STATISTICAL ANALYSIS PLAN
FOR PROTOCOL SRN-705-006

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

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SAP Version:	SAP – Final Version 3.0
SAP Date:	20 Mar 2023

I have read and approve the Statistical Analysis Plan specified above and agree on its content:

Statistician, Amarex Clinical Research	Date
Sirnaomics, Inc. Representative	Date

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ABBREVIATIONS, ACRONYMS, AND DEFINITIONS

Abbreviation/Acronym	**Definition**
ADA	Anti-drug Antibody
AE	Adverse Event
ALT	Alanine Transaminase
ASA	American Statistical Association
AST	Aspartate Transaminase
BCC	Basal Cell Carcinoma
BUN	Blood Urea Nitrogen
BMI	Body Mass Index
bpm	Beat per Minute
°C	Celsius
cm	Centimeter
COX	Cyclooxygenase
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicities
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
FDA	U.S. Food and Drug Administration
FU1	Follow Up Visits at 2 weeks
FU2	Follow Up Visits at 4 weeks
FU	Follow-Up
Hb	Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HC	Histological Clearance
HEENT	Head, Ears, Eyes, Nose, and Throat
HIV	Human Immunodeficiency Virus
i.e.	id est; Latin for “that is”

Abbreviation/Acronym	**Definition**
IA	Interim Analysis
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IP	Investigational Product
IRR	Infusion-Related Reaction
ITT	Intent-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
LSR	Local Skin Response
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mmHg	Millimeters of Mercury
msec	Millisecond
NCS	Not Clinically Significant
PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SV	Screening Visit
T1	Baseline/Treatment Visit
TEAE	Treatment Emergent Adverse Events
USA	United States of America

1. INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for the clinical trial protocol SRN-705-006, conducted by Sirnaomics. The reader of this Statistical Analysis Plan (SAP) is encouraged to review the complete protocol and amendments as this plan contains only a limited overview of protocol information. The main objectives of this plan are to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

The format and content of this SAP are structured to provide sufficient detail to meet the requirements specified by the International Council on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. All work planned and presented in this Statistical Analysis Plan will follow the ethical guidelines published by the American Statistical Association (ASA).

The following documents were reviewed in preparation of this Statistical Analysis Plan:

- Final protocol Version 4.0/24-AUG-2022
- ASA Ethical Guidelines for Statistical Practice (2016)
- The Royal Statistical Society: Code of Conduct (2014)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3(R1), 2013)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9(R1), 2017)

2. PROTOCOL DESIGN

2.1 Design Overview

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 30 subjects may be enrolled in six (6) cohorts: 30, 60, 90, 120, 180, 240 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 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) and 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 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

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

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.

