THERAPEUTICS INC.
The Dermatology CRO

# STATISTICAL ANALYSIS PLAN

VERSION: 1.0

DATE: 01-MAY-2023

| | |
|---|---|
| **SPONSOR:** | Sirnaomics, Inc. |
| **PROTOCOL NUMBER:** | SRN-705-011 |
| **TI PROJECT NUMBER:** | 254-13251-202 |
| **PROTOCOL TITLE:** | An Open Label, Dose Escalation Study to Evaluate the Safety and Efficacy of Intralesional Injection of STP705 in Adult Subjects with Facial Cutaneous Squamous Cell Carcinoma in situ (isSCC) |
| **PROTOCOL DATE:** | April 18, 2022 |



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## SAP APPROVAL

The following individuals approve version 1.0 of the SAP dated 01-MAY-2023. All changes to this version of the SAP must have written approval and require an amendment.

The **Project Statistician** is signing below to confirm he/she has developed the SAP to provide a comprehensive description of the methods of data analyses for the clinical study.

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The **Statistical Reviewer** is signing below to confirm he/she has reviewed and verified the SAP has been written with proper statistical methods to be used to analyze the results from the clinical study.

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**ABBREVIATIONS**

| | |
|---|---|
| ADA | Anti-Drug Antibody |
| AE | Adverse Event |
| ALT | Alanine Transaminase |
| AST | Aspartate Aminotransferase |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| COX-2 | Cyclooxygenase-2 |
| CRO | Contract Research Organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose Limiting Toxicity |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EOT | End of Treatment |
| HEENT | Head, Ears, Eyes, Nose, and Throat |
| ICF | Informed Consent Form |
| isSCC | In-situ Squamous Cell Carcinoma |
| ITT | Intent-to-Treat |
| LSR | Local Skin Response |
| QTc | Q-T Corrected Interval |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SCC | Squamous Cell Carcinoma |
| SV | Screening Visit |
| TGF-β1 | Transforming Growth Factor Beta |
| TEAE | Treatment Emergent Adverse Event |
| VAS | Visual Analogue Scale |



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# 1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for data from Protocol SRN-705-011, "An Open Label, Dose Escalation Study to Evaluate the Safety and Efficacy of Intralesional Injection of STP705 in Adult Subjects with Facial Cutaneous Squamous Cell Carcinoma in situ (isSCC)".

This SAP was created using Clinical Protocol SRN-705-011 Version 1.0 dated 18 April 2022, and the Electronic Case Report Forms (eCRF) Version 1.0 dated 08 July 2022.

# 2. PURPOSE OF THE ANALYSES

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for Protocol SRN-705-011. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

# 3. STUDY OBJECTIVES AND ENDPOINTS

## 3.1 Objectives

The purpose of this trial is to evaluate the safety, tolerability, and efficacy of various doses of STP705 administered as intralesional injection in subjects with facial isSCC.

Goals:

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

## 3.2 Efficacy Endpoints

### *3.2.1 Primary Endpoint*

Proportion of participants with histological clearance of treated facial isSCC lesion at the End of Treatment (EOT). Histological clearance (HC) will be defined as the absence of detectable evidence of isSCC tumor cell nests as determined by central pathology review.

### *3.2.2 Secondary Endpoints*

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



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### 3.3 Safety Endpoints

- Incidence of adverse events (AEs) and serious adverse events (SAEs).
- Incidence of AEs and SAEs leading to discontinuation of trial medication.
- Incidence and severity of Local Skin Response (LSR), hypopigmentation and hyperpigmentation following treatment.
- Tolerability of repeated intralesional administration of STP705 as assessed by investigator evaluation of injection site responses for all subjects.
- Clinically relevant changes or new abnormal findings in laboratory values, vital signs, electrocardiograms (ECGs), and physical examinations.

### 3.4 Biomarker Endpoints

Tissues obtained from the original diagnosis (within 6 months prior to the Screening Visit [SV], if available] or at screening) and the tissue excised at the end of the study will be used in exploratory analysis of biomarker expression common to the isSCC tumor formation pathway such as TGF-β1, and 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 testng will be performed.

## 4. STUDY DESIGN

This is an open label study designed to evaluate the safety and efficacy of various doses of STP705 administered as an intralesional injection in subjects with isSCC.

