An Open Label, Dose Escalation Study to Evaluate the Safety and Efficacy of Localized Injection of STP705 in Adult Patients with Basal Cell Carcinoma

Protocol Number:	**SRN-705-006**
Version:	**4.0**
Date:	**24-Aug-2022**

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PROTOCOL APPROVAL PAGE

Protocol Number:	**SRN-705-006**
Version:	**4.0**
Date:	**24-Aug-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.

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INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**SRN-705-006**
Version:	**4.0**
Date:	**24-Aug-2022**

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.

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PROTOCOL SYNOPSIS

Name of Sponsor/Company: Sirnaomics, Inc.	
Name of Study Product: STP705	
Protocol Number: SRN-705-006	**Indication:** Basal Cell Carcinoma
Title of Study: An Open Label, Dose Escalation Study to Evaluate the Safety and Efficacy of Localized Injection of STP705 in Adult Patients with Basal Cell Carcinoma	
Study Center(s): Up to 3 centers in the United States	
Planned Number of Subjects: Up to 35 subjects total	**Study Development Phase:** Phase 2

Objectives:

The purpose of this trial is to evaluate the safety, tolerability, and efficacy of various doses of STP705 administered as localized injection in subjects with Basal Cell Carcinoma (BCC)

Goals:

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

Outcome Measure:

Primary Outcome Measure:

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

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

Secondary Outcome Measure:

- Change in clinical diameter of the treated basal cell carcinoma lesion over the 6-week treatment period.

  A base line assessment of lesion clinical diameter *will be made by investigator at T1 (first visit). The change in size will be assessed every week until the surgical excision of BCC 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 localized administration of STP705 as assessed by investigator-evaluation of

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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 variables.

Trial Design:

This open label, dose escalation study is designed to evaluate the safety and efficacy of various doses of STP705 administered as localized injection in subjects with Basal Cell Carcinoma (BCC). Up to 35 subjects may be enrolled in seven (7) cohorts: 30, 60, 90, 120, 180, 240, and 320 μg dose level with five (5) evaluable subjects each. Subjects who withdraw consent or drop out after first visit will be replaced.

Participants in the first cohort will attend the study center once weekly for an injection of STP705 into the BCC lesion. The participants will receive injections of STP705 once a week for 6 weeks. The clinician will evaluate the change in tumor size at each treatment visit. At the End of Treatment visit, the residual tumor, or former tumor location, will be excised for analysis.

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.

Each cohort will be evaluated by the following criteria before the dose escalation and treatment begins with the next cohort:

(1) All study subjects in a given cohort (dose level) have been enrolled, and

(2) All such subjects have been followed for at least 3 weeks after the first injection, and

(3) The Sponsor's Medical Monitor has reviewed the available safety data (and has had the opportunity to discuss the data with the CRO's Medical Monitor and PI, if necessary), and recommends the next dose escalation.

(4) The PI has determined that none of the SAEs, or dose limiting toxicities outlined below, has occurred.

a. Death in any subject in which the cause of death is judged to be possibly, probably, or definitely related to STP705

b. The occurrence in any subject of an anaphylactic reaction to STP705

c. The occurrence in any subject of a severe local injection site reaction (grade 3 which is not resolved or recurs; or grade 4) that preclude administration of consecutive doses.

d. The occurrence, in any subject, of a life-threatening SAE whose causal relationship to STP705 is judged to be probable or definite

e. The occurrence of one or more non-life-threatening SAEs whose causal relationship to STP705 is judged to be definite

f. The occurrence, in one or more subjects, of grade 4 laboratory abnormalities, judged to be probably or

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definitely related to receipt of STP705

g. The occurrence of any new onset, systemic Grade ≥2 AE for cardiac and/or blood/bone marrow categories (or for subjects that enroll with Grade 2 findings then a 1-point increase to Grade 3 shall apply), or any systemic or non-systemic (local) non-hematological adverse events, judged to be possibly, probably or definitely related to receipt of 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.

If any of the SAEs or dose limiting toxicities outlined above has occurred, the Data and Safety Monitoring Board (DSMB) will conduct independent review of the data and will make a final decision for dose escalation to the next cohort.

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

Screening Period (up to 4 weeks):

Screening assessments will commence after obtaining signed informed consent, and will include review of medical and medication history, eligibility evaluation of Basal Cell Carcinoma, physical examination, vital signs, height and weight, concomitant medications, electrocardiogram (ECG), routine serum biochemical, hematologic, coagulation, urinalysis, serum pregnancy (if applicable), serologic testing for hepatitis B, hepatitis C, and HIV, baseline Local Skin Response (LSR Grading Scale), 2D photograph of lesion, measurement of longest diameter and area of lesion. These assessments must be conducted within 28 days of the Treatment Visit.

Treatment Period (6 weeks ± allowed windows):

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 treatment: review of any changes in medical and medication history, vital signs, weight measurement, symptom-directed physical examination, concomitant medications, ECG, routine serum biochemical, hematologic, urinalysis, urine pregnancy (if applicable), blood collected for Anti-Drug Antibody analysis, measurement of longest diameter and area of the lesion, and 2D digital imaging of the lesion, baseline Local Skin Response (LSR) Grading Scale assessment, and baseline pigmentation prior to dosing.

Eligible subjects will be enrolled and 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 are as follows:

Cohort A: STP705 30 μg dose, localized injection, given once a week for 6 weeks

Cohort B: STP705 60 μg dose, localized injection, given once a week for 6 weeks

Cohort C: STP705 90 μg dose, localized injection, given once a week for 6 weeks

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Cohort D: STP705 120 µg dose, localized injection, given once a week for 6 weeks

Cohort E: STP705 180 µg dose, localized injection, given once a week for 6 weeks

Cohort F: STP705 240 µg dose, localized injection, given once a week for 6 weeks

Cohort G: STP705 320 µg dose, localized injection, given once a week for 6 weeks

Schedule of Treatment visits

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

The study treatment STP705 will be administered by the licensed medical professional. Post-treatment pain assessment at the site of lesion (11-point Numeric Pain Rating Scale) will be evaluated within 15 minutes of the STP705 administration.

ECG will be performed before the first study drug administration at T1 and at EOT during the treatment phase.

Vital signs will be assessed before the injection, and within 15 minutes after the injection.

The End of Treatment (EOT) visit will be performed 7 (±3) Days after the T6 visit. The surgical excision at the site of treated BCC lesion will be performed at the EOT visit. The excised specimens will be assessed for the histological clearance of lesion.

Adverse events and medications will be monitored throughout the study.

Follow Up Period (2 and 4 weeks after EOT± allowed windows)

There will be Follow Up Visits at 2 weeks (FU1) and 4 weeks (FU2) after the excision of the lesion. The following assessments will be performed at FU1 and FU2 visit: 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 routine serum biochemical, hematologic, and urine laboratory assessments (FU2 only).

Duration of Treatment:

- **Screening Period:** Up to 4 Weeks

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- **Treatment Period:** 6 Weeks (± allowed windows) including EOT excision.
- **Follow-Up Phase:** 4 Weeks (± allowed windows)

Total Study Duration: Up to 14 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 trunk or extremity (non-peri-orbital/-anogenital/-facial/-scalp) basal cell carcinoma lesion suitable for excision with a minimum diameter of 0.5 cm and with a maximum diameter of 2.0 cm.
3. Histological diagnosis made no more than 6 months prior to the screening visit.
4. Histological biopsy removed ≤25% of the original volume of the target lesion.
5. No other dermatological disease in the BCC target site or surrounding area, which in the opinion of the investigator, could interfere with the study.
6. Willing to refrain from using non-approved lotions or creams on the target site and surrounding area during the treatment period.
7. 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.
8. Laboratory values for the tests (listed in the Study Schedule) within the reference ranges as defined by the central laboratory, or “out of range” test results that is clinically acceptable to the investigator. 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 BCC lesion to be used as part of the study data and documentation.
11. For females of childbearing potential, a negative pregnancy test at screening and using an acceptable form of birth control (oral / implant/ injectable/ transdermal contraceptives, intrauterine device, condom, diaphragm, abstinence, or a monogamous relationship with a partner who has had a vasectomy).

EXCLUSION CRITERIA

1. Pregnant or lactating.
2. Presence of known or suspected systemic cancer.

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3. Histological evidence of SCC, or any other non-BCC tumor in the biopsy specimen.
4. Histological evidence of infiltrative or other aggressive histological subtype growth patterns in the biopsy specimen.
5. History of recurrence of the target BCC lesion.
6. Evidence of dermatological disease or confounding skin condition with in 2 cm margin of the target BCC lesion, e.g., SCC, actinic keratosis, rosacea, psoriasis, atopic dermatitis, eczema, xeroderma pigmentosa.
7. Concurrent disease or treatment that suppresses the immune system;
8. Patients with baseline QTC > 480 msec using Frederica's formula.
9. 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.
10. Known sensitivity to any of the ingredients in the study medication.
11. Use of a tanning beds or other excessive or prolonged exposure to ultraviolet light or direct sunlight during the study.
12. Treatment with systemic chemotherapeutic agents within the 6 months prior to the screening visit.
13. Use of systemic retinoids within the 6 months prior to the screening period.
14. Treatment with systemic immunomodulators or immunosuppressants within the 6 months prior to the screening period.
15. Use of topical immunomodulators within 2 cm of the target BCC lesion within the 4 weeks prior to the screening period.
16. Treatment with the following topical agents within 2 cm of the target BCC lesion within the 4 weeks prior to the screening visit: amino-levulinic acid, 5-fluorouracil, corticosteroids, retinoids, diclofenac, ingenol mebutate, or imiquimod.
17. Treatment with liquid nitrogen, surgical excision (excluding diagnostic incisional biopsy) or curettage within 2 cm of the target BCC lesion during the 4 weeks prior to the screening visit.
18. Evidence of current chronic alcohol or drug abuse.
19. Current enrollment in an investigational drug or device study or participation in such a study within 4 weeks of the screening visit.
20. In the investigator's opinion, evidence of unwillingness, or inability to follow the restrictions and requirements of the protocol and complete the study.
21. Taking any other investigational product within 1 month of first dose of STP705.

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Statistical Considerations:

Sample Size Determination and Rationale:

The sample size calculation is based on clinical judgment. No statistical power calculation is used to establish the sample size.

Analysis Populations:

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.

The **Per Protocol (PP) population** is defined as the set of subjects who meet the ITT population requirements and were not associated with a major protocol violation. This population will be identified before the database lock.

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

Safety Evaluations:

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.

