T6	Prior to sixth study drug administration at Treatment Visit 6

Visit Day	ADA Sample Collection Time Points (Blood Serum)
Observation Visit	At Observation Visit
EOT	Prior to surgical excision of the lesion at EOT visit
FU1	At Follow-Up Visit 1

7.12 PAIN ASSESSMENT USING VISUAL ANALOGUE SCALE (VAS)

Tolerability of repeated localized administration of STP705 is evaluated based on assessment of subject-perceived injection site pain using the Visual Analogue Scale (VAS).

Before dose administration and within 15 minutes (±5 min) after dose administration at T1-T6, subjects will be asked to mark the point that best represents the pain intensity at the time of injection administration on a horizontal line (100 mm in length) anchored by the following word descriptors at each end, "no pain" on the left side and "pain as bad as it could possibly be" on the right side of the line. The subject marks on the line or points to a position on the line representing their perception of their pain state. The VAS score is determined by measuring in millimeter the perception of pain from the left-hand end of the line to the point that the patient marks. Record as a whole number (e.g., 10, 30, 95) in millimeters from 0 (no pain) to 100 (pain as bad as it could possibly be). Round to the nearest whole number if the measurement falls in between numbers.

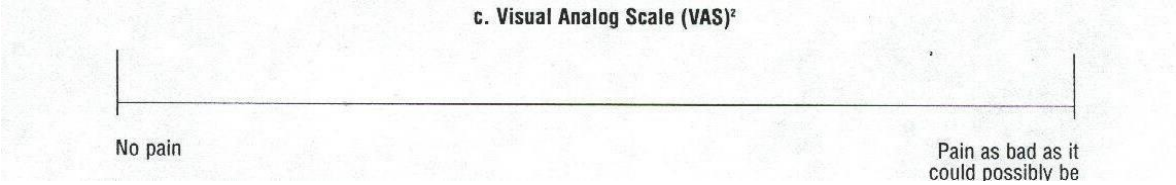
Note:

(1) Post-treatment VAS assessment will be performed within 15 minutes (±5 min) of the study drug administration.

(2) Use of pain block anesthesia would also be documented on the Pain Assessment eCRF and as a concomitant medication.

(3) Subjects will be asked to mark the point that best represents the pain intensity at the injection site during the observation visit.

FIGURE 7-1: VISUAL ANALOGUE SCALE



7.13 LOCAL SKIN RESPONSE GRADING SCALE (LSR)

The Local Skin Response (LSR) Grading Scale will be used to evaluate the changes in the baseline lesion location and will be measured pre-dose and within 15 minutes (±5 min) post-dose administration at T1-T6. LSR will also be assessed at observation visit and at EOT. The incidence and grade of LSRs will be summarized by cohort at each visit. LSR grades will be summarized by frequency counts and descriptive statistics per cohort and visit for each of the six individual LSRs: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration.

A composite (sum) score will be obtained by summing the six individual LSR scores at each visit. The composite score and change from baseline will be summarized by cohort at each visit using descriptive statistics. The first visit at which the highest sum score is obtained will be summarized by cohort. For those subjects whose LSR sum score increased in intensity from baseline, the first visit at which the LSR returned to the baseline intensity will be presented by cohort.

Local skin response will be graded based on Local Skin Response Grading Scale (Table 7-3) pre and post treatment.

TABLE 7-3: LOCAL SKIN RESPONSE GRADING SCALE

Local Response	Grading Scale				
	0	1	2	3	4
Erythema	Not Present	Slight Pink, <50%	Pink or light red,>50%	Red, restricted to treatment area	Red, extending outside treatment area
Flaking/Scaling	Not present	Isolated to scale, specific lesion	Scale <50%	Scale >50%	Scaling extended outside treatment area
Crusting	Not present	Isolated crusting	Crusting <50%	Crusting >50%	Crusting extended outside treatment area
Swelling	Not Present	Slight lesion specific edema	Palpable edema extending beyond individual lesions.	Confluent and/or visible edema	Marked swelling extending outside treatment area
Vesiculation/ Pustulation	Not Present	Vesicles only	Transudate or pustules, with or without vesicles, <50%	Transudate or pustules, with or without vesicles, >50%	Transudate or pustules, with or without vesicles extending outside treatment area
Erosion/ Ulceration	Not present	Lesion specific erosion	Erosion extending beyond individual lesions	Erosion >50%	Black eschar or ulceration

The highest-grade post-baseline and incidence of any response (post-baseline) for each LSR type will also be presented by frequency distribution for each cohort. The study day of the highest grade greater than baseline for each LSR type and the study day at which the grade returns to a level at or below the baseline level will also be presented by frequency distribution for each cohort.

