16.1.9. Documentation of Statistical Methods

Statistical Analysis Plan (SAP)

SAP Version 1.0 dated 27 September 2022 (Phase 1)

SAP Version 1.0 dated 19 July 2023 (Phase 2a)

STATISTICAL ANALYSIS PLAN

Study Title:	A Multicenter Phase 1/2a, Open-Label Study of SQ3370 in Patients with Advanced Solid Tumors
Sponsor	Shasqi Inc 665 3rd Street Suite 501 San Francisco, CA 94107 USA
Protocol Number	SQ3370-001 Amendment 7 (25JUL2022)
IND Number	137024
Investigational Product	SQ3370
Phase of Development	Phase 1 / 2a
Analysis Plan Version	Draft Version 1.0
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STATISTICAL ANALYSIS PLAN APPROVAL

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADaM	Analysis data model
AE	Adverse event
AESI	Adverse event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AV	Atrioventricular
BP	Blood pressure
BSA	Body surface area
CAPAC™	Click Activated Protodrugs Against Cancer
CBC	Complete blood count
CHF	Congestive heart failure
CNS	Central nervous system
CS	Clinically significant
CSF	Colony-stimulating factor
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
Dox	Doxorubicin
Dox Eq	Doxorubicin hydrochloride molar equivalent (1 g of SQP33 protodrug is equivalent to 0.7153 g of doxorubicin hydrochloride)
Dox HCl	Doxorubicin hydrochloride
DOXIL/CAELYX	Liposomal doxorubicin
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
eCRF	Electronic case report form
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HNSTD	Highest non-severely toxic dose
ICF	Informed consent form
IRB	Institutional Review Board
IV	Intravenous(ly)
LFT	Liver function tests
LVEF	Left ventricular ejection fraction
MAD	Maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUFA	Multigated acquisition

N/A	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria
NOAEL	No-observed-adverse-effect level
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cell
PK	Pharmacokinetic(s)
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE SOC SRC	Serious adverse event
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the data analysis specifications for Shasqi, Inc protocol SQ3370-001 titled: "*A Multicenter Phase 1/2a, Open-Label Study of SQ3370 in Patients with Advanced Solid Tumors (Amendment 7)*. It details the inferential statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical study protocol.

This version of the SAP was prepared in accordance with the protocol SQ3370-001 Amendment 7 dated July 25, 2022. Other related documents are the annotated subject case report forms and the corresponding Medidata RAVE electronic data capture (EDC) data dictionary.

This SAP will be finalized prior to the Phase 1 dose escalation database lock data availability and describes the statistical analysis as it is foreseen when the study was being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the approved SAP after database lock data availability, reasons for such deviations, and all alternatives or additional statistical analyses that may be performed will be described in the final clinical study report. This SAP supersedes the statistical considerations identified in the protocol.

NOTE: This SAP will focus on the Phase 1 Dose Escalation part of this study. A separate SAP will be written for the Phase 2a Expansion part.

2. OVERVIEW OF STUDY TREATMENT AND STUDY DESIGN

2.1 Study Treatment

SQ3370 is a novel Investigational Product that enables local targeting and activation of a cytotoxic protodrug without the need for specific molecular biomarkers. SQ3370 utilizes Shasqi's proprietary Click Activated Protodrugs Against Cancer (CAPAC™) platform where mutually reactive click chemistry groups release doxorubicin (Dox) at the tumor site minimizing systemic exposure.

The therapeutic goal of SQ3370 is to enhance the antitumor efficacy of doxorubicin by increasing its concentration at a specific tumor site while minimizing its systemic toxicity.

The SQ3370 Investigational Product consists of 2 components:

(1) Intratumoral injection of a protodrug activating biopolymer (SQL70: 10 mL or 20 mL).

(2) five consecutive days of intravenous (IV) infusions of a trans-cyclooctene (TCO)-modified protodrug of Dox with attenuated cytotoxic activity (SQP33) for a 21-day cycle. In and around the tumor site, SQL70 biopolymer selectively and rapidly captures SQP33 protodrug via an irreversible covalent reaction between tetrazine and TCO (biorthogonal chemical groups), followed by local release of active Dox. SQP33 is the active component.