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCC	Basal Cell Carcinoma
BUN	Blood Urea Nitrogen
°C	Celsius
CFR	Code of Federal Regulations
COX	Cyclooxygenase
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
DDP	Cisplatin, Platinol
DLT	Dose Limiting Toxicities
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EOT	End of Treatment
°F	Fahrenheit
FDA	U.S. Food and Drug Administration
FUV	Follow-up Visit
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transpeptidase
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface Antigen
HC	Histological Clearance
HCV	Hepatitis C Virus
HEENT	Head, Ears, Eyes, Nose, and Throat
HIPAA	Health Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus

Abbreviation	Term
HKP	Histidine-Lysine Polypeptide
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
isSCC	*in situ* Squamous Cell Carcinoma
ITT	Intent-to-Treat
IV	Intravenous
LAR	Legally Authorized Representative
LSR	Local Skin Response
MAP	Mitogen-Activated Protein
MedDRA	Medical Dictionary for Regulatory Activities
MMS	Mohs Micrographic Surgery
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PTGS	Prostaglandin-Endoperoxide Synthase
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SOP	Standard Operating Procedure
SV	Screening Visit
TEAE	Treatment Emergent Adverse Event
TV	Treatment Visit
UV	Ultraviolet

1 INTRODUCTION AND BACKGROUND

1.1 STATEMENT OF INTENT

The design, conduct, and reporting of this study shall be conducted in compliance with the protocol, International Council 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 the most common form of cancer in the US with 3.5 million people diagnosed (American Cancer Society, 2015). NMSC is a growing public health problem due to its increasing incidence and medical care costs (Feehan, 2016). NMSC consists of two major subtypes: (i) basal cell carcinoma (BCC) and (ii) squamous cell carcinoma (SCC).

The incidence of non-melanoma skin cancers increases with advancing age (Christenson, 2005; Ley, 1993). Individuals with a suppressed immune system are also at increased risk for non-melanoma skin cancers (Athar, 2011). The rising incidence and morbidity of non-melanoma skin cancers has generated great interest in unravelling of their pathogenesis and in the search for new non-invasive treatments. Whereas the role of cumulative sun exposure in pathogenesis of squamous-cell carcinoma seems clear, the relation between sun-exposure patterns and subtypes of basal-cell carcinoma remains undetermined. Several complex genotypic, phenotypic, and environmental factors contribute to pathogenesis of non-melanoma skin cancers. (Madan, 2010)

Diagnosis of non-melanoma skin cancer is made clinically and confirmed by histological testing. Prognosis depends on lesion and host characteristics, which also dictate choice of treatment. Prevention strategies aim at reduction of sun exposure, but are of unproven benefit, especially for basal-cell carcinoma. Surgical excision with predetermined margins is the mainstay of treatment for squamous-cell carcinoma and for most basal-cell carcinomas. Of the new non-invasive treatments, only photodynamic therapy and topical imiquimod have become established treatments for specific superficial subtypes of basal-cell carcinoma, and the search for more effective and tissue-salvaging therapies continues. (Madan, 2010)

Development of primary malignancies in the skin including basal cell carcinoma (BCC) 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, 2018; Dotto, 2016).

Basal cell carcinoma occurs most often on areas of the skin that are exposed to the sun, such as head and neck. The most commonly found clinical feature of BCC is an elevated tumor with a pearly and translucent margin and telangiectasia. The color may vary widely from nearly normal skin color to erythematous to violaceous and may also be pigmented. BCC may also resemble

noncancerous skin conditions such as eczema or psoriasis. The majority of these cancers occur on areas of skin that are regularly exposed to sunlight or other ultraviolet radiation.

1.3 CURRENT TREATMENT OPTIONS

The gold standard of treatment for high-risk NMSC is surgical excision including Mohs micrographic surgery (MMS) when appropriate (Abramson, 2013; Stewart, 2014). Some of the non-surgical treatment options are pharmacotherapy, cryotherapy, photodynamic therapy, laser and radiotherapy (Lv, 2017). Though these treatments provide less invasive options for the patients, there is evidence in the literature that demonstrate that current non-surgical treatments are not as effective for curing the NMSC (Gracia-Cazana, 2016).

The 5-year recurrence rates for primary (previously untreated) BCCs by various modalities including surgical excision, curettage and electrodessication, and Mohs micrographic surgery is approximately 3.5%. (Chren, 2013). Recurrences usually occur 4 to 12 months after initial treatment, and the risk of developing a second lesion in 3 years is about 44%, which is a 10-fold increase over that of the general population (Marcil, 2000; Levi, 2006) . Tumors on the nose or T-zone of the face have a higher incidence of recurrence. Recurrence is most common on the nose and nasolabial fold. Infiltrative, micro, and multifocal types have higher rates of recurrence than types. Basal cell carcinoma rarely metastasizes (0.028% to 0.55%). The most common sites of metastasis are the lymph nodes, lungs, and bones.

1.4 ROLE OF TGF-B1 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 (Caestecker, 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, 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 heterotetrameric complex resulting in phosphorylation and activation of the cytoplasmic domain of TβRI by TβRII kinase (Ikushima, 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 elements, other suppressive elements, or through interaction with other transcription factors (Massague, 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 (Kushima, 2010).

Studies have shown that an increase in TGF-β1 expression is reported in human cutaneous SCC (Han, 2005) tissues. TGF-β1overexpression promotes tumor progression, metastasis, and epithelial-mesenchymal transition at the later stages of skin carcinogenesis (Li, 2005). The tumor promotion role is associated with its effect on the loss of epithelial cell adhesion, extracellular

matrix remodeling, and enhanced angiogenesis (Weeks, 2001). Additionally, current data suggests, that TGF-β1overexpression 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, 2005). A study analyzing BCC tissues samples from 24 patients reported that the lesional 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, 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, 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, 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, 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, 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 (Lu, 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 as act a proliferative factor for malignant cells by promoting the synthesis of prostaglandin E2 (PGE2) (Craig, 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, 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 (Craig, 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 into surrounding tissues and metastasize (Craig, 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 (Lu, 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) (Craig, 2010). There is also evidence from epidemiological studies that COX-inhibitors are associated with decreased risk of cutaneous SCCs (Butler, 2005; Grau, 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 papillomas and SCC (An, 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 (Tjiu, 2006). Overall, the positive correlation with COX-2 overexpression and NMSC renders it as an attractive therapeutic target.

1.6 PRE-CLINICAL STUDIES

1.6.1 Effect of STP705 on Human Cutaneous Squamous Carcinoma Cell Viability In Vitro

An *in vitro* study 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 reported an average cell viability of 53% (at 200nM) and cells transfected with siRNA for COX-2 reported 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 reported 32% cell viability. Figure 1-2 demonstrates that HSC-1 cells transfected with STP705 reported, at 72 hours post-transfection, 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

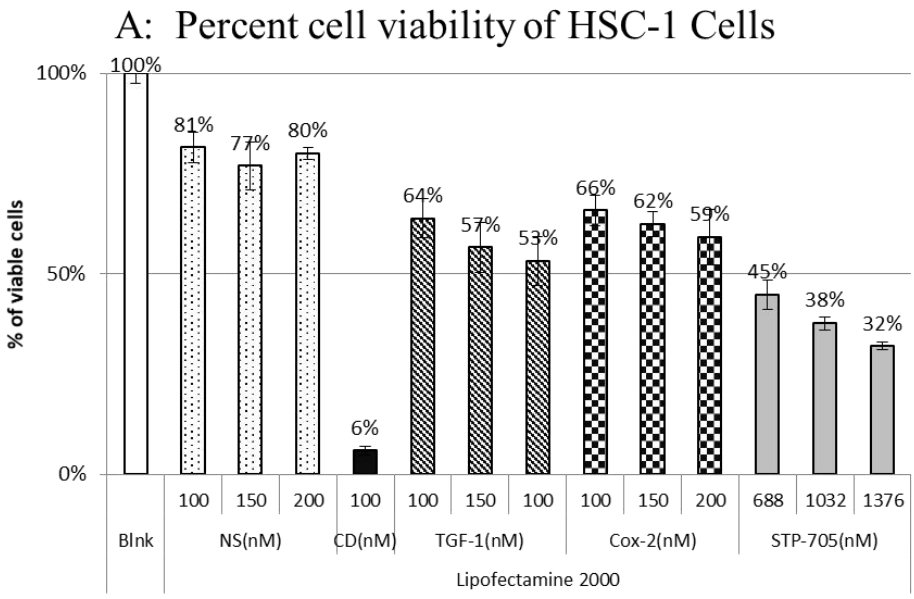


Figure 1- 1 illustrates the cell viability at 72 hours after transfection with CellTiter-Glo assay. Values are presented as percentage of non-transfected control ± standard deviation of four replicates. NS = non-silencing siRNA (QIAGEN); CD = Cell Death siRNA (QIAGEN).

Figure 1- 2: Dose-dependent Percent Cell Viability

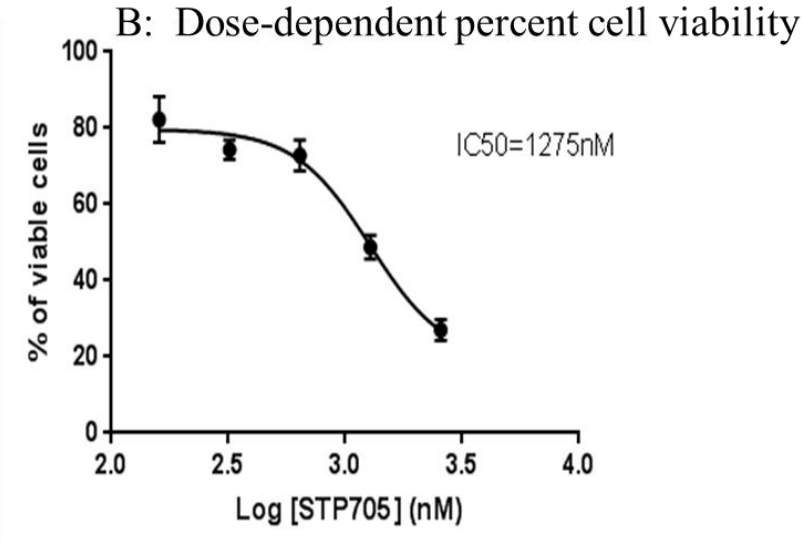


Figure 1- 2 illustrates the IC50 of STP705 on cell viability of HSC-1 cells at 72 hours post-transfection.

1.6.2 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).

Table 1- 1 : 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;

**Intratumor 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. Intratumor 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 reported no loss of body weight, or changes between the STP705-treated and control groups during the course of the study. However, there was reported loss of weight in the DDP-treated group at 11-, 13- and 15-days post-treatment as compared to the STP705-treated and control groups.

Figure 1-3: Body Weight Curve

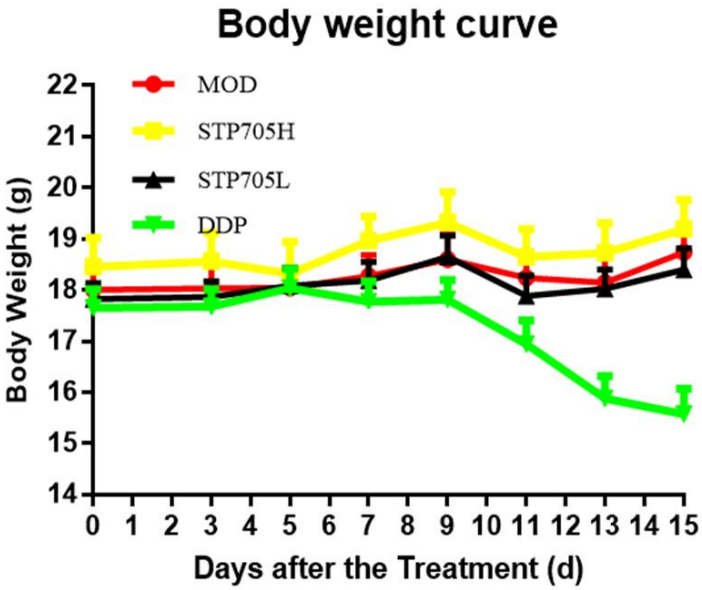


Figure 1-3 demonstrates the mean body weight of animals in control, STP705-high dose, STP705-low dose and DDP groups. There was no difference in body weight of animals between control (MOD) and STP705-treated groups. DDP group reported a drop in body weight at 11-, 13- and 15-days post-treatment.