Thirty subjects were to be sequentially enrolled to 3 cohorts 30, 60, or 90 μg STP705 of 10 subjects each. The study was terminated prematurely prior to the completion of enrollment into the first cohort (30μg). No additional subjects will be enrolled into the subsequent cohorts.

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

In the absence of dose limiting toxicities (DLT), the subsequent cohorts were to receive increasing doses of STP705, following the same schedule of administration as the first cohort. Dose escalation was to progress after ten subjects had been enrolled in the previous cohort, provided that none of the following SAEs or DLTs had occurred in any subject. Subject enrollment into the 60 μg and 90 μg cohorts was terminated following the completion of the 30 μg cohort.

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

**Optional Pre-Screening Biopsy:**
If a potential subject presents with a clinically suspicious facial isSCC lesion that was never biopsied, or cannot provide a confirmatory histopathology report, or that was biopsied more than 6 months prior to Screening, this lesion may be biopsied to determine eligibility (an optional pre-

screening biopsy) by the investigator (or his/her qualified designee) as a consented procedure under this protocol prior to Screening.

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

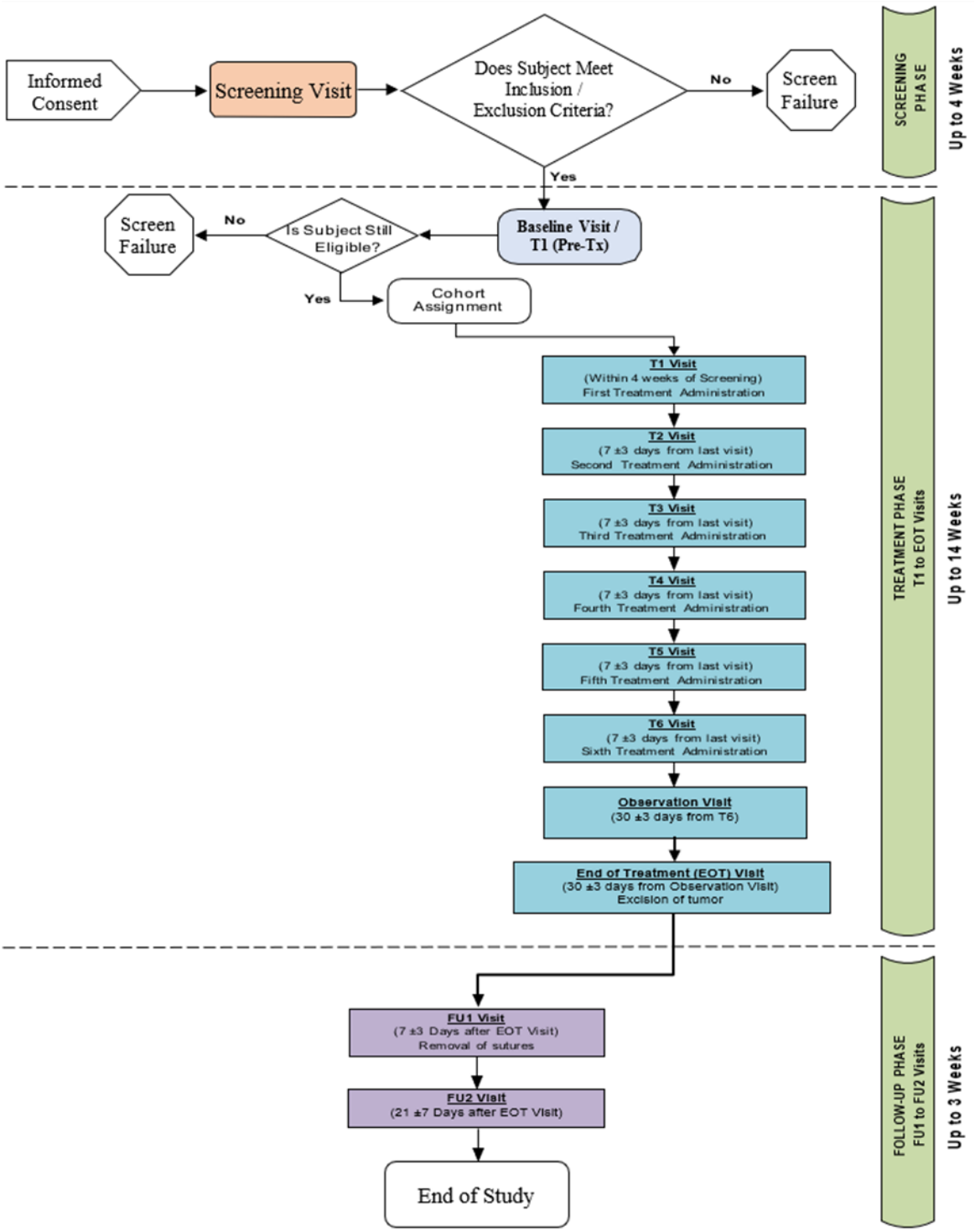
**Treatment Phase (Visit 2 – Visit 9) (up to 14 weeks ± allowed windows):**
Subjects who meet eligibility criteria will check-in to the clinic on the day the first treatment is scheduled. The following assessments will be performed prior to the first treatment: review of any changes in medical and medication history, vital signs, weight measurement, symptom-directed physical examination, concomitant medications, ECG, chemistry, hematology, urinalysis, urine pregnancy (if applicable), blood collected for Anti-Drug Antibody (ADA) analysis, creation of a pre-treatment lesion template along with measurement of longest diameter and area of the lesion using a ruler or a caliper, and 2D digital imaging of the lesion pre-marked with a surgical skin marker, baseline LSR Grading Scale assessment, baseline pigmentation, and Visual Analogue Scale (VAS) pain assessment at the site of lesion prior to dosing. The marking of the lesion using the skin marker should be repeated every visit.