  o 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

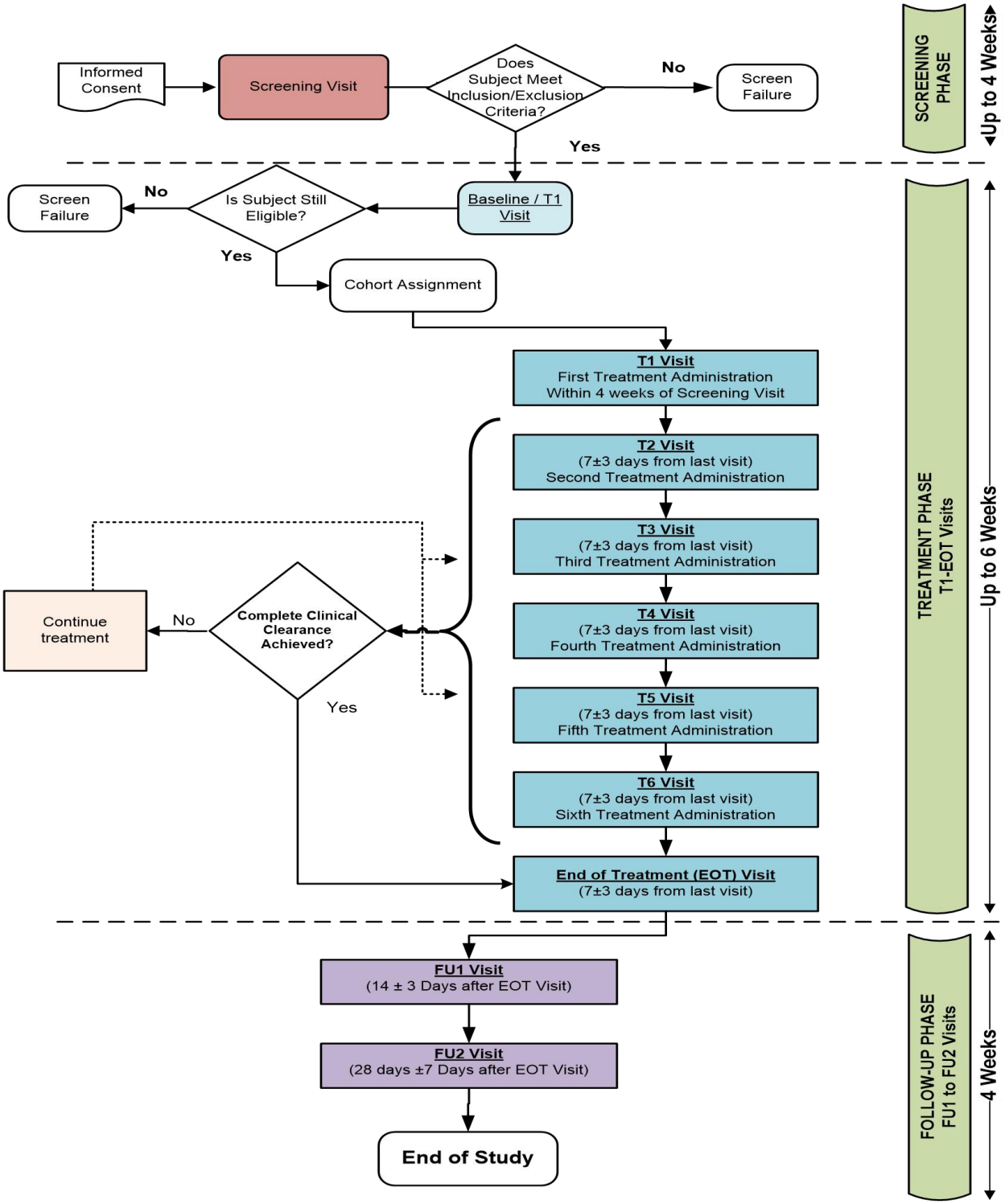
concomitant medications, symptom-directed physical examination, vital signs, 2D digital imaging of lesion/surgical site, pigmentation assessment, blood collection for Anti-drug antibody (ADA) assay (FU1 only) and blood collection for routine serum biochemical, hematologic, and urine laboratory assessments (FU2 only).

Duration of Treatment:

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

Total Study Duration: Up to 14 Weeks

Figure 2- 1: Study Schematics



2.2 Treatment Groups

The treatment groups to be evaluated in this study are described below.

Table 2- 1 Treatment Groups

Group	Description
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

2.3 Randomization and Stratification

Not applicable.

2.4 Blinding

Not applicable.

2.5 Protocol Objective

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.

2.6 Efficacy Outcome Measures

2.6.1 Primary Efficacy Outcome Measure

The primary outcome measure for the study 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.

2.6.2 Secondary Efficacy Outcome Measure

The secondary outcome measure for the study will be the 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.

2.6.3 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 Intralesional administration of STP705 as assessed by investigator-evaluation of injection site reactions for all patients and within each cohort.

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

3. Sample Size Determination, Statistical Power, And Significance Level

A total of up to 30 subjects (6 cohorts of 5 evaluable subjects each) will be assigned to receive study treatment. The sample size calculation is based on clinical judgment. Subjects who withdraw consent or drop out after first visit will be replaced. No statistical power calculation is used to establish the sample size.

4. 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 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) and 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.

5. PRIMARY HYPOTHESIS TO BE TESTED

There is no formal hypothesis testing for this study as the study is a Phase II evaluation and is not intended to be hypothesis generating. The study is not powered to reliably yield statistically significant conclusions.