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 1-2 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 1-2: 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 1-3 demonstrates that at 11-days post-treatment, the low dose of STP705 (STP705-L) treated animals achieved comparable tumor growth inhibition index and ratio of tumor volume reported by DDP-treated animals at 15-days post-treatment.

Table 1-3: 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).

Figure 1-4. Average tumor weight. STP705-H (p=0.004), STP705-L (p=0.012) and DDP-treated (p=0.026) groups reported significantly lower tumor weight as compared to the control group. This indicates that STP705-treatment inhibits tumor growth.

Figure 1-4: Tumor Weight

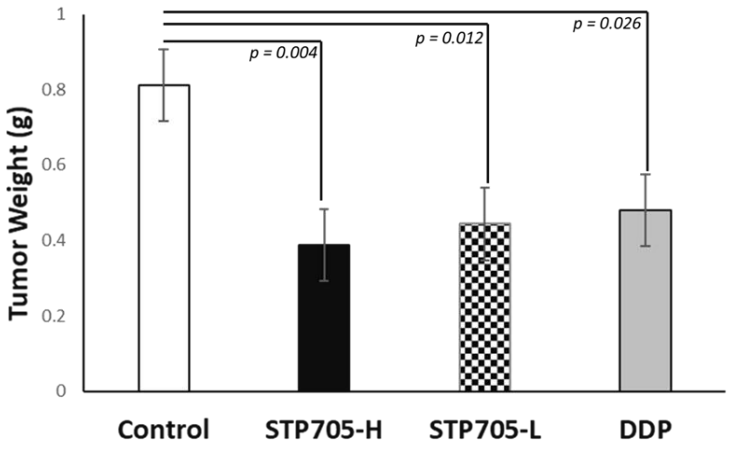


Figure 1-4 demonstrates the mean tumor weight (± standard error) of STP705-H, STP705-L, DDP, and control animals at day-15 post-treatment in A431 xenograft mouse tumor model. Animals treated with STP705 and DDP reported significantly lower tumor weights (indicative of reduced tumor growth) as compared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

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 reported that STP705-low and high dose groups were able to significantly inhibit tumor growth at 13- and 15-days post-treatment. 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 by STP705-treatmet as compared to the control.

Tumor growth inhibition index, ratio of tumor volume (V/C) and slope of tumor growth analyses suggested that STP705-low dose treatment accelerated the inhibition of tumor growth as compared to DDP-treatment. 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.

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.

1.7 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 injection in subjects with linear hypertrophic scar.

Twenty-four subjects were planned to be 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 was planned to receive 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 intradermal every 1 cm length on the hypertrophic scar.

The study entry criteria requiring subjects to have had the hypertrophic scar that meet all of the following criteria:

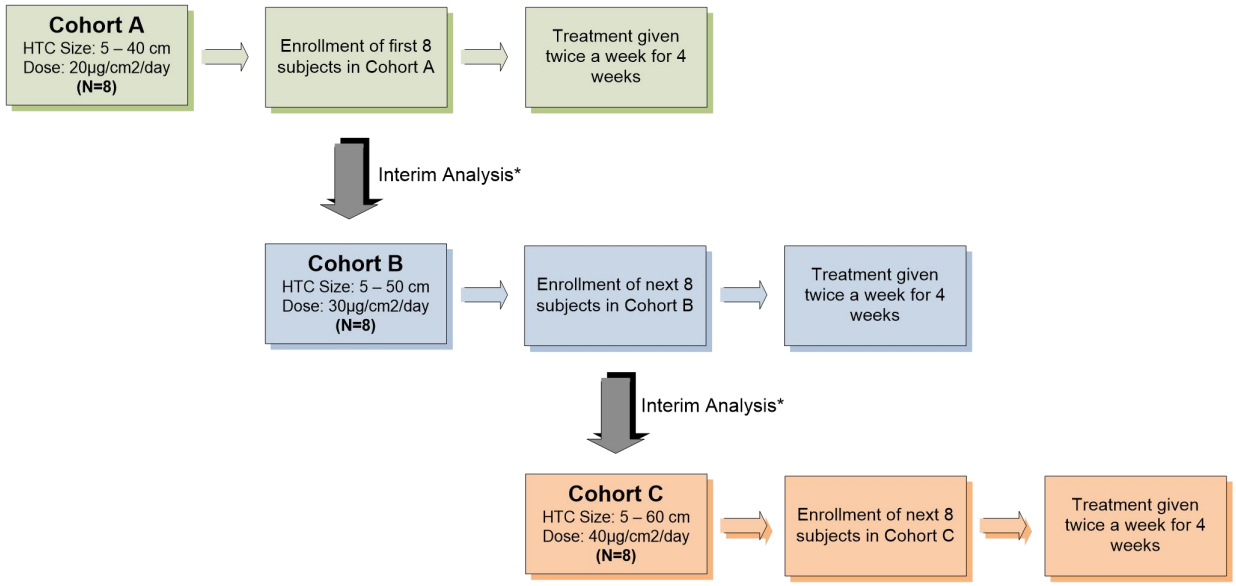
- linear scar, ≥5 to ≤40 cm in length (Cohort A), ≥5 to ≤50 cm in length (Cohort B), ≥5 to ≤60 cm in length (Cohort C)
- present for minimum 6 months and no greater than 24 months
- located anywhere in the body except on the face or front of neck
- resulting from surgical or traumatic injury

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

Under Cohort A, eight subjects have been 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 treatment 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 have 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 have been no clinically significant findings reported in physical examination or electrocardiogram results.

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.

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

- 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 with histological clearance of treated isSCC lesion at the End of Treatment (EOT). Three (3) subjects (60%, 3/5) in both the 10 μg and 20 μg treated groups achieved histological clearance of lesion. In the 30-μg treated group, four (4) subjects (80.0%, 4/5) achieved histological clearance of lesion. The final efficacy data analysis is pending for subjects enrolled under Cohort D (60 μg) and E (120 μg).

Treatment completed under 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 have been no serious adverse events or deaths reported in this study.

1.8 Risks / Benefits Assessment

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

- Single dose acute toxicity studies on 60 mice and 8 cynomolgus monkeys
- Repeat doses toxicity studies on 300 mouse and 40 cynomolgus monkeys
- Skin Sensitization using Guinea pig intact skin model
- Bioavailability (BA) and Bio-distribution (BD) using miniature pigs
- Irritations at Injection Site using 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.

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

***In Vivo* Results**

The objective of the A431 xenograft mouse tumor model study was to demonstrate the efficacy of STP705 on tumor suppression. 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 reported that STP705-low and high dose groups were able to significantly inhibit tumor growth at 13- and 15-days post-treatment.
3. 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 by STP705-treatmet as compared to the control.
4. Tumor growth inhibition index, ratio of tumor volume (V/C), and slope of tumor growth analyses suggested that STP705-low dose treatment accelerated the inhibition of tumor growth as compared to DDP-treatment (Cisplatin).
5. 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, Sirnaomics has 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.

1.8.1 Risks/Discomfort to Subjects and Precautions to Minimize Risk

1.8.1.1 Localized Injection for STP705 Administration

Localized injection for STP705 administration carries a risk of low-grade fever, local injection site reaction (pain, tenderness, erythema/redness, induration/swelling), discomfort and 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 STP705 administration is allowed as per discretion of the Investigator.

A cold pack may be applied to affected areas for up to 15 minutes up to 3 times daily to manage local site reactions. 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 local reaction is deemed moderate or severe by PI. For subjects who develop severe reaction (grade 3) 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.

1.8.1.2 Local Skin Reaction

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

1.8.1.3 Allergic Reaction

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

1.8.1.4 Immune Response

Subjects who used STP705 can also develop an immune response to STP705. In general, for the oligonucleotides, the formation of anti-drug antibodies has been shown to not impact efficacy.

1.8.1.5 Pregnancy

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

1.8.1.6 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.

1.8.1.7 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.

1.9 TREATMENT RATIONALE FOR THIS STUDY

Non-Melanoma Skin Cancer (NMSC) is the most common form of cancer in the US with 3.5 million people diagnosed (American Cancer Society, 2015). NMSC is a growing public health problem due to its increasing incidence and medical care costs (Feehan, 2016).

The gold standard of treatment for high-risk NMSC is Mohs micrographic surgery (MMS) when appropriate (Abamson, 2013; Stewart, 2014). Occasionally, surgery renders patients with the risk of infection, hematoma, and scar development. Surgery is usually not a treatment option for immunocompromised patients including those who have had organ transplants. Some of the non-surgical treatment options are pharmacotherapy, cryotherapy, photodynamic therapy, laser and radiotherapy (Lv, 2017; Gracia-Cazana, 2016).

Development of primary malignancies in the skin including basal cell carcinoma (BCC) is linked closely to genomic perturbations, genetic mutations (e.g., p53 gene mutation), and altered expression of key molecules, in particular, overexpression of TGF-β1 and COX-2. Overexpression of TGF-β1 and COX-2 impacts squamous cell lineage commitment and terminal differentiation (Howell, 2018; Dotto, 2016).

TGF-β1 and COX-2 have been well characterized in playing a major role in the progression of tumorigenesis of NMSC (both basal cell carcinomas and SCCs). The literature has reported several studies with NMSC patients having overexpression of TGF-β1 and COX-2 in the lesional tissues.

The STP705 drug substance is composed of two siRNA oligonucleotides, targeting the expression of 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 dry powder drug product.

The histidine-lysine polypeptide(HKP)-enhanced delivery of TGF-β1 and COX-2 specific siRNA combination is expected to downregulate TGF-β1 and COX-2 expression resulting in the inhibition of tumor growth and providing an alternative non-invasive approach for the treatment of basal cell carcinoma.

Pre-clinical *in vivo* studies have demonstrated 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. These studies demonstrate the following:

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 reported that STP705-low and high dose groups were able to significantly inhibit tumor growth at 13- and 15-days post-treatment.
3. 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 by STP705-treatmet as compared to the control.

4. Tumor growth inhibition index, ratio of tumor volume (V/C), and slope of tumor growth analyses suggested that STP705-low dose treatment accelerated the inhibition of tumor growth as compared to DDP-treatment (Cisplatin).
5. 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 conclude that the synergistic effect of simultaneous silencing of TGF-β1 and COX-2 may act to eliminate isSCCs through down regulation of immunosuppression and through increased apoptosis.