Local skin responses will be converted into MedDRA preferred terms applying the conversions in Table 7-4.

TABLE 7-4: CONVERSION OF LSRS TO MEDDRA PREFERRED TERMS

LSR Term	LSR Grade	MedDRA Preferred Term
Erythema	1-4	Injection site erythema
Flaking/Scaling	1-4	Injection site exfoliation
Crusting	1-4	Injection site scab
Swelling	1-4	Injection site swelling
Vesiculation/Pustulation	1	Injection site vesicles
	2-4	Injection site pustules
Erosion/Ulceration	1-3	Injection site erosion
	4	Injection site ulcer

7.14 2D PHOTOGRAPHS OF THE LESION

Two-dimensional color photographs of the lesion will be taken to document the changes in the appearance and size of the lesion. The lesion will be marked with a surgical skin marker before the photograph is taken. Photographs will be taken at each treatment visit (T1-T6), at Observation Visit, at the End of Treatment Visit (EOT), and at Follow-up Visits 1 and 2 (FU1 and FU2). At treatment Visits T1- T6, the photographs will be taken before the treatment is administered. At T1, photographs will also be taken after the treatment is administered.

In these clinical photographs, for the duration of the study, the only variable will be the skin condition itself. Therefore, anything extraneous to the condition (jewelry, clothing, furniture, walls, etc.) will be eliminated from the fields to be photographed, from the baseline through the final photographs. The necessity of good end-of-study photos and their importance will be conveyed to the subjects to ensure their cooperation. Lighting, framing, exposure, and reproduction ratios must be held constant. Refer to procedure manual for more information.

1. After obtaining informed consent, the subjects will be prepped for photography. All jewelry, makeup and clothing will be removed from the photographic fields prior to photography. A target SCC area on the face will be identified for photos using a surgical skin marker. The standard blue deluxe felt background should be used for photographs. Do not use folded or crimped material.

2. Upon completion of the patient's photographic session, the contents of the SD memory card will be uploaded to a secure online file sharing service at www.box.com. Refer to Target Lesion Identification, Measurement & Photography Guide) provided.

7.15 LONGEST DIAMETER AND AREA MEASUREMENTS OF THE LESION

Quantitative measurement will be performed manually. The longest lesion diameter will be identified and then measured to the nearest millimeter using a caliper or ruler, as appropriate, based on the location of the lesion. The area of the lesion will be estimated as the product of the longest diameter and the greatest width of the lesion, which is perpendicular to the longest diameter, in square millimeters. Measurements will be taken at Treatment Visits T1-T6 before treatment administration, at Observation Visit, and at the EOT Visit before excision.

7.16 PIGMENTATION ASSESSMENT

The pigmentation of the lesion at Baseline (or the lesion area at Baseline if there is partial or complete resolution of the lesion) will be assessed prior to dose administration at Treatment Visits T1-T6 pre-treatment, at Observation Visit, at the End of Treatment Visit (EOT) before excision, and at Follow-Up Visits 1 and 2 (FU1 and FU2) and quantified with a 0-3 scale (None=0, Mild=1, Moderate=2, Severe=3) using investigators' objective assessment of pigmentation for hyperpigmentation and hypopigmentation.

7.17 EXCISION OF THE ISSCC SITE

Post-treatment excisions will be performed by a licensed medical professional at EOT Visit. The excision will be performed with a 3-4 mm margin around the target lesion as delineated by a pretreatment template obtained from the pre-treatment measurement of the lesion (see Section 7.15). Note, in the unlikely event the target lesion has materially grown since Baseline, the excision requirements may exceed those suggested by the pretreatment template.

7.18 HISTOLOGICAL ASSESSMENT OF LESION BIOPSY PRIOR TO SCREENING AND CLEARANCE OF LESION AT END OF TREATMENT

Prior to Screening, if a potential subject presents with a clinically suspicious isSCC lesion that was never biopsied or that was biopsied more than 6 months prior to Screening, this lesion may be biopsied to determine eligibility (**an optional pre-screening biopsy**). In this case, after the subject has been consented, the biopsy shall be performed by the investigator (or his/her qualified designee) under this protocol prior to Screening. Only those subjects with a qualifying lesion and histopathology consistent with an isSCC lesion may advance to the Screening Phase.