6. ANALYSIS POPULATIONS

6.1 Intent-to-Treat (ITT) population

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

6.2 Per Protocol (PP) Population

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.

6.3 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.

6.4 Enrolled Population

The **Enrolled Population** will include all subjects who have met all of the eligibility criteria for enrollment into the study. This population will be used for the analysis of baseline parameters.

7. DATA CONVENTION AND RELATED DEFINITIONS

7.1 Baseline Definition

For all parameters, baseline will be defined as the last available value before the first treatment.

7.2 Duplicate Data

For unplanned duplicate data within a protocol-specified visit, all collected data will be listed and the last measured value will be used for the analysis. If it is not possible to identify the "last measured value," the average of the duplicate values will be used.

7.3 Outliers

Data points that appear to be outliers (i.e., clinically identified to be too small or too large) will be investigated and will not be excluded from the listings. If the clinician confirms that a data point is truly an outlier and is not clinically possible, two analyses will be performed, one with the outlier data point and one without it. Any such analysis will be clearly indicated and footnoted.

7.4 Handling of Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized to minimize missing data. Missing data will not be imputed.

7.5 Multicenter Clinical Trials

This is a multi-center clinical trial.

7.6 Multiple Comparisons and Multiplicity

There will be no adjustment for multiple testing or multiplicity for this phase II trial.

7.7 Covariates and Prognostic Factors

For efficacy analyses, the baseline values will be used as covariates in the analysis models.

7.8 Standard Calculations

7.8.1 Age

Age will be calculated according to the formula noted below.

Age (years) = integer of [(date of informed consent – date of birth)/ 365.25]

7.8.2 Body Mass Index (BMI)

BMI will be calculated using height (in cm) and weight (in kg) according to the formula noted below.

BMI (kg/m2) = Weight (kg)/[Height (cm)/100]^2

7.8.3 Change from baseline

Change from baseline will be calculated for each post baseline visit as follows:

Change From Baseline = Post baseline result at time - Baseline result

7.8.4 Percent Change from Baseline

Percent change from baseline will be calculated according to the formula noted below.

Percent change from Baseline = (Post baseline result at time - Baseline result) / Baseline result * 100

7.8.5 Height

For summary purposes height will be expressed in centimeters. Entries made in inches will be converted to centimeters using the formula noted below.

Height (cm) = Height (in)*2.54

7.8.6 Weight

For summary purposes weight will be expressed in kilograms. Entries made in pounds will be converted to kilograms using the formula noted below.

Weight (kg) = Weight (lb)/2.2046

8. STATISTICAL METHODS

All statistical analyses will be performed using SAS® for Windows, version 9.4 or later. All data collected during this study will be presented in subject data listings.

All the efficacy analyses presented here will be conducted using ITT and PP populations. All safety analyses will be conducted using the Safety population.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented by treatment group. For categorical variables both frequencies and percentages will be presented by treatment group.

8.1 Summarizing Disposition and Baseline Data

8.1.1 Subject Disposition and Withdrawals

There will be a detailed accounting of all subjects who sign an informed consent to participate in this trial. The following will be summarized by treatment group:

- The number of subjects who signed informed consent
- The number of subjects who are screen failures
- The number of subjects who received at least one study treatment
- The number of subjects who completed the study
- The number of subjects who discontinued prior to completion
    - Reasons for discontinuation prior to completion will also be summarized descriptively by treatment group.

The number of subjects in each analysis population will be summarized, reason for exclusion from analysis populations will be listed.

In addition, there will also be a listing of all subjects, which will provide the clinical trial center, nation, treatment group, study completion status and the specific reason for discontinuation.

8.1.2 Protocol Deviations

Protocol deviations will be identified and classified as minor or major before database lock.

Protocol deviations for all enrolled subjects will be listed as by-subject listing and major deviations will be summarized descriptively.

Additionally, a by-subject listing of all deviations will also be prepared.

8.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, race, gender and ethnicity) will be presented as by-subject listing and summarized by treatment group. See Section 7.1 for baseline definition.

Medical history results and serology will be provided as by-subject listings.

8.1.4 Prior and Concomitant Medications

Prior medication is defined as any medications with an end date prior to the first treatment date.