Figure 1- 6: Proposed Mode of Action – Hypothesis for STP705-Mediated Anti-Tumor Activities

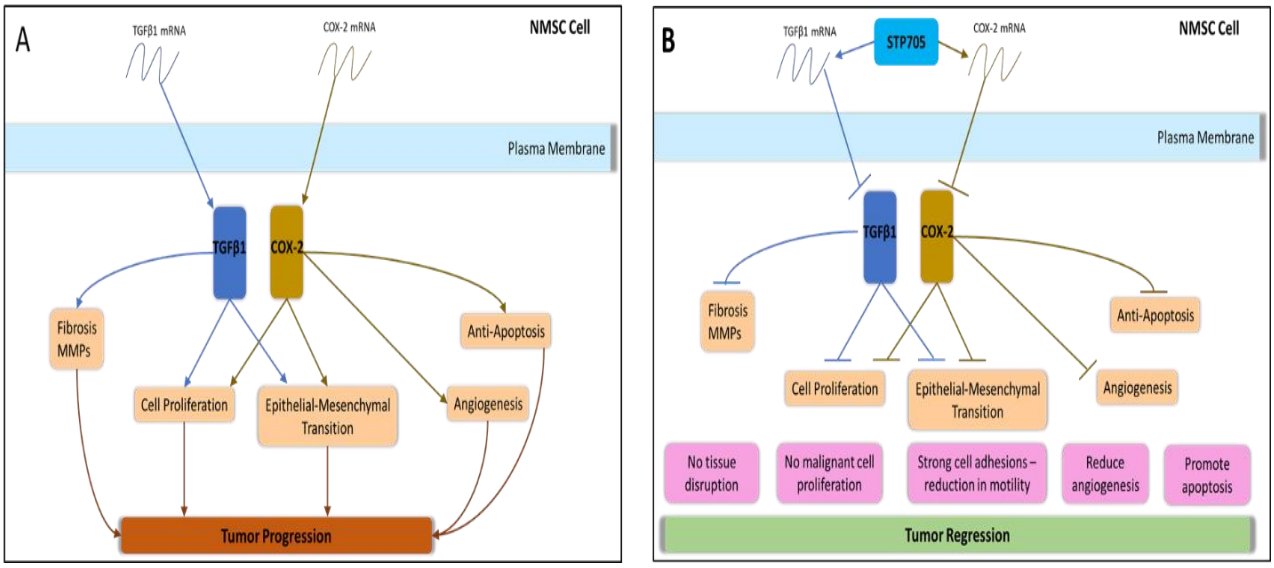


Figure 1- 6 demonstrates the hypothesized mode of action of STP705, a combination therapy containing siRNA for TGF-β1 and COX-2. (A) Outlines the proposed mechanism of TGF-β1 and COX-2, in NMSC cells, that induces tumor progression by promoting tissue disruption, cell proliferation, epithelial-mesenchymal 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 proposes 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 use potential, 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 intratumor 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.

1.9.1 Rationale for IP [Dose] Selection

Pre-clinical studies using the human squamous cell carcinoma cell line A431 in a xenograft mouse tumor model established that intratumoral injections with low dose (20ug) and high dose (40ug) of STP705 were effective in reducing the growth of the tumor as compared to controls.

Nude mice bearing A431 xenograft tumors were treated with either a low dose (20ug) or high dose (40ug) of STP705 solution by direct injection into the A431 tumor every two days (total 7 administrations). The results demonstrated that the low dose STP705 (STP705-L) treated animals reported significant reduction in tumor volume at 9-, 11-, 13- and 15-days post-treatment as compared to the control animals and compared to the active comparator, DDP (Cisplatin). STP705-H treated animals reported significant reduction in tumor volume at 13- and 15-days post-treatment as compared to the control animals and the active comparator, DDP (Cisplatin).

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

Based on the safety profile review for 10 μg, 20 μg, 30 μg, 60 μg, and 120 μg doses of STP705 (intralesional injections) in a recently completed isSCC study, STP705 is well-tolerated and no dose limiting toxicities (DLT) or serious adverse events were reported. In order to determine the optimal dose for treating patients with BCC, this study proposes an open-label, dose-escalation trial using 30 μg, 60 μg, 90 μg, 120 μg, 180 μg, 240 μg, and 320 μg doses of STP705 for intralesional injection. The dose escalation will be based on review of STP705 safety profile in the previous dosing cohorts. In addition, the starting clinical dose includes a 7-day interval between administrations to minimize the possibility of local irritations.

2 STUDY OBJECTIVES

The primary objective of this study is to evaluate the safety, tolerability, and efficacy of various doses of STP705 administered as localized injection in subjects with basal cell carcinoma (BCC). This study seeks to establish a safe and effective recommended dose of STP705 for the treatment of BCC. Expression of biomarkers common to the BCC formation pathway, including TGF-β1 and COX-2, will be evaluated.

The primary outcome measure will be the proportion of participants with histological clearance of treated basal cell carcinoma lesion at the End of Treatment (EOT). Histological clearance (HC) will be defined as the absence of detectable evidence of BCC tumor cell nests as determined by central pathology review.

Secondary outcome measure will be the change in size of the treated basal cell carcinoma lesion over the 6-week treatment period.

Safety and tolerability will be assessed by the number of incidence of adverse events (AEs) and serious adverse events (SAEs); the incidence of AEs and SAEs leading to discontinuation of trial medication; the incidence and severity of Local Skin Response (LSR); hypopigmentation and hyperpigmentation following treatment; and the tolerability of repeated localized 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 variables.

3 STUDY DESIGN

This open label, dose escalation study is designed to evaluate the safety and efficacy of various doses of STP705 administered as localized injection in subjects with basal cell carcinoma. Up to 35 subjects may be enrolled; seven (7) cohorts (30, 60, 90, 120, 180, 240, and 320 μg dose level) will be evaluated with each cohort enrolling five (5) evaluable subjects each. Subjects who withdraw consent or drop out after first visit will be replaced.

Participants in the first cohort will attend the study center once weekly for an injection of STP705 into the basal cell carcinoma lesion. The participants will receive injections of STP705 once a week for 6 weeks. The clinician will evaluate the change in tumor size (measurement of longest diameter and area of the lesion) at each treatment visit. At the End of Treatment visit, the residual tumor, or former tumor location will be excised for analysis.

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.

Each cohort will be evaluated by the following criteria before the dose escalation and treatment begins with the next cohort:

(1) All study subjects in a given cohort (dose level) have been enrolled, and

(2) All such subjects have been followed for at least 3 weeks after the first injection, and

(3) The Sponsor's Medical Monitor has reviewed the available safety data (and has had the opportunity to discuss the data with the CRO's Medical Monitor and PI, if necessary), and recommends the next dose escalation.

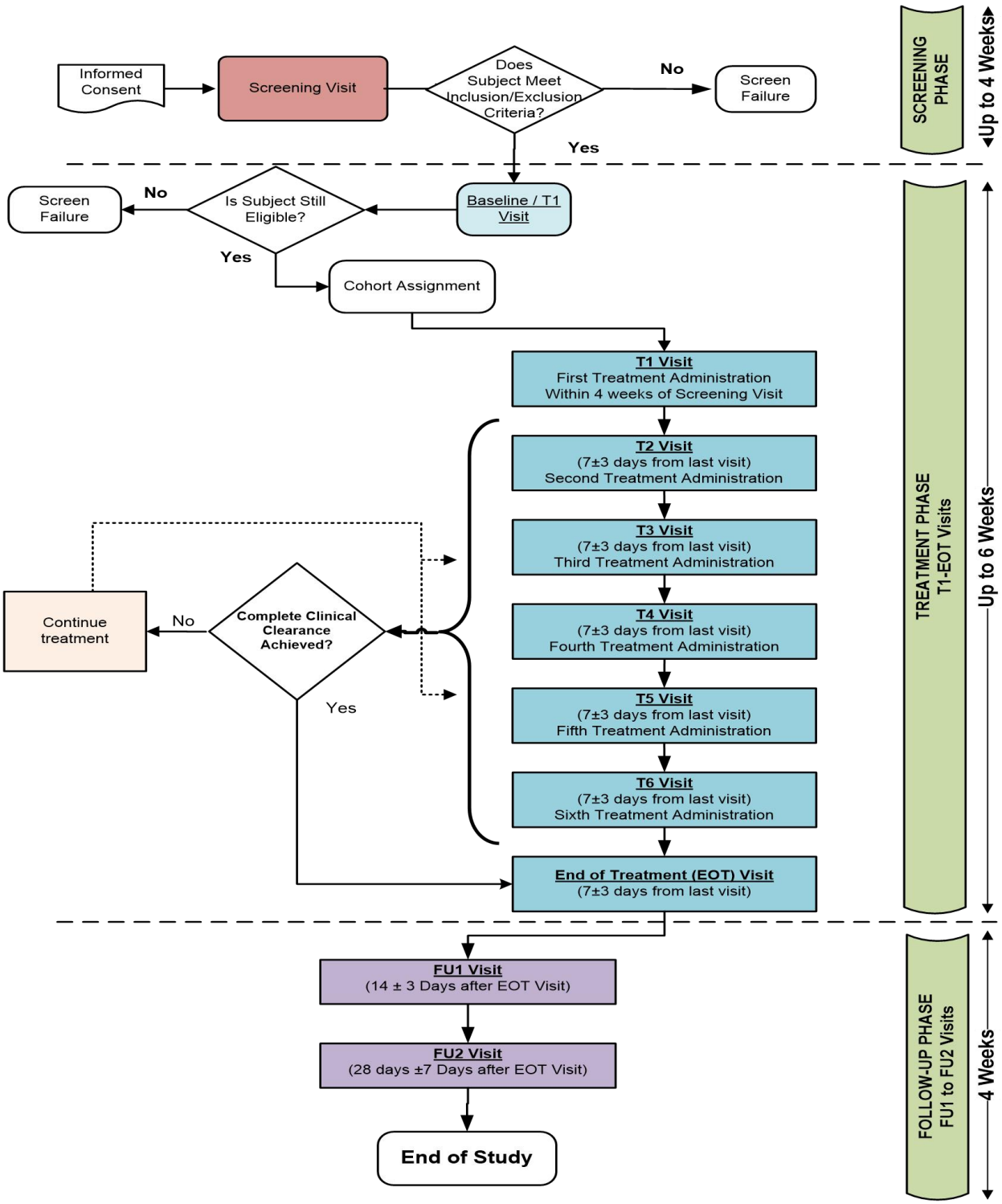
(4) The PI has determined that none of the SAEs, or dose limiting toxicities outlined below, has occurred.

a. Death in any subject in which the cause of death is judged to be possibly, probably, or definitely related to STP705
b. The occurrence in any subject of an anaphylactic reaction to STP705
c. The occurrence in any subject of a severe local injection site reaction (grade 3 which is not resolved or recurs; or grade 4) that preclude administration of consecutive doses.
d. The occurrence, in any subject, of a life-threatening SAE whose causal relationship to STP705 is judged to be probable or definite
e. The occurrence of one or more non-life-threatening SAEs whose causal relationship to STP705 is judged to be definite
f. The occurrence, in one or more subjects, of grade 4 laboratory abnormalities, judged to be probably or definitely related to receipt of STP705

g. The occurrence of any new onset, systemic Grade ≥2 AE for cardiac and/or blood/bone marrow categories (or for subjects that enroll with Grade 2 findings then a 1-point increase to Grade 3 shall apply), or any systemic or non-systemic (local) non-hematological adverse events, judged to be possibly, probably or definitely related to receipt of 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.

If any of the SAEs or dose limiting toxicities outlined above has occurred, the Data and Safety Monitoring Board (DSMB) will conduct independent review of the data and will make a final decision for dose escalation to the next cohort.

Figure 3- 1: Study Schematics



3.1 STUDY CENTERS

Up to 3 centers in the United States will be used for this study.

3.2 STUDY POPULATION

Up to 35 subjects will be enrolled in this study.