After excision of the lesion site at EOT, the excised area of tissue will be evaluated for Histological Clearance.

Post-treatment excision specimens are to be examined by the primary dermatopathologist, blind to the clinician's assessment of the presence or absence of isSCC at the post treatment visit. A

laboratory manual will be provided with instructions for collecting, processing, and shipping the samples.

7.19 FUTURE OR EXPLORATORY SPECIMEN RESEARCH

Tissues obtained from the original diagnosis (within 6 months prior to the screening visit (if available) or at screening) and the tissue excised at the end of the study will be used in exploratory analysis of biomarker expression common to the isSCC tumor formation pathway such as TGF-β1, COX-2. Additionally, tissues collected may also be used in future research into the causes of cancer, its complications, and other conditions for which individuals with cancer are at increased risk, and to improve treatment. No genetic testing will be performed.

The tissues may be stored indefinitely and will be identified only by the subject number assigned for this study. In the results of the study, the subjects will only be referred to by the study assigned number. No name or identifying information will be used in publication.

Investigators, including investigators from collaborating institutions, can request these samples, or information about them, for new research. Samples and information may also be shared with outside non-profit academic investigators, as well as with for-profit pharmaceutical investigators or commercial entities, under collaboration with Sirnaomics, Inc, the company sponsoring the study.

Subject can choose to withdraw consent to have tissue specimens stored for future research.

8. STATISTICAL ANALYSIS

This section presents general information about statistical considerations and concepts and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions that will be used in this study will be in a separate document, i.e., the Statistical Analysis Plan (SAP).

8.1 TREATMENT COHORTS

The below treatment cohorts will be assessed:
Cohort A: STP705 30 μg dose, intralesional injection, given once a week for 6 weeks.
Cohort B: STP705 60 μg dose, intralesional injection, given once a week for 6 weeks.
Cohort C: STP705 90 μg dose, intralesional injection, given once a week for 6 weeks.

8.2 DESCRIPTION OF OUTCOMES (ENDPOINTS)

8.2.1 PRIMARY EFFICACY OUTCOME MEASURE

The primary outcome (endpoint) measure is listed below:

- Proportion of participants with histological clearance of treated isSCC lesion at the End of Treatment (EOT).

  Histological clearance (HC) will be defined as the absence of detectable evidence of isSCC tumor cell nests as determined by central pathology review.

8.2.2 SECONDARY EFFICACY OUTCOME MEASURE

The secondary outcome (endpoint) measures for the study are:

- Change in size of the treated isSCC lesion over the pre-excision treatment period.

  A baseline assessment of lesion size will be made by investigator at T1 (first visit). This is measured by widest width and longest length using a caliper or a ruler as deemed by the investigator judgement. The change in size will be assessed every visit until the surgical excision of isSCC at the End of Treatment (EOT) visit.

8.2.3 SAFETY ASSESSMENTS

- Incidence of adverse events (AEs) and serious adverse events (SAEs).
- Incidence of AEs and SAEs leading to discontinuation of trial medication.
- Incidence and severity of Local Skin Response (LSR), hypopigmentation and hyperpigmentation following treatment.
- Tolerability of repeated Intralesional administration of STP705 as assessed by investigator- evaluation of injection site reactions for all patients and within each cohort.

In addition, safety measures will include clinically relevant changes or new abnormal findings in laboratory values, vital signs, electrocardiograms (ECGs), and physical examination.

8.3 Sample Size Determination and Rationale

A total of 30 eligible subjects (10 per cohort) will receive treatment with 30 μg, 60 μg, 90 μg STP705. No statistical power calculation is used to establish the sample size.

8.3.1 Stopping Rule

The trial will not be stopped early when extremely strong efficacy is observed.

8.4 General Statistical Considerations

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS®. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented by cohort for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables. Summaries will be provided for each treatment group and will include 95% confidence interval where appropriate and as designated in the Statistical Analysis Plan (SAP).

8.4.1 Analysis Populations

8.4.1.1 ITT Population

The **Intent-to-Treat (ITT) population** is defined as all enrolled subjects. The ITT population will be the primary population for the analysis of primary and secondary outcome measures.