Eligible subjects will be sequentially 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 is as follows:
**Cohort A:** STP705 30 μg dose, intralesional injection, given once a week for 6 weeks. The study treatment STP705 will be administered by the licensed medical professional. All treatments are 0.6 mL administered as an intralesional injection.

**Follow-Up Phase**
There will be Follow-Up Visits at 7 days (±3 days) (Visit 10/FU1) and 21 days (±3 days) (Visit 11/FU2) after the lesion was excised at EOT (Visit 9).

**Study Flow Diagram**






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## 4.1 Schedule of Events

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



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



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

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

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

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



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the excision at the EOT visit.

**16.** Surgical excision of tumor: Post-treatment excisions should be performed around the target lesion. The surgery will be performed by a licensed medical professional.

**17.** Suture removal: per standard of care at FU1 visit.

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

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



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# 5. DEFINITIONS

- The **Study Day** is the day of the study relative to the first dose (Baseline Visit / T1) of the study drug. Study day is derived as:
  Assessment visit date – First dose date + 1.
- The **baseline assessment** is defined as the last non-missing measurement collected at Screening or Baseline/T1 (Day 1) visit prior to the first administration of the study drug.
- **Post-baseline** is defined as a measurement taken after the administration of the first dose of study drug. **Change from baseline** will be calculated as:
  Post-baseline value – Baseline value
  Correspondingly, **percent change from baseline** will be calculated as:
  100 × (Post-baseline value – Baseline value) / Baseline value
- **Histological Clearance (HC)** will be defined as the absence of detectable evidence of isSCC tumor cell nests as determined by central pathology review.

# 6. CLINICAL EVALUATIONS

## 6.1 Assessment of Histological Clearance of the Lesion

During the Screening Phase and prior to first treatment dosing at T1, the Investigator will assess a subject's continued suitability and eligibility for the trial. To be eligible for the study, the subject must have a histologically confirmed facial isSCC lesion (evidenced by a confirmatory histopathology report made no more than 6 months prior to the SV) suitable for excision with a minimum diameter of 0.5 cm and with a maximum diameter of 2.0 cm and meet other inclusion criteria.

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

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

## 6.2 Longest Diameter and Area Measurements of the Lesion

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



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# 7. SAFETY EVALUATIONS

## 7.1 Adverse Events

All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the test articles, and outcome. Verbatim terms will be coded to preferred terms (PTs) and system organ class (SOC) using version 25.0 of the Medical Dictionary for Regulatory Activities (MedDRA) mapping system.

## 7.2 Local Skin Response Grading Scale

The LSR Grading Scale (0 – 4) will be used to evaluate the changes in the baseline lesion location and will be measured pre-dose and within 15 minutes (±5 min) post-dose administration at T1-T6. LSR will also be assessed at the observation visit and at EOT. A composite (sum) score will be obtained by summing the six (T1-T6) individual LSR scores at each visit.

**Local Skin Response Grading Scale**

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



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LSRs will be converted into MedDRA preferred terms applying the conversions below.