An individual cycle of treatment is defined as a 3-week (21-day) period where SQL70 biopolymer is injected into lesion(s) on Day 1 followed by 5 consecutive daily infusions of SQP33 protodrug (Day 1 – Day 5).

The SQL70 biopolymer and SQP33 protodrug are packaged separately given that the number of SQP33 protodrug vials needed will vary by subject/cohort dose level.

2.2 Experimental Design

This multicenter, Phase 1/2a, first-in-human, single-arm, open-label, dose-escalation study will be conducted in two stages. This includes a dose escalation stage to evaluate the safety and tolerability, PK, and preliminary efficacy of SQ3370 in subjects with locally advanced or metastatic solid tumors for which an anthracycline-containing regimen is appropriate and who have an injectable tumor. The dose- escalation portion of the study will be used to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of SQ3370. The SQL70 biopolymer will be administered intra and/or peritumorally at a dose of either 10 mL or 20 mL injection volume. The 10 mL dose is intended for a single lesion or cluster of lesions, and the 20 mL dose is for concurrent treatment of 2 lesions, or for a single larger lesion.

2.2.1 Dose Escalation Cohorts Phase 1

Subjects enrolled into this study will be divided into two groups:

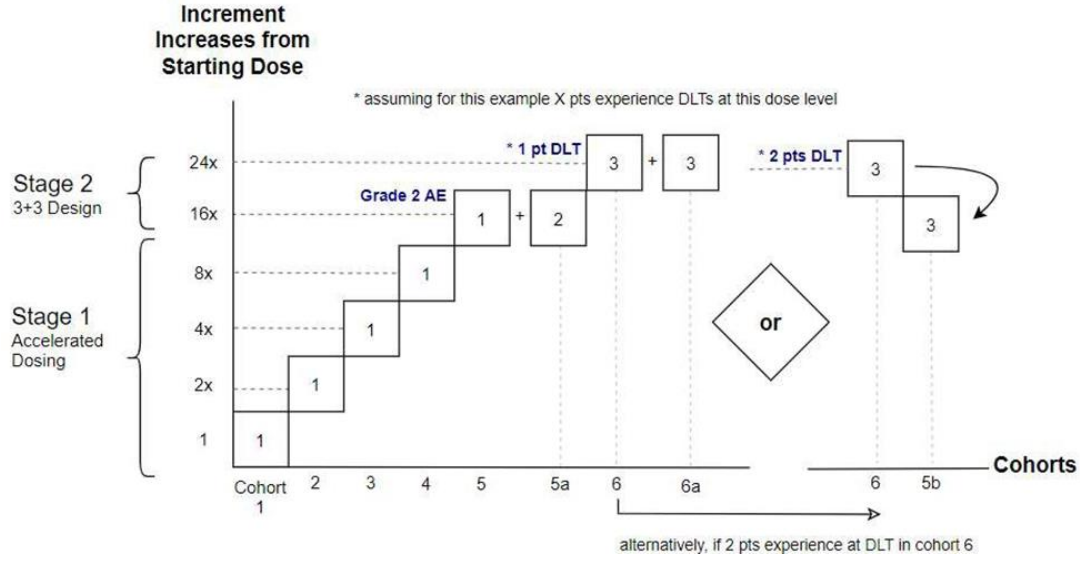
Group 1- 10 mL SQL70 Biopolymer (post-Cycle 1) Cohort: Subjects that will have one lesion injected during cycle 1 (10 mL injection volume) with the possibility of additional lesions injected in later cycles. This group consists of an accelerated dose-escalation with 1 subject per dose (stage 1) followed by a 3+3 (Rolling 6 design where between 3-6 subjects may be enrolled concurrently) (stage 2) beginning with the highest dose evaluated during stage 1.