8.4.1.2 Safety Population

The **Safety Population** will include all subjects who have received at least one dose of study treatment (any dose of STP705). This population will be used for the analysis of safety parameters.

8.4.2 Missing Data

For the primary efficacy end point of histological clearance of treated isSCC lesion at EOT, missing data due to early termination or other reasons will be imputed as histological clearance = No.

8.5 Analysis Methods

An SAP will be developed and approved before the database is locked. The SAP will include the detailed statistical methods to be used in analyzing data from this trial.

8.5.1 Subject Disposition

The disposition of all subjects who signed an ICF will be provided. The number of subjects screened, screen failed, received at least one treatment, completed, and discontinued during the study, as well as the reasons for all discontinuations will be summarized by treatment group. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

8.5.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics including medical history, prior and concomitant medications/therapies will be summarized by treatment group using appropriate descriptive statistics.

8.5.3 Concomitant Medications/Therapies

Concomitant medications/therapies will be listed for the Safety population. All prior and concomitant medications recorded in the eCRFs will be coded to match Anatomic Therapeutic Classification codes using the most recent version (at the time of study start) of WHO Drug dictionary. Descriptive summaries, by treatment group and stage of the study, will be prepared using the coded terminology. All concomitant medications/therapies recorded in the case report form will be listed.

8.6 Efficacy Analysis

The primary analyses of the primary and secondary efficacy outcome measures will be conducted on the ITT population. Primary Efficacy Analyses

- The proportion of subjects with histological clearance of treated isSCC lesion will be summarized by treatment group.

8.6.1 Secondary Efficacy Analyses

- Change in size of the treated isSCC lesion over the pre-excision treatment period.

  A baseline assessment of lesion size will be made by investigator at T1 (first visit).

  This is measured by widest width and longest length using a caliper or a ruler as deemed

  by the investigator judgement. The change in size will be assessed every visit until the surgical excision of isSCC at the End of Treatment (EOT) visit.

8.6.2 Safety Assessment

The safety population will be used for the analysis of safety endpoints.
Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will calculated for continuous variables. Frequencies and percentages will be presented for categorical variables.

8.6.2.1 Adverse Events

Adverse events (AEs) will be coded using the most recent version (at study start) of Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent AEs (TEAEs) are defined as events with an onset on or after the first treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- Overall (i.e., regardless of severity or relationship to treatment).
- By intensity (mild, moderate, severe, life threatening or death).
- By causality (definitely, probably, possibly, unlikely, or unrelated).
- By impact on study treatment (dose increased, dose not changed, dose rate reduced, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown).

In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

8.6.2.2 Clinical Laboratory Data

All laboratory values will be listed. Laboratory measurements will also be summarized and presented by treatment group and time point.

8.6.2.3 ECG

All ECG values will be listed. ECG measurements will also be summarized and presented by treatment group and time point.

8.6.2.4 Vital Signs

All vital sign findings will be listed and/or summarized.

8.6.2.5 Physical Examination

All clinically significant physical examination findings will be listed as Medical History (from Visit 1 or Visit 2) or Adverse Events (all visits' activities with and after the administration of treatment at Baseline).

9. ADVERSE EVENTS (DEFINITIONS AND REPORTING)

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs as detailed in this Section of the protocol.

9.1 ADVERSE EVENT (AE)

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the patient to have occurred, or a worsening of a pre-existing condition. An adverse event may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormality in physical examination findings or laboratory results that the investigator believes is clinically significant (CS) to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

9.2 REPORTING OF PREGNANCY

Female subjects of childbearing potential must have a pregnancy test prior to study enrollment. Prior to study enrollment, female subjects of childbearing potential must be advised of the importance of avoiding pregnancy during the study and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

Female subjects of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If a subject or investigator suspects that a subject may be pregnant at any time during the study, the IP must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive further IP and must be discontinued from the study unless the Medical Monitor elects to retain the subject for all or part of the remaining study period to follow the subject for safety.

If following initiation of study treatment, it is subsequently discovered that a subject was pregnant or may have been pregnant at the time of IP exposure, the investigator must immediately notify the Medical Monitor of this event and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to TI. The investigator will also report any pregnancy associated with the study treatment as required by their IRB and keep careful source documentation of the event.

Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated, including counseling of the subject by the investigator and her managing physician or health care provider (e.g., obstetrician). In addition, the investigator must report to TI, on the appropriate pregnancy surveillance form(s), any follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Although pregnancy itself is not an AE, any complications during pregnancy should be recorded as AEs or SAEs (if they fulfill the SAE criteria). Offspring should be followed for a minimum of 8 weeks. Any congenital anomaly/birth defect in a child born to a subject exposed to the IP should be recorded as a SAE with details documented in the pregnancy surveillance form. Abortion, whether accidental, therapeutic, or spontaneous should be reported as an SAE.

If a subject, including the female partners of a male study subject becomes pregnant during the course of the study, the investigator or site personnel must notify the Medical Monitor (see page 3 for details) within 5 working days after the investigator or site personnel become aware of the pregnancy. If an SAE occurs in conjunction with the pregnancy, then the reporting time frame for an SAE (within 24 hours) must be met.

If a female subject becomes pregnant within 6 months after the last dose of STP705 administration, the investigator or site personnel must notify the Medical Monitor (see page 3 for details) within 5 working days after the investigator or site personnel become aware of the pregnancy. If the female partner of a male study subject becomes pregnant within 3 months after the last dose of STP705 administration, the investigator or site personnel must notify the Medical Monitor (see page 3 for details) within 5 working days after the investigator or site personnel become aware of the pregnancy.

9.3 Reporting of Adverse Events

Report initiation for all AEs and SAEs will begin at the time of the first treatment visit and continue until the end of final study visit. All events will be followed to resolution or until the subject completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the subject's medical records and on the eCRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be a SAE (see Section 9.4), the impact the event had on study treatment (see Section 9.3.1), the Common Terminology Criteria for Adverse Events (CTCAE) grade (intensity) of the event (see Section 9.3.2), the causality of the event (see Section 9.3.3), whether treatment was given as a result of the event (see Section 9.3.4), and the outcome of the event (see Section 9.3.5).

9.3.1 Impact on Study Treatment

The impact the event had on the study treatment will be assessed as either: none, drug interrupted, drug withdrawn, not applicable, or unknown. The "not applicable" assessment will be used only when the subject is no longer in the treatment phase of the protocol.

9.3.2 CTCAE Grade (Intensity Assessment)

The guidelines outlined in CTCAE v5.0 will be used for assessing the intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at: https://evs.nci.nih.gov/ftp1/CTCAE/ .

Table 9-1: CTCAE v5.0 General Guidelines

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

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

†Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

-Common Terminology Criteria for Adverse Events (CTCAE), v5.0: November 27, 2017

9.3.3 CAUSALITY ASSESSMENT

AEs will be assigned a relationship (causality) to the study treatment. The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Definitely related**: This category applies to those AEs that the Investigator feels are incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it follows a known response pattern to treatment with the study treatment.

2. **Probably related:** This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.

3. **Possibly related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are determined unlikely but cannot be ruled out with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.

4. **Unlikely related**: In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are determined likely to be unrelated to the study treatment. An AE may be considered unlikely if or when (must have two): (1) it does not follow a reasonable temporal sequence from

administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It does not follow a known response pattern to treatment with the study treatment.

5. **Unrelated**: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and determined with certainty to have no relationship to the study treatment.

9.3.4 Treatment Given as a Result of the Event

The event impact in terms of treatment provided will be as either: none, medication administered, non-drug therapy administered, surgery performed, hospitalization, or other (with a specification).

9.3.5 Outcome Assessment

The outcome of the event will be assessed as either: fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, or unknown. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

9.3.6 Injection-Site Reactions

Injection-site reactions thought to be directly related to the injection are considered to be AEs of special interest, and a separate guideline for the acquisition of data related to this AE of special interest is provided in Section 7.13.

For subjects who develop grade 1 or grade 2 events, therapy will be continued as per protocol. If a subject chooses to discontinue study treatment, the site should notify the protocol team leadership, and encourage the subject to complete any remaining study visits until the toxicity resolves.

For subjects who develop grade 3 events following study drug injection, the subject should be reevaluated closely until the AE returns to grade 1 or less, at which time study treatment may be reintroduced at the discretion of the site investigator. If the same grade 3 AE recurs following the next administration of study drug, study treatment must be permanently discontinued. Subjects

experiencing grade 3 AEs requiring permanent discontinuation of study treatment should be followed closely for resolution of the AE to grade 1 or less and the team leadership must be notified.

For grade 4 events permanently discontinue therapy.