3.3 ELIGIBILITY CRITERIA

3.3.1 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 trunk or extremity (non-peri-orbital/-anogenital/-facial/-scalp) basal cell carcinoma lesion suitable for excision with a minimum diameter of 0.5cm and with a maximum diameter of 2.0cm.
3. Histological diagnosis made no more than 6 months prior to the screening visit.
4. Histological biopsy removed ≤25% of the original volume of the target lesion.
5. No other dermatological disease in the BCC target site or surrounding area, which in the opinion of the investigator, could interfere with the study.
6. Willing to refrain from using non-approved lotions or creams on the target site and surrounding area during the treatment period.
7. 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.
8. Laboratory values for the tests (listed in the Study Schedule) within the reference ranges as defined by the central laboratory, or "out of range" test results that is clinically acceptable to the investigator. 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 BCC lesion to be used as part of the study data and documentation.
11. For females of childbearing potential, a negative pregnancy test at screening and using an acceptable form of birth control (oral / implant/ injectable/ transdermal contraceptives, intrauterine device, condom, diaphragm, abstinence, or a monogamous relationship with a partner who has had a vasectomy).

3.3.2 Exclusion Criteria

1. Pregnant or lactating.
2. Presence of known or suspected systemic cancer.
3. Histological evidence of SCC, or any other non-BCC tumor in the biopsy specimen.
4. Histological evidence of infiltrative or other aggressive histological subtype growth patterns in the biopsy specimen.
5. History of recurrence of the target BCC lesion.
6. Evidence of dermatological disease or confounding skin condition with in 2 cm margin of the target BCC lesion, e.g., SCC, actinic keratosis, rosacea, psoriasis, atopic dermatitis, eczema, xeroderma pigmentosa.
7. Concurrent disease or treatment that suppresses the immune system;
8. Patients with baseline QTC > 480 msec using Frederica's formula.
9. 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.
10. Known sensitivity to any of the ingredients in the study medication.
11. Use of a tanning beds or other excessive or prolonged exposure to ultraviolet light or direct sunlight during the study.
12. Treatment with systemic chemotherapeutic agents within the 6 months prior to the screening visit.
13. Use of systemic retinoids within the 6 months prior to the screening period.
14. Treatment with systemic immunomodulators or immunosuppressants within the 6 months prior to the screening period.
15. Use of topical immunomodulators within 2 cm of the target BCC lesion within the 4 weeks prior to the screening period.
16. Treatment with the following topical agents within 2 cm of the target BCC lesion within the 4 weeks prior to the screening visit: amino-levulinic acid, 5-fluorouracil, corticosteroids, retinoids, diclofenac, hyaluronic acid or imiquimod.
17. Treatment with liquid nitrogen, surgical excision (excluding diagnostic incisional biopsy) or curettage within 2 cm of the target BCC lesion during the 4 weeks prior to the screening visit.
18. Evidence of current chronic alcohol or drug abuse.
19. Current enrollment in an investigational drug or device study or participation in such a study within 4 weeks of the screening visit.

20. In the investigator's opinion, evidence of unwillingness, or inability to follow the restrictions and requirements of the protocol and complete the study.
21. Taking any investigational product within 1 month of first dose of STP705.

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4 STUDY SCHEDULE

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

4.1.1 Screening Period (up to 4 weeks):

Screening assessments will commence after obtaining signed informed consent, and will include review of medical and medication history, eligibility evaluation of Basal Cell Carcinoma, physical examination, vital signs, height and weight, concomitant medications, electrocardiogram (ECG), routine serum biochemical, hematologic, coagulation, urinalysis, serum pregnancy (if applicable), serologic testing for hepatitis B, hepatitis C, and HIV, baseline Local Skin Response (LSR Grading Scale), 2D photograph of lesion, measurement of longest diameter and area of lesion. These assessments must be conducted within 28 days of the Treatment Visit.

4.1.2 Treatment Period (6 weeks ± allowed windows):

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 treatment: review of any changes in medical and medication history, vital signs, weight measurement, symptom-directed physical examination, concomitant medications, ECG, routine serum biochemical, hematologic, , urinalysis, urine pregnancy (if applicable), blood collected for Anti-Drug Antibody analysis, measurement of longest diameter and area of the lesion, and 2D digital imaging of the lesion, baseline Local Skin Response (LSR) Grading Scale assessment, and baseline pigmentation prior to dosing.

Eligible subjects will be enrolled and 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 are as follows:

Cohort A: STP705 30 µg dose, localized injection, given once a week for 6 weeks

Cohort B: STP705 60 µg dose, localized injection, given once a week for 6 weeks

Cohort C: STP705 90 µg dose, localized injection, given once a week for 6 weeks

Cohort D: STP705 120 µg dose, localized injection, given once a week for 6 weeks

Cohort E: STP705 180 µg dose, localized injection, given once a week for 6 weeks

Cohort F: STP705 240 µg dose, localized injection, given once a week for 6 weeks

Cohort G: STP705 320 µg dose, localized injection, given once a week for 6 weeks

Schedule of Treatment Visits

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

The study treatment STP705 will be administered by the licensed medical professional. Post-treatment pain assessment at the site of lesion (11-point Numeric Pain Rating Scale) will be evaluated within 15 minutes of the STP705 administration.

ECG will be performed before the first study drug administration at T1 and at EOT during the treatment phase.

Vital signs will be assessed before the injection, and within 15 minutes after the injection.

The End of Treatment (EOT) visit will be performed 7(±3) Days after the T6 visit. The surgical excision at the site of treated BCC lesion will be performed at the EOT visit. The excised specimens will be assessed for the histological clearance of lesion.

Adverse events and medications will be monitored throughout the study.

4.1.3 Follow-Up Period (2 and 4 weeks after EOT ± allowed windows)

There will be Follow-Up Visits at 2 weeks (FU1) and 4 weeks (FU2) after the excision of the lesion. The following assessments will be performed at FU1 and FU2 visit: 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 routine serum biochemical, hematologic, and urine laboratory assessments (FU2 only).

Procedures to be performed during each of the study periods are described below and provided as a Schedule of Assessments in Table 4- 1.

Table 4- 1: Schedule of Assessments

	Screening Phase	Treatment Phase								Follow-Up Phase	
Study Visits	**SV**	**Baseline /T1**		**T2**	**T3**	**T4**	**T5**	**T6**	**EOT**	**FU1**	**FU2**
		(Pre Rx)	**(Post Rx)**								
Days		**Day 0**		**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**			
Window Period		Within 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 T4 visit	7(±3) Days from T5 visit	7(±3) Days from T6 visit	14 (±3) Days from EOT	28 (±7) Days from EOT
Informed Consent	X										
Demographics	X										
Medical and Medication History	X	X									
Vital Signs[a]	X	X	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Height and Weight	X	X[c]		X[c]	X[c]	X[c]	X[c]	X[c]	X[c]		
Physical Exam	X	X[d]		X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Electrocardiogram, 12-lead	X	X[e]							X		
Biochemistries, Hematology, Coagulation, Urinalysis [f]	X	X							X		X
Serology: HbsAg, Hepatitis C Antibody, HIV[g]	X										
Serum pregnancy test	X[h]										
Urine pregnancy test		X[h]									
Eligibility Assessment	X	X									
Enrollment/Cohort Assignment		X									
Blood collection: Anti-Drug Antibody (ADA) Analysis		X		X	X	X	X	X	X	X	
Study Drug Administration [i]		X		X	X	X	X	X			
Adverse events [j]			X	X	X	X	X	X	X	X	X
Concomitant medications assessment	X	X	X	X	X	X	X	X	X	X	X
Local Skin Response (LSR Grading Scale)[k]	X	X	X	X	X	X	X	X	X		
Injection Site Pain Assessment (11-point			X	X	X	X	X	X			

	Screening Phase	Treatment Phase							Follow-Up Phase	
Study Visits	**SV**	**Baseline /T1**		**T2**	**T3**	**T4**	**T5**	**T6**	**EOT**	**FU1**	**FU2**
		(Pre Rx)	**(Post Rx)**								
Days		**Day 0**		**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**			
Window Period		Within 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 T4 visit	7(±3) Days from T5 visit	7(±3) Days from T6 visit	14 (±3) Days from EOT	28 (±7) Days from EOT
Numeric Pain Rating Scale) [l]											
2D Photography of lesion [m]	X	X	X	X	X	X	X	X	X	X	X
Longest diameter and Area Measurement of lesion [n]	X	X		X	X	X	X	X	X		
Pigmentation assessment [o]		X	X	X	X	X	X	X	X	X	X
Surgical excision of tumor [p]									X		
Assess. of Histological Clearance of lesion [q]									X		
Immunohistochemistry analysis [r]									X		

[a] Vital signs including heart rate, respiratory rate, blood pressure and body temperature.

[b] Vital signs will be assessed before the injection, and within 15 minutes after the injection.

[c] Weight only

[d] An abbreviated, symptom-directed physical examination will be performed.

[e] ECG will be performed before the first study drug administration at T1.

[f] Hematology: Hemoglobin, Hematocrit, MCV, MCHC, MCH, RBC count, WBC count, WBC Differential, Absolute neutrophil count and Platelet count

Coagulation: aPTT, PT, and INR (for subjects receiving anticoagulation therapy, performed at Screening Visit only)

Chemistry: Total Bilirubin, Alkaline Phosphatase, ALT, AST, Gamma GT, LDH, Albumin, Total Protein, Creatinine, Urea (BUN), Sodium, Potassium, Calcium, Chloride, Bicarbonate, Cholesterol (total), Triglyceride and Glucose (Random)

Urinalysis: pH, Appearance, Color, Specific gravity, Turbidity, Ketones, Bilirubin, Blood, Glucose, Protein, Nitrites, Urobilinogen, Leukocyte esterases, Microscopic exam includes bacteria, cast, crystals, epithelial cells, RBC, and WBC.

[g] Prior document results within 6 months of screening visit are acceptable.

[h] For women of childbearing potential.

[i] STP705 will be injected in and around the tumor (intra-and peri-lesional). 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 STP705 administration is allowed as per discretion of the Investigator**.**

[j] The AE reporting will begin from the application of the first dose of the IP at T1 visit.

[k] Local Skin Response (LSR) Assessment: screening, T1–T6 (pre-dose and post-dose), and at EOT visit using the LSR Grading Scale. See Section 7.13 for LSR Grading scale assessment.

[l] Injection site pain evaluation via 11-point Numeric Pain Rating Scale. This assessment will be performed within 15 minutes of the STP705 administration at T1 to T6 to assess the severity of pain at the site of lesion during the injection. See Section 7.12 for details. Note: Use of pain block anesthesia would also be documented on the Pain Assessment Sheet.

[m] See Section 7.14 for details of digital imaging/2D photography of lesion. 2D imaging will be taken at screening, T1 (pre-dose and post-dose), and T2 to T6 (pre-dose), EOT, FU1, and FU2 visit

[n] Measurement of the longest diameter and area measurement of lesion: screening, T1–T6 (pre-dose), and at EOT visit .

[o] Pigmentation assessment: at T1 (pre-dose and post-dose), and T2-T6 (pre-dose), EOT, FU1 and FU2 visit. Presence and severity of hyperpigmentation/ hypopigmentation/depigmentation will be assessed and quantified as 0-3 (None, Mild, Moderate, Severe).