Group 2- 20 mL SQL70 Biopolymer (from Cycle 1) Cohort: Subjects that may have one or more lesions injected during cycle 1 (20 mL injection volume) and consists of a cohort of subjects to be evaluated following administration of 20 mL of SQL70 biopolymer in one or two lesions starting at Cycle 1. This cohort of subjects will be enrolled at an initial dose level of SQP33 protodrug that is lower than the dose level being evaluated in the standard dose escalation (Group 1) at the time of initiation of this cohort. This 20 mL SQL70 biopolymer (from cycle 1) cohort will follow the same 3+3 (Rolling 6) escalation design as described below. The SRC will decide if another cohort of subjects should be enrolled at a higher SQP33 protodrug dose with the same 20 mL SQL70 biopolymer volume.

2.2.2 Dose Escalation Methods

The dose escalation portion of the study comprises an initial period of accelerated titration cohorts (Stage 1) followed by 3+3 (Rolling 6) design (Stage 2). Subjects will receive specific dose levels of SQP33 protodrug assigned according to the dose escalation design described below. This design is appropriate for cytotoxic therapies to minimize subject dosing at subtherapeutic levels. Additionally, two Phase 1 clinical trials with similar aminoglycoside-modified Dox-based drugs used similar accelerated dosing protocols and dose adjustment criteria (DiPaola 2002; Schöffski 2017).

Schema of Single Patient Accelerated Dose Escalation Followed by 3+3 Design with Modified Fibonacci Dose Escalation



The SRC will review all available safety data at the completion of Cycle 1 for each of the dose escalation cohorts and the cohort receiving 20 mL SQL70 biopolymer from Cycle 1 to

evaluate possible DLTs, recommend whether more subjects should be enrolled at a given dose level / cohort, and recommend whether to dose escalate or to stop enrollment based on the definition of DLTs in addition to its members' best clinical judgement.

Stage 1: Accelerated Titration

In the absence of AEs considered by the SRC to be clinically relevant during any cycle, the SQP33 protodrug accelerated dose titration stage includes 1 subject enrolled per cohort with a doubling of the SQP33 protodrug dose level between cohorts.

Escalation transitions to a standard 3+3 modified Fibonacci design (see below) upon identification during the DLT period of either:

- a DLT, or
- any Grade ≥2 AE considered to be at least possibly related to study drug

Stage 2: 3+3 (Rolling 6) Design

The 3+3 (Rolling 6) design stage includes 3-6 subjects enrolled per cohort and utilizes a modified Fibonacci scale to determine the dose level increase and minimum number of subjects enrolled per dose level (Table 3). In the Rolling 6 design, a minimum of three, and up to six subjects may be concurrently enrolled at each dose level in the study prior to convening the SRC to evaluate the safety and tolerability of the dose level.

The first cohort of subjects enrolled in the Stage 2 dose escalation portion will be at the same dose level as the highest evaluated Stage 1 dose level. This will ensure that any dose level resulting in a DLT is tested in additional subjects prior to continued dose escalation. If 2 subjects experience 1 or more DLTs in any cohort, no additional subjects will be enrolled at that dose level and further subjects will be enrolled at a lower dose level.

Decisions as to whether to allow additional enrollment beyond the minimum of three into a cohort or pause accrual for that cohort will be made by the Sponsor based on available data (i.e., the Sponsor will inform sites if a cohort is still open for additional accrual or if the cohort is closed to accruals). Dose level assignments are based on the number of participants currently enrolled in the cohort, the number of DLTs observed, the number of participants who have not completed the DLT period, general tolerability observed, and any available PK data.

Modified Fibonacci Dose Escalation Scale (Stage 2)

Number of Patients with DLTs in a Dose Level	Action
0 patients with DLTs across 3-6 patients in a dose level	Enroll an additional 3 to 6 patients at a dose level escalation of 50%
1 patient with a DLT across 3-5 patients in a dose level	• Enroll additional patients (for a total of 6 at this dose level) ○ If no patients experience additional DLTs across the 6 total patients, then enroll 3 patients at a dose level escalation of 33% ○ If a second patient experiences a DLT, see the below (≥ 2 DLTs across ≥ 3 patients at a dose level)
≥ 2 patients with DLTs in a dose level	• Dose escalation will be stopped. ○ An intermediate dose level may be explored that is not higher than the MAD

Finally, a determination of the recommended Phase 2 dose(s) (RP2D) will be determined based on all available dose escalation data. This includes PK/PD analysis, tolerability that will include the incidence and severity of DLTs, other AEs and the evidence for biological activity at each dose level tested. The RP2D will be defined by an SQP33 protodrug dose and a SQL70 biopolymer volume and carried forward into the Phase 2a dose expansion phase of this study.