9.4 Serious Adverse Events

A SAE is defined as any AE that:

- Results in death.
- Is life threatening (the subject is at immediate risk of dying from the adverse experience).
- Requires subject hospitalization or prolongs existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse effect when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.5 Reporting of Serious Adverse Events (SAE) [For US Sites Only]

The Investigator is required to report all SAEs that occur during the time period specified in Section 9.4. Once the Investigator becomes aware of an SAE, he/she must report the SAE to Medical Monitor by telephone within 24 hours. In the event that the Medical Monitor is unavailable, the Investigator will notify the Project Manager listed on page 4 of the protocol.

Medical Monitor	Dan Piacquadio, M.D. Therapeutics, Inc. 9025 Balboa Ave., Suite 100 San Diego, CA 92123 U.S.A. Email: danp@therapeuticsinc.com Phone: +1 (619) 889-7058 Fax: +1 (858) 571-1234

The Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, electrocardiogram [ECG] reports, discharge summary, hospital notes, etc., if

applicable. Additional follow-up information as it becomes available must be reported to the Medical Monitor.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

9.6 SAE Follow-Up

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

9.7 Expected / Anticipated Events

Refer to the Investigator Brochure for expected/anticipated events.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Subjects will be identified on eCRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The local IRB, FDA, the monitors, auditors, and personnel authorized by the Sponsor are eligible to review the medical and research records related to this study as part of their responsibility to protect human subjects in clinical research. They will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy and each site will be required to ensure access while remaining compliant with institutional requirements.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring Requirements

The specific obligations outlined in 21 Code of Federal Regulations (CFR) and ICH guidelines require the Sponsor to maintain current personal knowledge of the progress of a study. Therefore, the Sponsor's designated monitor will visit the site during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical

records to ensure that data are being recorded adequately, that data are verifiable, and that protocol adherence is satisfactory.

As delineated above, the Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all eCRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the eCRF. In addition to the original medical records, these data may include but are not limited to study, laboratory reports, etc.

In accordance with federal regulations, site inspections will serve to verify strict adherence to the protocol and the accuracy of the data that is being entered on the case report forms. A Monitoring Log will be maintained at each study site. The Monitoring Log will be signed by the monitor, dated, and stated the type of visit. The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA or other regional regulatory authority.

11.2 Acceptability of Case Report Forms

For this study, electronic case report forms (eCRFs) will be used. For each subject who has signed an informed consent form, an eCRF must be completed. For subjects who are screen failures, this would be limited to the screen failure eCRF page. All source documents and eCRFs will be completed as soon as possible after the subject's visit and corrections to data on the eCRFs will be documented, if applicable. The Investigator will review the eCRFs to indicate that, to his/her knowledge, they are complete and accurate. eCRFs will be reviewed by the Sponsor’s or designated CRO’s monitor, who will decide as to their acceptability.

For eCRFs, validated 21 CFR Part 11 compliant electronic data capture (EDC) software will be used to collect data. When changes or corrections are made in the eCRF, the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change, and the reason for the change. Only individuals who have completed EDC training and are listed on the Delegation of Responsibilities Log with responsibility for eCRF completion will be provided usernames and passwords in order to access the system and make entries on the eCRF.

The investigator or physician sub-investigator must electronically sign and date each subject’s eCRF. Individuals who will be providing electronic signatures must first submit documentation

with a handwritten signature acknowledging that their electronic signature is a legally binding equivalent to their handwritten signature.

11.3 Modification of the Protocol

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator's IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary, to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the informed consent form. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor. An amendment must be in writing, and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

11.4 Reporting Protocol Deviations

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the CRFs.

11.4.1 Major Protocol Deviation or Violation

A major protocol deviation or violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or wellbeing and/or the completeness, accuracy, and reliability of the study data. Examples of this include:

- A research subject received the wrong treatment or incorrect dose.
- A research subject met withdrawal criteria during the study but was not withdrawn.
- A research subject received a prohibited concomitant medication.
- A research subject does not meet the protocol's eligibility criteria but was enrolled without prior approval from the sponsor.
- Failure to obtain informed consent prior to initiation of study-related procedures.

- Failure to treat research subjects per protocol procedures that specifically relate to primary study outcomes.
- Changing the protocol without prior sponsor and IRB approval.
- Multiple minor violations of the same nature after multiple warnings.