[p] Surgical excision of tumor - Post-treatment excisions should be performed with a 3-4 mm margin around the target site as delineated by a pre-treatment template. The investigator should mark the superior 12 o'clock position of the excised specimen with a suture for orientation. The surgery will be performed by a licensed medical professional.

[q] Assessment of histological clearance of lesion - The excised specimens are transected at the mid-point across the short axis of the ellipse. Three gross sections of 2 mm each are taken in either direction from the center. These are level sectioned to achieve representative sections at 1mm intervals. The remainder of the specimen is serially sectioned at 3-mm intervals to the tips of the elliptical excision specimen. At least 10 microscopic sections (stained with hematoxylin and eosin) per case should be examined to ensure that the specimens are thoroughly evaluated for residual BCC. Pre-study biopsies and post-treatment excision specimens are to be examined by the primary dermatopathologist, independent of the clinician's assessment of the presence or absence of BCC at the post treatment visit.

[r] Immunohistochemistry analysis – Residual tissue from the excision, if available, will be used for analysis of biomarker expression common to the BCC tumor formation pathway such as TGF-β1, COX-2.

4.2 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.

4.2.1 Screening Visits (SV)

The Screening Visit (SV) will take place within the 28 days (4 weeks) 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 (screening number) will be assigned to each subject who has provided written informed consent. The subject screening number will incorporate a three-digit Study Center number (e.g., 001) 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., 001-001, 001-002).

Subject Screening #: **XXX - YYY**

XXX=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 assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened and can 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)

- 12-lead safety Electrocardiogram (see Section 7.10)
- Clinical laboratory assessments (see Section 7.11)
    - Safety laboratory tests (serum chemistry, hematology and coagulation, urinalysis)
    - Serology: Hepatitis B surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) 1 and 2 antibodies (a positive result will exclude the subject)
    - Serum pregnancy test (HCG) for women of childbearing potential (a positive result will exclude the subject from the study).
        - Childbearing potential is defined as someone who is not surgically sterile or is not more than one year past complete cessation of menstrual cycles.
    - Local Skin Response (LSR Grading Scale)
    - 2D photography of lesion
    - Longest diameter and area measurement of lesion

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.

4.3 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 treatment: review of any changes in medical and medication history, vital signs, weight measurement, symptom-directed physical examination, concomitant medications, ECG, routine serum biochemical, hematologic, urinalysis, urine pregnancy (if applicable), blood collected for Anti-Drug Antibody analysis, 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 prior to dosing.

Eligible subjects will be enrolled and 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.

4.3.1 Treatment Visit 1

4.3.1.1 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 on admission and also prior to dosing (see Section 7.6)
- Weight measurement (see Section 7.7)
- An abbreviated symptom directed physical examination (see Section 7.5)
- 12-lead safety Electrocardiogram (see Section 7.10)
- Clinical laboratory assessments (see Section 7.11)
    - Urine pregnancy test prior to dosing (*for women of childbearing potential*)
    - Safety laboratory tests (serum chemistry, hematology, urinalysis)
    - Blood draws for anti-drug antibody (ADA) analysis just prior to dosing
- 2D Photography of Lesion (see Section 7.14)
- 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)

Eligible subjects will be enrolled and assigned to a 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.

4.3.1.2 Treatment Visit 1– Dosing

The study treatment (STP705 injections) will be administered in and around the tumor (intra-and peri-lesional) by a licensed medical professional. The investigator/physician will discuss the option of using pain block medication with the subject prior to STP705 injection. 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 Pharmacy Manual for further details.

4.3.1.3 Treatment Visit 1– 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 post-administration on T1. (see Section 7.6)
- Injection Site Pain Assessment (11-Point Numeric Pain Rating Scale) 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) (see Section 7.13)
- 2D Photography of Lesion (see Section 7.14)
- Pigmentation assessment (see Section 7.16)

4.3.2 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 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)
- Study drug administration (see Section 6)
- Injection Site Pain Assessment (11-point Numeric Pain Rating Scale) post-dosing (see Section 7.12)
- Local Skin Response (LSR Grading Scale) (see Section 7.13) pre-dose and post-dose
- Longest diameter and Area Measurement of lesion (see Section 7.15) pre-dose
- 2D Photography of lesion before treatment administration (see Section 7.14)
- Pigmentation assessment (see Section 7.16) pre-dose and post-dose

4.3.3 End of Treatment Visit

Treatment with STP705 once per week for 6 weeks until one of the following events triggers exit from the study and End of Treatment Visit (EOT):

- Unacceptable toxicity
- Withdrawal of consent
- Completion of Treatment Phase

The flowing 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)
- Body Weight measurements (see Section 7.7)
- An abbreviated symptom directed physical examination (see Section 7.5)
- 12-lead safety Electrocardiogram (see Section 7.10)
- Clinical laboratory assessments (see Section 7.11)
    - Safety laboratory tests (serum chemistry, hematology, urinalysis)
    - Blood draw for anti-drug antibody (ADA) analysis
- 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)
- Immunohistochemistry analysis (see Section 7.19)

4.3.4 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)

FU2 Only

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

4.3.5 Unscheduled Visits

In the event that the subject returns to clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. Assessments at unscheduled visits are at the discretion of the Investigator.

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

A subject is considered to have completed the study 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 after dosing, subjects will be monitored until they are stable for discharge from the clinic. All data normally collected at the 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 patients 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.

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 screening 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 assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened again and can 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 dry powder drug product. Following reconstitution with Water for Injection, the administration route will be intra-and peri-lesional injection.

6.2 INVESTIGATIONAL PRODUCT PACKAGING AND LABELING

Study drug will be packaged, labeled, and shipped by Sirnaomics Inc (or designee). 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. The amount of the IP (STP705) to be administered will vary depending upon the cohort assignment.

Table 6- 1: Composition of STP705 Powder for Injection

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

A comprehensive table with the following information is presented in the Pharmacy Manual for each cohort.

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; sponsor’s name and address; and the lot number.

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

6.3 Investigational Product Storage

Study drug will be shipped refrigerated from the distribution center at a controlled temperature 2°C to 8°C (36°F to 46°F) to the Investigator's site. Upon receipt at the site, the responsible site staff or pharmacist should verify the integrity of the vials. Study drug should be stored at 2°C to 8°C (36°F to 46°F). 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. A study CRA assigned to monitor the investigational site will review these documents once study drug has been received by the investigational site. Study drug will be accounted for on an ongoing basis during the study.

6.4 Investigational Product Administration

The study treatment (STP705 injections) will be administered at the site of the lesion by a licensed medical professional.

The dosing regimen for each cohort are as follows:

Cohort A: STP705 30 μg dose, localized injection, given once a week for 6 weeks

Cohort B: STP705 60 μg dose, localized injection, given once a week for 6 weeks

Cohort C: STP705 90 μg dose, localized injection, given once a week for 6 weeks

Cohort D: STP705 120 μg dose, localized injection, given once a week for 6 weeks

Cohort E: STP705 180 μg dose, localized injection, given once a week for 6 weeks

Cohort F: STP705 240 μg dose, localized injection, given once a week for 6 weeks

Cohort G: STP705 320 μg dose, localized 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	120 µg dose	180 µg dose	240 µg dose	320 µg dose
0.5 to ≤ 2.0cm diameter	1	30 µg/0.6 mL	60 µg/0.6 mL	90 µg/0.6 mL	120 µg/0.6 mL	180 µg/0.9 mL	240 µg/0.9 mL	320 µg/0.9 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	1. 320 µg vial diluted with 1.6 mL of Water for Injection (WFI). 2. Withdraw 0.6 mL from 1.6 mL and inject into lesion	1. 320 µg vial diluted with 1.6 mL of Water for Injection (WFI). 2. Withdraw 0.9 mL from 1.6 mL and inject into lesion	1. 320 µg vial diluted with 1.2 mL of Water for Injection (WFI). 2. Withdraw 0.9 mL from 1.2 mL and inject into lesion	1. 320 µg vial diluted with 0.9 mL of Water for Injection (WFI). 2. Withdraw 0.9 mL and inject into lesion

Refer to Pharmacy Manual for further details.

6.4.1 Injection Procedure and Post-Injection Monitoring

Study treatment (IP Injection) will be administered in and around the tumor (intra-and peri-lesional) by a licensed medical professional.

Post-Injection Monitoring

- **Applicable for all treatment administrations:**
  - Vital signs will be monitored within 15 minutes post-administration
  - Subject will be observed for approximately 30 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 localized administration of STP705 is evaluated based on assessment of subject-perceived injection site pain using the 11-point Numeric Pain Rating Scale. This assessment will be performed within 15 minutes after each study treatment administration.

6.4.1.1 Treatment Modification

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

Dose interruption: Refer to table below. Recovery to acceptable levels of toxicity must occur to allow STP705 continuation.

Permanent discontinuation of Treatment: If Dose Limiting Toxicity (DLT) is reported.

Table 6-3: Dose Modification and Management

CTCAE Grade	Treatment Modifications
Grade 1 or 2*	No dose adjustment is required. **See note below*
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
Dose Limiting Toxicities (DLT) as outlined under Section 3 (Study	Study treatment will be permanently discontinued

Design)

Note:

- *If Grade 2 event does not meet the DLT criteria: No dose adjustment is required*
- *If Grade 2 or 3 event meets the DLT criteria: Study treatment will be permanently discontinued*
- *If Grade 3 event does not meet the DLT criteria: Study treatment will be withheld until symptoms resolve to Grade 1 or less before administrating next injection.*

6.4.1.2 Dose Reduction Plan

If a dose-response relationship for toxicity is observed, a reduced dose can be given to the subject. Dose adjustments will be allowed based on the toxicity, efficacy evaluation, and clinical judgment by physician.

Cohort B:

Dose reduction: If a dose-response relationship for toxicity is observed at STP705 60 µg dose, the dose can be reduced to 30 µg. No more dose reductions will be allowed if another toxicity event is observed at a reduced dose level.

Cohort C:

Dose reduction: If a dose-response relationship for toxicity is observed at STP705 90 µg dose, the dose can be reduced to 60 µg. One more dose reduction (to 30 µg) will be allowed as per discretion of the treating physician.

Cohort D:

Dose reduction: If a dose-response relationship for toxicity is observed at STP705 120 µg dose, the dose can be reduced to 90 µg. One more dose reduction (to 60 µg) will be allowed as per discretion of the treating physician.

Cohort E:

Dose reduction: If a dose-response relationship for toxicity is observed at STP705 180 µg dose, the dose can be reduced to 120 µg. One more dose reduction (to 90 µg) will be allowed as per discretion of the treating physician.

Cohort F:

Dose reduction: If a dose-response relationship for toxicity is observed at STP705 240 µg dose, the dose can be reduced to 180 µg. One more dose reduction (to 120 µg) will be allowed as per discretion of the treating physician.

Cohort G:

Dose reduction: If a dose-response relationship for toxicity is observed at STP705 320 µg dose, the dose can be reduced to 240 µg. One more dose reduction (to 180 µg) will be allowed as per discretion of the treating physician.

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.

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 un-used IP as instructed by the Sponsor. Further details will be provided in the Pharmacy Binder.