**Conversion of LSRs to MedDRA Preferred Terms**

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

## 7.3 Clinical Laboratory Assessments

Samples will be collected for analysis for the following parameters:

- Hematology Parameters (Blood Sample): SV, T1, EOT, and FU2
- Serum Chemistry Parameters (Blood Sample): SV, T1, EOT, and FU2
- Coagulation Parameters (Blood Sample): SV (only for subjects receiving anticoagulation therapy)
- Serum pregnancy test (for female subjects of childbearing potential): SV and EOT
- Urinalysis (Urine Sample) SV, T1, EOT, and FU2
- Urine pregnancy test (for female subjects of childbearing potential): T1
- ADA Analysis (Blood Sample): T1-FU1

The analysis of samples collected for evaluation of ADA is outside the scope of this analysis plan and will be performed under the direction of the Sponsor.



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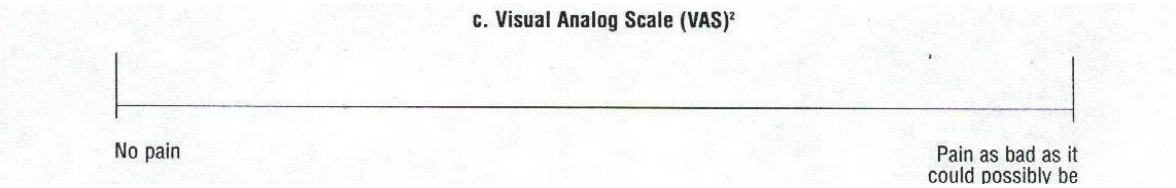
**LAB PARAMETERS**

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

## 7.4 Pain Assessment Using Visual Analogue Scale

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

**VISUAL ANALOGUE SCALE**




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

a whole number (e.g., 10, 30, 95) in millimeters from 0 (no pain) to 100 (pain as bad as it could possibly be). Round to the nearest whole number if the measurement falls in between numbers.

## 7.5 Vital Signs

Vital signs will be collected per the Schedule of Assessments and include: blood pressure, heart rate, respiratory rate, and temperature.

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

## 7.6 Body Height and Weight Measurements

Height will be measured only at SV. Weight will be measured pre-dose at T1-T6.

## 7.7 Electrocardiogram

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

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

## 7.8 Physical Examination

A complete physical exam will be done at screening only. An abbreviated symptom directed physical exam will be done at T1 and thereafter, per the Schedule of Assessment. The physical examination will include routine examinations for the following:

- General Appearance
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Lymph Nodes
- Heart/Cardiovascular abnormalities
- Respiratory
- Abdomen
- Musculoskeletal and Extremities



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- 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.

### 7.9 Pigmentation Assessment

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

### 7.10 Prior and Concomitant Medications

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

### 7.11 Prohibited Medications and Therapies

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

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

### 7.12 Tissue Biomarker

Tissues obtained from the original diagnosis (within 6 months prior to the SV (if available) or at screening) and the tissue excised at the end of the study will be used in exploratory analysis of



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biomarker expression common to the isSCC tumor formation pathway such as TGF- β1 and COX-2.

# 8. STATISTICAL METHODS

## 8.1 General Considerations

All statistical analyses will be performed using SAS®, version 9.4 or higher, unless otherwise stated. No formal tests of hypotheses will be performed. If present, p-values, will be provided for descriptive purposes only.

Continuous variables will be summarized by descriptive statistics including the number of subjects with non-missing data (n), mean, standard deviation (SD), median, minimum, and maximum values by each visit (if applicable) and by treatment group. Means will be presented to one additional decimal place and SD will be presented by 2 additional decimal places than the presentation level of the respective subject data. Minimum and maximum values will be presented using the same number of decimal places as the subject data.

For categorical variables, the number and percentage of subjects within each category will be presented.

Percentages will be presented to 1 decimal place if not otherwise stated. If the number of subjects in a category is 0, then percentage will not be displayed, and only a count of 0 will be shown.

Subject data listings will be sorted by treatment group, study site, subject number and visit, as applicable.

## 8.2 Analysis Populations

### *8.2.1 Safety Population*

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

### *8.2.2 Intent-to-Treat Population*

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

## 8.3 Final Analyses and Reporting

Final database lock will occur after all subjects have completed the study assessment period (or withdrawn from the study prematurely) and all subject data have been monitored and all queries resolved.



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Further exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not described in this SAP will be clearly identified as such in the CSR.