2.3 Phase 2a: Expansion Groups

Subjects will be enrolled in the Phase 2a expansion groups to study the preliminary activity and gain additional SQ3370 safety data, dosing schedules, as well as PK and immune changes in blood and tumor tissue.

A separate SAP will be written for the Phase 2a Expansion Group part of this study.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Dose Escalation Primary Objectives

Assess the safety and tolerability of SQ3370 treatment, including determination of the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of SQP33 protodrug administered with 10 mL and/or 20 mL of SQL70 biopolymer

3.1.2 Dose Escalation Secondary Objectives

- Characterize the PK profile of SQP33 protodrug and active doxorubicin (Dox) following SQ3370 treatment

- Assess preliminary signals of SQ3370 anti-tumor activity

3.1.3 Dose Escalation Exploratory Objectives

- Assess the concentration of active Dox and SQP33 protodrug following SQ3370 treatment at the local site through analysis of tumor biopsies
- Assess immune response through biomarker analysis of tumor biopsies and peripheral blood specimens
- To study the pharmacodynamics (PD) of SQ3370 therapy by assessing potential biomarkers in archival tumor tissue and peripheral blood.

3.2 Study Endpoints

3.2.1 Safety Endpoints

Frequency of adverse events (AEs), Serious Adverse Events (SAEs) and dose-limiting toxicities (DLTs), as well as changes from baseline in vital signs, clinical laboratory parameters, physical examination findings, ECHO/MUGA, and electrocardiogram (ECG) results.

3.2.2 Efficacy Endpoints

- Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Duration of Response (DoR) in target lesion(s) (including both injected and, if available, non-injected tumors).
- Disease Control Rate (DCR)
- Duration of Stable Disease
- Change in size of target lesion(s) (including both injected and, if available, non-injected tumors).

3.2.3 Pharmacokinetic (PK) Endpoints

Plasma concentration and pharmacokinetics (PK) parameters for SQP33 protodrug and active Dox following SQ3370 treatment.

3.2.4 Exploratory Endpoints

- Assess the presence of SQP33 protodrug and active Dox in tumor tissue.
- Characterize immune response in blood and tumor tissue over time following treatment with SQ3370.

4. SAMPLE SIZE JUSTIFICATION

The dose escalation portion of the study is based on Design 4 in Simon 1997 and comprises an initial period of accelerated titration cohorts (Stage 1) followed by 3+3 (Rolling 6) cohorts (Stage 2). No formal sample size calculations were used to determine sample sizes. Total enrollment is not predefined and is dependent upon the Dose Limiting Toxicities (DLT) observed and the number of escalation cohorts.

The following sample sizes are planned:

- Accelerated Dose-Escalation: n=1 subject per cohort
- 3+3 Dose Escalation: n=3 to 6 subjects per cohort

Additional subjects may be enrolled for the cohorts having multiple lesions injected during cycle 1 (3+3 cohorts and any additional cohorts recommended by the SRC).

Subjects may be replaced if they were enrolled into the study but did not receive the intended doses of study drug during Cycle 1 for reasons other than adverse events (AEs).

5. RANDOMIZATION, BLINDING, AND REPLACEMENT OF SUBJECTS

This is an open-label study with the identity of the treatment known to the subjects, Investigators, and Sponsor; therefore, no randomization or blinding procedures will be performed.

All subjects will receive SQ3370 treatment according to the dose cohort in which they are enrolled. Subjects will be enrolled into open dosing cohorts from all participating centers.

Subjects who are lost to follow-up or withdraw consent for study participation prior to administration of study drug may be replaced, at sponsor’s discretion.