7 DESCRIPTION OF PROTOCOL ASSESSMENT AND PROCEDURES

7.1 INFORMED CONSENT

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

In obtaining and documenting informed consent the Investigator must comply with applicable regulatory requirements and must adhere to Good Clinical Practice (GCP). The Investigator, or designee, must fully inform subjects of all pertinent aspects of the study. Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, must provide the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the trial. All questions about the trial 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 (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.

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
- Genitourinary
- Other

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of diagnosis
- History status (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
- Genitourinary
- 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 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 (within 15 minutes after the injection) on Treatment Visits T1-T6*

7.7 Body Height and Weight Measurements

The following information will be collected:

- Height
- Weight

Note: *Only weight will be taken at T1-T6.*

BMI (derived from the height and weight measurements)

7.8 Concomitant Medication

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 electronic Case Report Form (eCRF). 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, with the exception of 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 course of study.

a) Immunosuppressants
b) Cytotoxic chemotherapy
c) Cytostatic therapy
d) Autoimmune disease therapy
e) Use of any investigational drug(s)

7.10 ELECTROCARDIOGRAM (ECG)

A resting 12-lead ECG will be conducted at the Screening Visit (SV) and prior to the first study treatment and the results will be evaluated by the Investigator. The following parameters will be recorded: ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and 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 on the data transfer along with all ECG results .

Only those subjects who have normal or not-clinically significant results at the Screening Visit (SV) and prior to the first study treatment will be enrolled in this study.

Additionally, ECG will be performed at the End of Treatment (EOT) Visit.

7.11 CLINICAL LABORATORY ASSESSMENTS

Blood samples will be collected for analysis of the following parameters:

- Hematology Parameters (Blood Sample): SV, T1, EOT, FU2
- Serum Chemistry Parameters (Blood Sample): SV, T1, EOT, FU2
- Coagulation Parameters (for subjects receiving anticoagulation therapy): SV
- Serum pregnancy test (for female subjects of childbearing potential): At SV
- Urine pregnancy test (for female subjects of childbearing potential): At T1
- Urinalysis (Urine Sample): SV, T1, EOT, FU2
- Anti-Drug Antibody (ADA) Analysis (Blood Sample) (refer to Table 7-2 for details)
- HbsAg, Hepatitis C antibody, HIV (Blood Sample): SV

All laboratory reports will be reviewed by the Investigator.

Post-treatment 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 in order to make the determination of clinical significance. Validated, quality-controlled laboratory data will be transferred to the main database for analyses.

Table 7-1: Lab Parameters

Hematological Parameters	Serum Chemistry Parameters	Urinalysis**
Hemoglobin	**Liver Function Tests**	pH
Hematocrit	Total Bilirubin	Appearance
MCV	Alkaline Phosphatase (ALP)	Color
MCHC	Alanine Aminotransferase (ALT)	Specific gravity
MCH	Aspartate Aminotransferase (AST)	Turbidity
RBC count	Gamma-glutamyl Transpeptidase (GGT)	Ketones
WBC count	LDH	Bilirubin
WBC Differential	**Protein**	Blood
Absolute neutrophil count	Albumin	Glucose
Platelet count	Total Protein	Protein
Coagulation Parameters*	**Renal Function Tests**	Nitrites
aPTT	Creatinine	Urobilinogen
PT	Urea (BUN)	Leukocyte esterases
INR	**Electrolytes**	Microscopic exam includes bacteria,
**for subjects receiving*		

anticoagulation therapy, performed at SV only	Sodium Potassium Calcium Chloride Bicarbonate **Lipid Profile** Cholesterol, Total Triglyceride **Other:** Glucose, Random, Serum Vitamin D, 25-Hydroxy, Total	cast, crystals, epithelial cells, RBC and WBC.
Miscellaneous		
Serum pregnancy test Urine pregnancy test (for female subjects of childbearing potential) HbsAg, Hep C antibody, HIV ADA		

***Urinalysis assessments will be performed using a local lab. Some of the macroscopic parameters, such as urobilinogen and turbidity, listed under urinalysis will not be available in the lab results conducted by the local lab.*

Any missed macroscopic parameters in the local lab report will not be documented as a protocol deviation.

Table 7- 2: Sample Collection Time Points for Anti-drug Antibody Assessments

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

7.12 Pain Assessment Using 11-Point Numeric Pain Rating Scale

Tolerability of repeated localized administration of STP705 is evaluated based on assessment of subject-perceived injection site pain using the 11-point Numeric Pain Rating Scale.

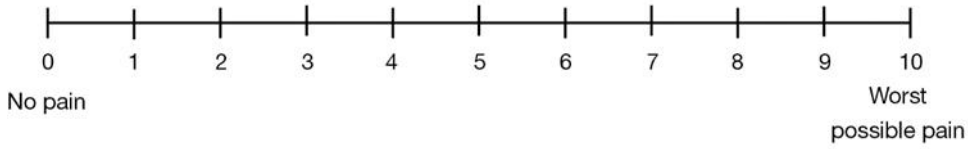
After each study treatment administration, subjects will be asked to evaluate the pain intensity at the time of injection administration based on 11-point Numeric Rating Scale from 0 to 10. “0” meaning “no pain” and “10” meaning “worst possible pain”

Note:

(1) Post-treatment Numeric Pain Rating Scale assessment will be performed within 15 minutes of the study drug administration.

(2) Use of pain block anesthesia would also be documented on the Pain Assessment Sheet.

Figure 7-1: 11-Point Numeric Pain Rating 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 lesion. The incidence and grade of LSRs will be summarized by treatment arm at each visit. Local skin reaction grades will be summarized by frequency counts and descriptive statistics per treatment arm 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 treatment arm at each visit using descriptive statistics. The first visit at which the highest sum score is attained will be summarized by treatment arm. 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 treatment arm.

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 treatment arm. 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 treatment arm.

Local skin reactions will be converted into MedDRA preferred terms applying the conversions in Table 7-3.

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

Local Response	Grading Scale				
	0	1	2	3	4
Flaking/Scaling	Not present	Isolated scale, specific to 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 the treatment area
Erosion/ Ulceration	Not present	Lesion specific erosion	Erosion extending beyond individual lesions	Erosion >50%	Black eschar or ulceration

Table 7- 4: Conversion of LSRs to MedDRA Preferred Terms

LSR Term	LSR Grade	MedDRA Preferred Term
Erythema	1-4	Application site erythema
Flaking/Scaling	1-4	Application site exfoliation
Crusting	1-4	Application site scab
Swelling	1-4	Application site swelling
Vesiculation/Pustulation	1	Application site blister
	2-4	Application site pustules
Erosion/Ulceration	1-3	Application site erosion
	4	Application 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. Photographs will be taken at each treatment visit (T1-T6), 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. The details of the procedure can be found in the Operations Manual.

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 will be stressed to the patients to ensure their cooperation. Lighting, framing, exposure, and reproduction ratios must be held constant.

1. After obtaining informed consent, the patients 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 trunk or extremity (non-peri-orbital/-anogenital/-facial/ -scalp) will be identified for photos. The supplied standardized blue deluxe felt background will be used for the 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 the Site's local, secure server.

7.15 Longest Diameter and Area Measurement of the Lesion

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. Measurements will be taken at Treatment Visits T1-T6, and at the End of Treatment Visit. For Treatment Visits T1-T6, measurements will be taken before the treatment is administered. The details of the procedure can be found in the Operations Manual.

7.16 Pigmentation Assessment

The pigmentation of the lesion will be assessed at Treatment Visits T1-T6, at the End of Treatment Visit (EOT), and at Follow-Up Visits 1 and 2 (FU1 and FU2), and quantified with a 0-3 scale (None, Mild, Moderate, Severe).

7.17 Excision of the BCC Site

Post-treatment excisions will be performed by a licensed medical professional. The excision will be performed with a 3-4 mm margin around the target site as delineated by a pretreatment template obtained from the pre-treatment measurement of the lesion (see Section 7.15). The investigator should mark the superior 12 o'clock position of the excised specimen with a suture for orientation.

7.18 Histological Clearance of Lesion

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

Dermatopathology: The excised specimens will be transected at the mid-point across the short axis of the ellipse. Three gross sections of 2 mm each will be taken in either direction from the center. These are level sectioned to achieve representative sections at1mm intervals. The remainder of the specimen is serially sectioned at 3-mm intervals to the tips of the elliptical excision specimen. At

least 10 microscopic sections (stained with hematoxylin and eosin) per case should be examined to ensure that the specimens are thoroughly evaluated for residual BCC. Pre-study biopsies and post-treatment excision specimens are to be examined by the primary dermatopathologist, independent of the clinician's assessment of the presence or absence of BCC at the post treatment visit.

7.19 FUTURE OR EXPLORATORY SPECIMEN RESEARCH

Tissues obtained during protocol SRN-705-006 (from original diagnosis and the tissue excised at the end of the study) will be used in exploratory analysis of biomarker expression common to the BCC 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 such as statistical power, sample size, 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 GROUPS

The dosing regimen for each cohort are as follows:

Cohort A: STP705 30 µg dose, localized injection(s), given once a week for 6 weeks

Cohort B: STP705 60 µg dose, localized injection(s), given once a week for 6 weeks

Cohort C: STP705 90 µg dose, localized injection(s), given once a week for 6 weeks

Cohort D: STP705 120 µg dose, localized injection(s), given once a week for 6 weeks

Cohort E: STP705 180 µg dose, localized injection(s), given once a week for 6 weeks

Cohort F: STP705 240 µg dose, localized injection(s), given once a week for 6 weeks

Cohort G: STP705 320 µg dose, localized injection(s), given once a week for 6 weeks

8.2 DESCRIPTION OF STUDY OUTCOME MEASURES

8.2.1 Primary Outcome Measure

The primary outcome measure for the study is:

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

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

8.2.2 Secondary Outcome Measure

- Change in size of the treated basal cell carcinoma lesion over the 6-week treatment period.

  A base line assessment of lesion size will be made by investigator at T1 (first visit). The change in size will be assessed every week until the surgical excision of BCC at the End of Treatment (EOT) visit.

8.2.3 Safety Assessments

The safety of trial subjects will be assessed according to the following criteria:

- 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 localized 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 variables.

In addition to spontaneously reported SAEs and AEs, AEs will be elicited during questioning and examination of a patient during all Treatment and Follow-Up visits. The Investigator will give particular attention to physical examination findings and laboratory results.

8.3 Sample Size and Determination and Rationale

A total of up to 35 subjects (7 cohorts of 5 evaluable subjects each) will be assigned to receive study treatment. Subjects who withdraw consent or drop out after first visit will be replaced. The sample size calculation is based on clinical judgment. No statistical power calculation is used to establish the sample size.

8.4 Randomization

Not applicable.

8.5 Blinding

Not applicable.

8.6 Interim Analysis

No interim analysis (IA) will be performed for efficacy. There will be a safety review, once all five subjects from each cohort exit the treatment phase.

The Sponsor's Medical Monitor, CRO Medical Monitor and study investigators must be satisfied with data obtained in lower dose cohort before allowing subsequent enrollment under next higher dose cohort. For example, they must be satisfied with data obtained in Cohort A before allowing subsequent enrollment in Cohort B. The similar approach for data review prior to dose escalation to continue for all subsequent cohorts.