11.4.2 Minor Protocol Deviation or Violation

A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Examples of this include:

- Follow up visits that occurred outside the protocol required time frame because of the participant's schedule.
- Blood samples obtained at times close to but not precisely at the time points specified in the protocol.

12. DATA SAFETY MONITORING BOARD (DSMB)

This section is not applicable for this study.

13. ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, GCP, 21 CFR, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the subject's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research subject. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, the study product used in this study is manufactured, handled, and stored in accordance with applicable GMP. The study product provided for this study will be used only in accordance with this protocol.

13.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The Principal Investigator (PI) at each site will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the modification does not involve the subject's participation in the trial.

13.2 INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations. Information regarding to the study center participating in this study that cannot comply with these standards will be documented.

13.3 SUBJECT INFORMED CONSENT REQUIREMENTS

All subjects participating in this study will be given to by the Investigator and/or designee, written and oral information about the study in a language understandable by the subject. Written informed consent will be obtained from each subject prior any procedures or assessments that would not otherwise be required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written Informed Consent Form (ICF) will follow CFR 21 Part 50.27 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. The study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject's medical record, if allowed by institutional policy.

14. DATA HANDLING AND RECORD KEEPING

14.1 RECORDING AND COLLECTION OF DATA

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to approve eCRFs. The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and eCRFs will be completed as soon as possible after the subject's visit.

The Investigator will review the eCRFs to indicate that, to his/her knowledge, they are complete and accurate. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and eCRFs for each subject participating in the study.

All research data will be entered, either electronically or manually, into a computerized database. The clinical database will be designed by the clinical data manager in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor in association with the Lead Investigator.

The Investigator will maintain a confidential list of study subjects that will include each subject's study number, name, date of birth, and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the

subjects screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated subject number, if applicable.

14.2 CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor's or CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor's or the CRO's SOPs as well as provisions of the study-specific Data Management Plan.

14.3 ARCHIVING

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two (2) years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two (2) years after all investigations have been completed, terminated, or discontinued and the FDA has been notified.

These documents should be retained for a longer period however, if required by the applicable regulatory requirements or if needed by Sponsor or its authorized representative (as per GCP 5.5.11).

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time. Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study).
- Completed eCRFs.
- Signed protocols and protocol amendments.
- Laboratory results, ranges, and certifications.
- IP and accountability records.
- Study personnel signature log.
- Monitoring logs.
- Correspondence to and from the Sponsor, designee, and IRB.

- Investigator and sub-investigator CVs
- Signed informed consent and protected health information consent forms.
- Subject screening
- SAE reports
- IRB approval and re-approval letters.
- Completed quality of life questionnaire
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

Study records should not be transferred from site or destroyed without prior written agreement between the Sponsor and the study Investigator. Study records are subject to inspection by applicable health and regulatory agencies at any time.

15. PUBLICATION PLAN

All information supplied by Sirnaomics in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of Sirnaomics, shall not be disclosed to others without the written consent of Sirnaomics, and shall not be used except in the performance of this study.

It is understood by the Investigator that the Sponsor will use the information collected in this clinical trial in connection with the development of STP705. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities. By agreeing to participate in this clinical trial, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this trial.

Publication and Disclosure: Because this is a multi-center trial, the site and Investigator shall not independently publish, publicly disclose, present, or discuss any results of or information pertaining to the sites and Investigator's activities conducted under this protocol until such multi-center publication is released with the written approval and under the direction of Sponsor. Notwithstanding the foregoing, if a multi-center publication is not released within eighteen (18) months after completion of analysis of all study data from all studies conducted within the multi-center trial, both the site and Investigator shall have the right to publish the results of and information pertaining to the sites and Investigator's activities conducted under this protocol and

the clinical trial agreement, subject to the prior review and written approval of Sponsor. The site and Investigator agree to submit any proposed manuscript, presentation, or other public disclosure regarding the study to Sponsor for review at least thirty (30) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within thirty (30) days of its receipt, Sponsor shall advise the site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair Sponsor's ability to obtain patent protection. Sponsor shall have the right to require the site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation, or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. The site and Investigator shall not publish, publicly disclose, present, or discuss any results of or information pertaining to the sites and Investigator's activities prior to completion of the trial, even if the multi-center trial or the study is terminated before its completion and the final clinical study report is signed off, or with respect to any outcome measures or analyses other than those specified in this protocol.

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