6. DEFINITIONS OF SUBJECT POPULATIONS TO BE ANALYZED

This study will have six analysis populations:

- Enrolled: All subjects who sign consent.
- Treated / Full Analysis Set: All subjects who receive at least 1 dose of SQL70 biopolymer and 1 dose of SQP33 protodrug.
- Safety Analysis Set: All subjects who received at least 1 dose of SQL70 biopolymer and/or SQP33 protodrug.

- Efficacy Evaluable Analysis Set: All subjects who receive at least 1 dose of SQL70 biopolymer and 1 dose of SQP33 protodrug and undergo at least 1 post baseline tumor evaluation
- PK Analysis Set: All subjects in the Safety Population who have the necessary Day 1 and on-study measurements to provide interpretable results for the specific parameters of interest.
- Biomarker Analysis Set: All subjects with available biomarker data.

7. PLANNED ANALYSES

7.1 Interim Analysis

There are no formal interim analyses planned for this Phase 1 open-label study. All subjects will receive SQ3370 treatment according to the dose cohort in which they are enrolled. A Safety Review Committee (SRC) will review the data in an ongoing manner and include the study team led by the medial monitor, and the active Investigator(s). The SRC will review all available safety data at the completion of Cycle 1 for each cohort to evaluate possible DLTs, recommend whether more subjects should be enrolled at a given dose level / cohort, and whether to dose escalate or to stop enrollment based on the definition of DLTs in addition to its members' best clinical judgement and will provide recommendations to the sponsor.

With agreement from the sponsor, the dose escalation scheme may be modified (e.g., smaller increases or decreases in dose may be permitted, infusion timing, duration, or schedule may be modified) based on available PK and pharmacodynamic data, and/or the timing and severity of AEs observed. Changes that can only be made with a protocol amendment will include:

- Dose level escalations that are increased by larger increments than the scheme in the protocol
- Administration of more than 5 SQP33 infusions per cycle
- Administration of more than 20 mL of SQL70 biopolymer per cycle

Summary tables and listings will be generated after the Dose Escalation phase has been completed.

7.2 Final Analysis

The final tables, listings, graphs, and data analysis will be conducted once all study participants have completed the study (dose escalation phase) and the clinical database has been locked.

8. DATA PRESENTATION AND HANDLING

8.1 Table and Individual Subject Data Listing Considerations

Summary tables and listings will be prepared according to ICH Guideline E3 (as appropriate for a Phase I study).

In general, summary tables will be organized with respect to:

- SQL70 biopolymer dose (10 mL and 20 mL)
- SQP33 protodrug Dose Escalation: lowest dose to highest dose
- Total per SQL70 biopolymer dose

Row entries in post text tables are made only if data exists for at least one subject (e.g., a row with all zeros will not appear). The only exception to this rule will apply to tables that summarize the study termination status of subjects (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables will clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

Summary tables for any concomitant medications will be coded according to the World Health Organization (WHO) Drug dictionary September 2020. Adverse event preferred terms and body/organ systems and medical history conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary Version 24.1 (or later).

Listings will also be sorted by dose cohort (where applicable) and subject number. Listings will also include visit number, visit date/time and days relative to the initiation of study treatment.

In general, missing data will not be imputed unless otherwise specified. Any imputed or derived data will be flagged in the individual subject data listings. Imputed data will not be incorporated into any raw or primary datasets. These data will be retained in derived analysis datasets.

8.2 Format Considerations

The tables, figures and listings will be numbered using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with two digits per level (e.g., Table XX.YY.ZZ. …).

1. The first level number will be consistent with the corresponding Clinical Study Report (CSR) appendix in which the tables or listings will appear. For example, the post text tables will appear in Appendix 14 (and will be numbered 14.XX.YY) and the

individual subject data listings will appear in Appendix 16 (and will be numbered 16.XX.YY). The subject disposition table will be first in the first section of the report and will be numbered Table 14.1. The supportive subject data listing will be Listing 16.1. Any subset table will have the number Table 14.1.2, etc.