In addition, should any of the following events occur in any cohort during the Treatment Phase, the Data and Safety Monitoring Board (DSMB) will meet to review available study data and make a final decision for dose escalation to the next cohort:

a. Death in any subject in which the cause of death is judged to be possibly, probably or definitely related to STP705.

b. The occurrence in any subject of an anaphylactic reaction to STP705.

c. The occurrence in any subject of a severe local injection site reaction (grade 3 which is not resolved or recurs; or grade 4) that preclude administration of consecutive doses.

d. The occurrence in any subject of a life-threatening SAE whose causal relationship to STP705 is judged to be probable or definite.

e. The occurrence of one or more non-life-threatening SAEs whose causal relationship to STP705 is judged to be definite.

f. The occurrence, in one or more subjects, of grade 4 laboratory abnormalities, judged to be probably or definitely related to receipt of STP705.

g. The occurrence of any new onset, systemic Grade ≥2 AE for cardiac and/or blood/bone marrow categories (or for subjects that enroll with Grade 2 findings then a 1-point increase to Grade 3 shall apply), or any systemic or non-systemic (local) non-hematological adverse events, judged to be possibly, probably or definitely related to receipt of 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.

8.7 General Statistical Considerations

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.3 or later. Descriptive statistics (N, mean, standard deviation, median, minimum and maximum) will be presented by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

8.7.1 Analysis Populations

8.7.1.1 Intent to Treat Populations (ITT)

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.

8.7.1.2 Per Protocol Population (PP)

The Per Protocol (PP) population is defined as the set of subjects who meet the ITT population requirements and were not associated with a major protocol violation. This population will be identified before the database lock.

8.7.1.3 Safety Population

The Safety Population will include all subjects who have received one dose of study treatment. This population will be used for the analysis of safety parameters.

8.7.2 Covariates

For efficacy analyses, the baseline values will be used as covariates in the analysis models. Other important prognostic factors will be specified in the SAP for the study.

8.7.3 Missing Data

For efficacy evaluation, appropriate methods will be used to handle any missing data. The details of techniques for handling of missing data will be included in the SAP for the study which will be finalized prior to database lock.

8.8 Analysis Methods

A SAP will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this trial.

8.8.1 Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, enrolled, completed, and discontinued during the study, as well as the reasons for all post-enrollment discontinuations will be summarized by treatment group, for all centers combined and each center separately. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

8.8.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group using appropriate descriptive statistics.

8.8.3 Efficacy Analysis

8.8.3.1 Primary Analysis

The primary analysis will be conducted on the Intent-to-treat (ITT) population.

Primary Outcome Measure: Proportion of participants with histological clearance of treated basal cell carcinoma lesion at the End of Treatment (EOT).

Secondary Outcome Measure: Change in size of the treated basal cell carcinoma lesion over the 6-week treatment period.

8.8.4 Safety Analyses

The Safety population will be used for the analysis of safety outcome measures.

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.

Adverse Events:

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent AE's (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 severity grade (mild, moderate, severe, or life threatening for SAEs)
- By relationship to clinical trial treatment according to the mapping scheme below:
  - Potentially related: will include all adverse events with a relationship rating of "definitely", "probably" or "possibly".
  - Unlikely/not related: will include all adverse events with a relationship rating of "unlikely" or "unrelated".

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

Clinical Laboratory Data

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

Physical Examination

All physical examination findings will be listed and/or summarized.

Vital Signs

All vital sign findings will be listed and summarized.

Anti-drug Antibodies (ADA) immunogenicity

All ADA findings will be listed and summarized.

Electrocardiograms (ECGs)

All ECG findings will be listed and summarized.

Size of lesion

All measurements of the greatest diameter and the area will be listed and summarized.

Pigmentation

All findings will be listed and summarized.

LSR Grading Scale

All findings will be listed and summarized.

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 subject 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 abnormalities in visit evaluations, physical examination findings or laboratory results that the investigator believes are clinically significant 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 AND FOLLOW-UP OF ADVERSE EVENTS

Report initiation for all AEs and serious adverse events (SAEs) (see Section 9.3), will begin at the time of the first treatment and continue up to the final study visit. All events will be followed to resolution or until 30 days after 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 9.3), the impact the event had on study treatment (see Section 9.2.1), the CTCAE grade (intensity) of the event (see Section 9.2.2), the causality of the event (see Section 9.2.3), whether treatment was given as a result of the event (see Section 9.2.5), and the outcome of the event (see Section 9.2.6).

9.2.1 Impact on Study Treatment

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

9.2.2 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://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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.
‡Unlike the AE outcome assessment (see Section 9.2.6), a subject may have more than one Grade 5 event.

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

9.2.3 Causality Assessment

Adverse events 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. **Unrelated** – The event is definitely not associated with the study biologic or control. Other conditions including concurrent illness, progression or expression of the disease state, or reaction to a concurrent medication explain the reported AE.
2. **Unlikely** – The temporal association, patient history and/or circumstances are such that the study biologic or control is not likely to have had an association with the observed event. Other conditions including concurrent illness, progression or expression of the disease state, or reaction to a concurrent medication, appear to explain the reported AE.
3. **Possibly** – The event follows a reasonable temporal sequence from study biologic or control but could have been produced by the patient's clinical state or other therapies administered to the patient.
4. **Probably** – The event follows a reasonable temporal sequence from the study biologic or control, abates upon discontinuation of the study drug or control, or cannot be reasonably explained by known characteristics of the patient's clinical state.
5. **Definitely** – The event follows a reasonable temporal sequence from the study biologic or

control, abates upon discontinuation and cannot be explained by known characteristics of the patient's clinical state.

9.2.4 Subject Stopping Rules

AEs will be classified based on CTCAE, Version 5.0; any subjects with a new onset, systemic Grade ≥2 AE for cardiac and/or blood/bone marrow categories (or for subjects that enroll with Grade 2 findings then a 1-point increase to Grade 3 shall apply) or other systemic or non-systemic (local) Grade ≥3 AE with no clear alternative causative explanation will be discontinued from test article injections, continued in the study, and followed until resolution of the AE or until the event is deemed clinically stable by the investigator.

9.2.5 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).

9.2.6 Outcome Assessment

The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, or death. 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.

9.2.7 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.

Adverse reactions to intravenous (IV) infusion of STP707, a drug similar to STP705 investigated by Sirnaomics, have been reported. The two siRNAs in the investigational products (STP705 and STP707) are the same, but the product formulation and routes of administration are different. The infusion-related reaction (IRR) that was reported occurred after IV administration of a 12 mg dose of STP707. No serious IRRs have been observed with STP705 administered by subcutaneous intradermal, peridermal, or intratumoral administration in humans or animals. Therefore, Sirnaomics does not have any evidence that there is a greater safety risk for subjects receiving STP705 as prescribed in the protocols for studies investigating this product.

9.3 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 device effect when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.4 Reporting Serious Adverse Events

The Investigator is required to report all SAEs that occur during the time period specified in Section 9.2. Once the Investigator becomes aware of an SAE, he/she must report the SAE to Amarex Safety and Pharmacovigilance Department within 24 hours:

CRO Medical Monitor	Amarex LLC 20201 Century Boulevard, 4th Floor Germantown, MD 20874 Email: saereporting@amarexcro.com Phone: +1 (240) 454-6844 Fax: +1 (240) 454-6602

A written SAE reports must include a full description of the event as described in Section 9.2 and must follow within 24 hours from the time the Investigator first learned of the event. The Amarex 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.

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.

9.5 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.

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 monitors, auditors, personnel authorized by the Sponsor, the local IRB, and the FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research and 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

In an effort to fulfill the obligations outlined in 21 Code of Federal Regulations (CFR) Part 312 and ICH guidelines which requires the Sponsor to maintain current personal knowledge of the progress of a study, the Sponsor's designated monitor will visit the center(s) 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.

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 and diagnostic reports, cancer images, quality of life questionnaire, etc.

Site inspections serve to verify strict adherence to the protocol and the accuracy of the data being entered on the case report forms, in accordance with federal regulations. A Monitoring Log will be maintained at each study site which the monitor will sign, date and state 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.

The final statistical analysis of data will be performed after all clinical monitoring has been completed, all data queries have been resolved, and all data have been verified (Quality Control checked) prior to formal database lock. The Sponsor will authorize the final database lock.

11.2 ACCEPTABILITY OF ELECTRONIC CASE REPORT FORMS (ECRFS)

Electronic CRFs (eCRFs) must be completed for each subject who has signed an informed consent form. 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. Corrections to data on the eCRFs will be documented. The Investigator will review eCRFs to indicate that, to his/her knowledge, they are complete and accurate. Electronic CRFs will be reviewed by the Sponsor's or designated CRO's monitor, who will make a decision as to their acceptability.

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 eCRFs.

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 well-being 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 INDEPENDENT DATA AND SAFETY MONITORING BOARD (DSMB)

The study will be monitored by an independent DSMB to ensure patient safety. The CRO is responsible for the overall management of DSMB, including development of its charter and membership selection. The DSMB will be managed in conformance with the FDA guidelines for DSMB independence, management, and oversight.

The DSMB will consist of at least three members and will review all unexpected AEs, all related AEs, all SAEs, and all deaths during the Treatment and Follow-Up Phases.

If any of the SAEs or dose limiting toxicities outlined below occurs, the DSMB will conduct an independent review of the data and will make a final decision for dose escalation to the next cohort:

a. Death in any subject in which the cause of death is judged to be possibly, probably or definitely related to STP705

b. The occurrence in any subject of an anaphylactic reaction to STP705

c. The occurrence in any subject of a severe local injection site reaction (grade 3 if not resolved or recurs or grade 4) that preclude administration of consecutive doses.

d. The occurrence in any subject of a life-threatening SAE whose causal relationship to STP705 is judged to be probable or definite

e. The occurrence of one or more non-life-threatening SAEs whose causal relationship to STP705 is judged to be definite

f. The occurrence, in one or more subjects, of grade 4 laboratory abnormalities, judged to be probably or definitely related to receipt of STP705

g. The occurrence of any new onset, systemic Grade ≥2 AE for cardiac and/or blood/bone marrow categories (or for subjects that enroll with Grade 2 findings then a 1-point increase to Grade 3 shall apply), or any systemic or non-systemic (local) non-hematological adverse events, judged to be possibly, probably or definitely related to receipt of 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.

All expedited safety reports will be provided in real time to the DSMB chair upon being reported to FDA.

Note: For the purpose of expedited safety reporting, all adverse events except skin reactions will be considered unexpected.

The DSMB will make the following recommendations at each safety evaluation:

- Continue the study as planned;
- Assess a specific aspect of safety that is not conclusive;

- Gather more data to address a specific safety issue; and
- Stop the study due to safety concerns.

The Sponsor retains the responsibility to contact FDA and the final decision regarding the recommendation to continue or to terminate the 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 Part 312, 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, all study products used in this study are manufactured, handled and stored in accordance with applicable GMP and the products 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 the 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 any study centers participating in this study that cannot comply with these standards will be documented.

13.3 SUBJECT INFORMED CONSENT REQUIREMENTS

Written and oral information about the study in a language understandable by the subject will be given to all subjects by the Investigator and/or designee. Written informed consent will be obtained from each subject before 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) is to be in compliance with 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. Each 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 the approved electronic case report forms (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 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 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 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
- Product (e.g., IP, Standard Care supplies) 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 and enrollment/cohort log
- SAE reports
- IRB approval and re-approval letters
- 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.

At the completion of the study, details of the archival process must be provided to the Sponsor. 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 site's 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 site's 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 site's 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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