## 8.4 Sample Size

A total of 10 eligible subjects per cohort were to receive treatment with 30 μg, 60 μg, 90 μg STP705. This sample size is not based on a statistical power calculation.

## 8.5 Subject Disposition

The number and percent of subjects who were enrolled in the study, who completed the study, who withdrew from the study and their reasons for discontinuation (including death), as well as, the number of subjects by site and by assessment will be summarized for the ITT Population and the Safety Population.

Informed consent information and subject eligibility status will be provided in a listing.

Subjects who were screen failures with their reason for screen failure will be listed.

## 8.6 Screening and Baseline Assessments

### *8.6.1 Demographics*

Demographic information including sex, age, race, and ethnicity will be summarized by treatment group for the ITT and Safety populations. Demographic data for screen failures will be summarized separately.

### *8.6.2 Physical Examination*

Any clinically significant physical examination findings at Screening or Visit T1 (prior to dosing) will be recorded as medical history.

### *8.6.3 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.

Medical history will be provided in a subject data listing by treatment group.

### *8.6.4 Baseline Clinical Evaluations*

Descriptive statistics will be provided for the baseline isSCC lesion size by treatment group for the ITT population.

## 8.7 Efficacy Evaluation

The analysis of the primary and secondary efficacy outcome measures will be conducted on the ITT Population. No inferential analyses will be performed.

### *8.7.1 Analysis of Efficacy*

8.7.1.1 Primary Efficacy Analysis

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

8.7.1.2 Secondary Efficacy Analyses

Change in size of the treated isSCC lesion over the pre-excision treatment period will be descriptively summarized by treatment group.

### *8.7.2 Statistical / Analytical Issues*

8.7.2.1 Analysis Visit Windows for Assigning Observed Data

Efficacy data will be assigned to analysis visits based on its nominal scheduled visit.

An early termination visit will be assigned to analysis visits as defined in the visit window tables below. If 2 or more visits occur within the same analysis window, the value under nominal scheduled visit will be used; otherwise, the value closest to the target day will be used. If the assessments are the same distance from the target day, the latest one will be used. After applying visit window, each analysis visit should contain no more than one record and is considered observed data.



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**VISIT TIME WINDOWS**

| *Visit* | *Target Day* | *Study Days*[1] |
|---|---|---|
| Baseline/T1 | Day 1 | Days ≤ 1 |
| Visit 3/T2 | Day 8 | Days [2, 11] |
| Visit 4/T3 | Day 15 | Days [12, 18] |
| Visit 5/T4 | Day 22 | Days [19, 25] |
| Visit 6/T5 | Day 29 | Days [26, 32] |
| Visit 7/T6 | Day 36 | Days [33, 51] |
| Visit 8/Observation | Day 66 | Days [52, 81] |
| Visit 9/End of Treatment | Day 96 | Days >= 82 |

[1] Relative to the day of first injection of study treatment.

8.7.2.2 Handling of Dropouts or Missing Data

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

## 8.8 Safety Evaluation

Summaries of the safety parameters will be provided as described below for the Safety population. No inferential analyses will be performed.

### *8.8.1 Extent of Exposure*

Descriptive statistics will be used to summarize the treatment duration, total number of injections, and total dose administered (μg). The treatment duration for a subject will be derived as:

Treatment duration = Date of last injection – Date of first injection + 1

### *8.8.2 Adverse Events*

All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the test articles, and outcome. Verbatim terms will be coded to PTs and SOC using version 25.0 of the MedDRA mapping system. The PTs and SOC will then be tabulated. For all AE summaries, if a subject has more than one AE within a PT, the subject is counted once in that PT. If a subject has more than one AE within a SOC, the subject is similarly counted once in that SOC.

The number and percentage of unique subjects reporting each treatment emergent AE (TEAE) will be summarized by SOC and PT. The number and percent of unique subjects reporting each TEAE will also be summarized by SOC, PT, maximum severity (mild, moderate, severe), CTCAE grade, closest relationship to test article (unrelated, unlikely related, possibly related, probably related, and definitely related), and by impact on study treatment (dose not changed, drug interrupted, drug withdrawn, not applicable, or unknown).

SAEs, if any, will be summarized by SOC, PT and treatment group.

### *8.8.3 Vital Signs*

Descriptive statistics will be provided for the observed and change from baseline values for weight, temperature, systolic and diastolic blood pressure, heart rate, and respiration rate by treatment group. A subject data listing will be provided.