All prior and concomitant medications recorded in the case report form will be listed and coded to the drug substance level (i.e., generic term) using the most recent version of WHO Drug dictionary, and summarized by treatment group and by the number and percentage of subjects taking each medication for the Safety population.

8.1.5 Extent of Exposure

All treatment administration and compliance data will be listed and summarized for the Safety population.

8.2 Analysis of Efficacy Data

The primary analysis will be conducted on the ITT population. The PP population will be used as a supportive analysis if there is at least 5% difference between the numbers of subjects in the two populations. Any observations excluded from the efficacy analyses will be listed as by-subject listings.

All efficacy data collected will be summarized and analyzed according to the variable type:

- Continuous data summaries will include number of observations, mean, standard deviation, median, and minimum and maximum values.
- Categorical data summaries will include frequency counts and percentages.

8.2.1 Primary Outcome Measure

The primary outcome measure 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.

The proportion of subject with histological clearance of treated basal cell carcinoma lesion at the End of Treatment (EOT) will be summarized descriptively by cohort group.

All data from this outcome will be presented as by-subject listing.

8.2.2 Secondary Outcome Measure

The Secondary outcome measure is the change in size of the treated basal cell carcinoma lesion over the 6 week treatment period.

A baseline 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.

The size (or area) to be calculated programmatically as “Longest diameter x Width measurement” for this analysis. The change from baseline in size of the treated basal cell carcinoma lesion over the 6 weeks treatment period will be presented and summarized descriptively by cohort group.

All data from this outcome will be presented as by-subject listing.

8.3 Analysis of Safety Data

All safety analyses will be conducted using the Safety population. All data collected will be summarized according to the variable type. No inferential statistics are planned.

8.3.1 Adverse Events

Adverse events will be classified by system organ class (SOC) and preferred term (PT) according to the most recent version of MedDRA dictionary.

TEAE are defined as adverse events with onset date 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:

a) Overall (*i.e.,* regardless of severity or relationship to treatment)
b) Sever adverse events
c) Related adverse events
d) Adverse events leading to treatment discontinuation
e) Adverse events leading to death

Unless otherwise specified, at each level of subject summarization, a subject will be counted only once. If there is more than one occurrence of an event, the event of the worst severity or the worst-case relationship category will be summarized.

AEs leading to premature discontinuation of clinical trial treatment and Serious Adverse Events (SAEs) will also be summarized by treatment group and relationship.

All adverse events recorded in the eCRF will be presented as by-subject listings.

8.3.2 Clinical Laboratory Evaluations

All results of laboratory evaluations will be presented as by-subject listings.

8.3.2.1 Laboratory Values over Time

Summary statistics of raw data and change from baseline values for biochemistry, hematology and urinalysis laboratory parameter will be presented by treatment group and time point. Data will be summarized as appropriate for the variable type.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.3.2.2 Individual Patient Changes

Laboratory data will be classified into grades according to CTCAE toxicity grading. A severity grade of 0 will be assigned when the value is within normal limits.

The following summaries will be produced for the hematology and biochemistry laboratory data (by laboratory parameter):

- Shift tables using CTCAE grades to compare baseline to the post-baseline value will be produced for hematology, biochemistry laboratory parameters with CTCAE grades

8.3.2.3 Individual Subject Changes on Interpretation

Shift tables will be presented for the investigator lab interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects, by treatment group for laboratory parameters.

8.3.3 Vital Signs

Vital sign assessments are performed in order to characterize basic body function. The parameters collected in this study are Height (cm), Weight (kg), systolic BP (mmHg), diastolic BP (mmHg), temperature (^{0}C), heart rate (bpm), respiratory rate (bpm).

8.3.3.1 Vital Signs Values over Time

Summary statistics of raw data and change from baseline values for each vital sign parameter will be presented by treatment group and time point. Data will be summarized as appropriate for the variable type.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.3.3.2 Individual Patient Changes on Notable Vital Sign Values

Clinically notable elevated values

- Systolic BP: >= 160 mmHg and an increase >= 20 mmHg from baseline
- Diastolic BP: >= 100 mmHg and an increase >= 15 mmHg from baseline
- Body temperature: >= 39.1°C
- Weight: increase from baseline of >= 10%
- Heart rate: >= 120 bpm with increase from baseline of >=15 bpm
- Respiration rate: >= 24 breaths per minute with increase from baseline of >= 6 breaths per minute from baseline

Clinically notable below normal values

- Systolic BP: <= 90 mmHg and a decrease >= 20 mmHg from baseline
- Diastolic BP: <= 50 mmHg and a decrease >= 15 mmHg from baseline

- Body temperature: <= 35°C
- Weight: decrease from baseline of <= 20%
- Heart rate: <= 50 bpm with decrease from baseline of >= 15 bpm
- Respiration rate: < 8 breaths per minute with decrease from baseline of >= 6 breaths per minute from baseline

Number and percentage of patients with at least one post-baseline vital sign abnormality (in both directions, i.e. both elevated and below normal values) will be summarized for by treatment group.

8.3.4 Physical Examination

Physical Examination findings will be presented as by-subject listing.

8.3.5 Electrocardiogram (ECGs)

The ECG parameters include ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec) QTcB Interval (msec), QTcF Interval (msec), RR Interval (msec), heart rate (beats per minute). Majority of the ECG parameters will be received as external data from Biotel Research (Cardiocore & VirtualScopics) and captured with in the EDC system as well. For all the summary purposes the data from the external source will be used.

8.3.5.1 ECG Values over Time

Summary statistics of raw data and change from baseline values for each ECG parameter will be presented by treatment group and time point. Data will be summarized as appropriate for the variable type.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.3.5.2 Individual Patient Changes on Notable ECG Values

The number and percentage of patients having notable ECG interval values and newly occurring qualitative ECG abnormalities will be summarized by treatment group.

The following notable ECG interval values for each parameter will be presented as by-subject listing. Number and percentage of subjects with at least one occurrence of the below notable ECG changes will be summarized.

QT and QTc and QTcB and QTcF:

(1) New >450 msec

(2) New >480 msec

(3) New >500 msec

(4) Increase from baseline >30 msec

(5) Increase from baseline >60 msec

Shift tables will also be presented using frequency and percentages for the categories of QT results (<=450, >450-480, >480-500, >500) with counts and percentages of subjects, for shift (change) from baseline.

PR:

(1) An increase >25% from baseline and PR >200 msec at any post-baseline assessment

RR:

(1) An increase >25% from baseline and RR >1200 msec at any post-baseline assessment

(2) Decrease >25% from baseline and RR <600 msec at any post-baseline assessment

QRS:

(1) An increase >25% from baseline and QRS >110 msec at any post-baseline assessment

Ventricular rate and Heart Rate:

(1) Increase >25% from baseline and HR >100 bpm at any post-baseline assessment

(2) Decrease >25% from baseline and HR <50 bpm at any post-baseline assessment

8.3.5.3 Individual Subject Changes on Interpretation

Individual subject changes will be identified through shift tables. Shift tables will be presented for the investigator ECG interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects, by treatment group, for shift (change) from baseline, using the normal ranges.

8.3.5.4 Clinically Significant Abnormalities

A by-subject listing of treatment-emergent clinically significant ECGs, by treatment group, will be prepared.

8.3.6 Serum Pregnancy Test

All the results for serum pregnancy test will be presented as a by-subject listing.

8.3.7 Urine Pregnancy Test

All data from Urine Pregnancy test will be presented as a by-subject listing.

8.3.8 Local Skin Response (LSR)

All data from Local Skin Response will be presented as a by-subject listing and summarized descriptively by cohort.

8.3.9 Injection Site Pain

All data from Injection Site Pain using 11-point numeric pain rating scale will be presented as a by-subject listing and summarized by cohort.

8.3.10 Pigmentation Assessment

The presence and severity of hyperpigmentation/hypopigmentation/depigmentation will be presented as a by-subject listing and summarized.

8.3.11 Surgical Excision of Tumor

All data from Surgical Excision of Tumor will be presented as a by-subject listing.

8.3.12 Serology

All data from Serology will be presented as a by-subject listing.