### *8.8.4 Electrocardiograms*

Descriptive statistics will be provided for the observed and change from baseline values for ECG parameters by treatment group at each visit. A shift table will be provided for cardiologist interpretation of the ECG results. A subject data listing will be provided.

### *8.8.5 Clinical Laboratory Assessments*

Shift tables will be provided for all clinical laboratory measurement results (chemistry, hematology, coagulation, and urinalysis) by treatment group at each post-treatment visit. Subject data listings will be provided.

### *8.8.6 Physical Examination*

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

### *8.8.7 Local Skin Response*

LSR grades will be measured pre-dose and within 15 minutes (± 5 min) post-dose administration at T1-T6. LSR will also be assessed at observation visit and at EOT. \

The following analyses will be performed:

- The incidence and grade of LSRs will be summarized at each visit. LSR grades will be summarized by frequency counts and descriptive statistics by visit for each of the six individual LSRs: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration.



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- 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 at each visit using descriptive statistics.
    - The first visit at which the highest sum score is obtained will be summarized.
    - 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.

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

The incidence and severity of local skin responses following treatment will be presented.

A composite (sum) score will be obtained by summing the six individual LSR scores at each visit. The following analyses will be performed:

- The composite score and change from baseline will be summarized at each visit (pre-injection assessment) using descriptive statistics.
- The frequency distribution of the first visit (pre-injection assessment) at which the highest sum score is obtained will be presented.
- The frequency distribution of the first visit (pre-injection assessment) at which the LSR composite score returned to the baseline intensity for those subjects whose pre-injection LSR sum score increased in intensity from baseline.

### *8.8.8 Injection Site Pain Assessment*

The injection site pain assessment score as measured by the VAS and change from Baseline will be summarized descriptively by treatment group at each visit.

### *8.8.9 Pigmentation Assessment*

The pigmentation of the lesion will be assessed with a 0-3 scale (None=0, Mild=1, Moderate=2, Severe=3) using investigators' objective assessment of pigmentation for hyperpigmentation and hypopigmentation. Frequency distributions of subjects in each assessment category will be summarized by frequency table (count and percentage) by treatment group at each visit.

The incidence and severity of hypopigmentation and hyperpigmentation following treatment will be presented.



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### *8.8.10 Prior/Concomitant Medications and Concurrent Procedures/Therapies*

All prior and concomitant medications recorded in the eCRFs will be coded to match Anatomic Therapeutic Classification codes using version 01March2022 of WHO Drug dictionary. Descriptive summaries, by treatment group will be prepared (Prior Medications and Concomitant Medications) using the coded terminology. All prior and concomitant medications/therapies recorded in the case report form will be listed.

## 8.9 Subgroup Analyses

No subgroup analyses are planned.

## 8.10 Interim Analysis

No interim analyses are planned.

## 8.11 Methods for Handling Missing Data

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

**Missing Dates for Medical History, Prior/Concomitant Medications and Concurrent Therapies/ Procedures**

For the purpose of calculating the Study Day, the following algorithms will be applied to missing and incomplete start and stop dates:

| **Missing Date** | **Imputation for Start Date** |
|---|---|
| Day missing | If the day portion of the start date is missing, then the start date will be estimated to be the first of the month in which the event occurred, "01." |
| Month Missing | If the month portion of the start date is missing, then the start date will be estimated to be the first month of the year, (e.g., "JAN"). |
| Completely Missing | If the start date is completely missing the study day will be estimated to be "UNKNOWN". |
| **Missing Date** | **Imputation for Stop Date** |
| Day missing | If the day portion of the stop date is missing, the day will be estimated to be the last day of the month (e.g., UN-JAN-2013 will be treated as 31-JAN-2013). |
| Day and Month Missing | If the Month portion of the stop date is missing, the month will be assumed to be the last month of the year (e.g., "DEC") |
| Completely Missing | If the stop date is completely missing the study day will be estimated to be "UNKNOWN". |

No additional imputation will be performed.

## 9. CHANGES TO PLANNED PROTOCOL ANALYSIS

Thirty subjects were to be sequentially enrolled to 3 cohorts 30, 60, or 90 μg STP705 of 10 subjects each. The study was terminated prematurely prior to the completion of enrollment into the first cohort (30μg). No additional subjects will be enrolled into the subsequent cohorts.

All planned analyses will be performed for this dose group and the Clinical Study Report will be written accordingly.



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