9. APPENDIX I: SCHEDULE OF ASSESSMENTS

Table 9-1: 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 Numeric Pain Rating Scale) [l]			X	X	X	X	X	X			
2D Photography of lesion [m]	X	X	X	X	X	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
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 protocol 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 protocol section 7.12 for details. Note: Use of pain block anesthesia would also be documented on the Pain Assessment Sheet.

[m] See protocol 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.

10. APPENDIX 2

10.1 Planned by-subject listings

DISPOSITION/WITHDRAWALS (LISTINGS 16.2.1.X)

PROTOCOL DEVIATIONS (LISTINGS 16.2.2.X)

SUBJECTS EXCLUDED FROM THE EFFICACY ANALYSIS (LISTINGS 16.2.3.X)

DEMOGRAPHIC DATA (LISTINGS 16.2.4.X)

INDIVIDUAL EFFICACY RESPONSE DATA (LISTINGS 16.2.6.X)

ADVERSE EVENT LISTINGS (LISTINGS 16.2.7.X)

INDIVIDUAL LABORATORY MEASUREMENTS (LISTINGS 16.2.8.1.X)

OTHER SAFETY DATA (LISTINGS 16.2.8.2.X)

OTHER LISTINGS (LISTINGS 16.2.8.3.X)

10.2 Planned Summary Tables

POPULATION DISPOSITION AND PROTOCOL DEVIATIONS
POPULATION DEMOGRAPHICS AND BASELINE CHARACTERISTICS
CONCOMITANT MEDICATION USAGE
EFFICACY SUMMARIES
SAFETY SUMMARIES
- ADVERSE EVENT SUMMARIES
- SERIOUS ADVERSE EVENTS
- LABORATORY
- VITAL SIGNS
- OTHER SAFETY

11. REFERENCES

1. ASA Ethical Guidelines for Statistical Practice (2016)
2. The Royal Statistical Society: Code of Conduct (2014)
3. ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
4. ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3(R1), 2013)
5. ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998)
6. ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9(R1), 2017)

12. VERSION HISTORY

Version 1

This is the first version of this document.

Changes included in the Version 2 of this document

Added 2 more cohorts D and E: 120 and 180 μg dose level.

Updated wording in vital signs section to include height and weight as parameters.

Included ECG parameters from external in ECG section: QTcB Interval (msec), QTcF Interval (msec), RR Interval (msec) and heart rate (beats per minute).

Editorial changes were made for clarity and per the updates from the protocol.

Changes included in the Version 3 of this document

This is the third version of this document and the chanes are outlined below:

1. Section 2.1: Design Overview

Change:

a. Up to ~~25~~ 30 subjects may be enrolled in six (~~5~~ 6) cohorts: 30, 60, 90, 120, 180 and 240 μg dose level with five (5) evaluable subjects each.

b. 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 that are of CTCAE grade 3 or greater severity

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

Rationale: Editorial changes were made for clarity and per Amendment 4.0 of the protocol

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2. Section 8.3.12: Serology

Change:

Adding a section for serology analysis.

Rationale: To present all the data collected for the study.

3. Section 8.3.8: Anti-Drug Antibody Analysis

Change: removed form the SAP

Rationale : per the commincation with the clinical team the data will not be transferred to Amarex.

4. Section 8.3.2.3: individual subject change on interpretation

Change:

Shift tables will be presented for the investigator lab interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects, by treatment group for laboratory parameters ~~without CTCAE grade~~.

Rationale: Shift tables will be presented per the Normal, Abnormal (not clinically significant) and Abnormal (clinically significant) findings from the investigator lab interpretation and not by CTCAE grading.

5. Section 8.3.12: Immunohistochemistry Analysis

Change: Section has been removed.

Rationale: per the confrimatoin from Clincal, the data for this has not been collected.

6. Section: 8.3.5: Electrocardiogram (ECGs).

Change: Added more parameters.

Rationale: To be consistent with the data collection.

7. Section: 8.3.5.2: Individual Patient Changes on Notable ECG Values.

Change: Added criterias to evaluate changes.

Rationale: Per discussion with internal safety team to present the data in a meaningful way.