2. Table numbering will follow ICH E3 for Phase I CSRs. Subject disposition, baseline and demography and prior and concomitant medications tables should appear as the second level number (Table 14.1 series). Efficacy tables will occupy the next sub-level (Table 14.2 series – 14.2.1, 14.2.2 and 14.2.3, respectively). Safety tables will follow next (Table 14.3 series). Similar conventions will be applied to the subject data listings.
3. Each table and listing title will be complete, accurate and concise. The last line of the title will provide the analysis group being summarized (e.g., Safety Population or Efficacy Evaluable Population).
4. If possible, variables being summarized, and statistics reported will appear in the left most column of a table. The next columns for (dose level) should report the data from left to right for the SQ3370 treatment dose cohort (from low to high).

8.3 Data Management

All data will be recorded by the site in individual source documents. An eCRF will be created by the data management vendor (Novotech) for recording of the required data in the study database. All eCRF information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be subject to data validation checks for consistency and completeness by the data management vendor and sponsor. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

Database build, AE coding, medication coding, data cleaning will be conducted according to the Novotech (vendor clinical research organization) Data Management Plan for this specific study.

Derived datasets (including SDTM and ADaM) will be created using SAS® software. Data analyses and summary tables will be generated using the currently supported version at the time of data analysis (currently version 9.4).

8.4 Data Presentation Conventions

Continuous safety variables (e.g., clinical laboratory values and vital signs) will be listed to the same precision as the source data. Derived variables will be calculated and listed using the same precision as the value(s) from which they were derived.

For the tabular reporting of descriptive statistics:

- Continuous variables: the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD.
- Categorical/discrete variables: the frequency count and the percentage (of available data) for each class of the variable will be presented and will be displayed in the form XX (XX.X%) where the percentage is in the parentheses. All percentages will be presented to 1 decimal place, unless otherwise specified. Percentages equal to 100 will be reported as 100% and percentages will not be presented for zero frequencies. Unless otherwise specified, percentages will be calculated based on the number of subjects specified by the appropriate population definition.
- Date variables: formatted as DDMMMYYYY for presentation. Time will be formatted in military time as HH:MM for presentation.

Extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables but will be included in subject listings. They will be used in summary tables which are not ‘time specific’, for example, summaries of minimum maximum, first, last, average post dose values.

All tables, listings, figures will be produced in landscape orientation using Arial 9-point font. Output files will be created in rich text file (RTF) format.

Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 9.5).

The table, figures and listing shells and table of contents as part of this SAP provide the expected layout and titles of the tables, listings, and figures. Any changes to format, layout, titles, numbering, etc. will not necessitate a revision to the SAP, nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling (e.g., change in the population used, change from statistical method/assumption listed, transformation of data type [e.g., continuous data transformed to categorical], exclusion of planned analysis, etc.) or additional unplanned analyses will necessitate a

revision to this SAP. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

8.5 Treatment Comparisons

The following labels for dose level will be used on all tabulations, in the following order:

Dose Escalation: 10mL SQL70 Biopolymer + SQP33 Dox Equiv. Dose (mg/m2)									
0.38x (N=00)	0.76x (N=00)	1.53x (N=00)	2.8x (N=00)	4x (N=00)	6x (N=00)	8x (N=00)	12x (N=00)	15x (N=00)	Total (N=00)

Dose Escalation: 20mL SQL70 Biopolymer + SQP33 Dox Equiv. Dose (mg/m2)		
4x (N=00)	6x (N=00)	Total (N=00)

8.6 Definitions, Computations, Derived Data

- Screening: Screening is defined as ≤ 28 days prior to Cycle 1 Day 1 prior to the first study drug administration.
- Baseline: Measurements taken at Screening or prior to receiving the first dose of study drug; whichever is latest.
- Study Day and Cycle Day follows the CDISC standard and is defined as:
    - On-study Assessment Days (Assessment date – First date of study drug dosing of the first cycle) + 1, where the assessment date is on or after the first date of dosing of the first cycle.
    - Screening Days (Assessment date – First date of study drug dosing of the first cycle), where the assessment date is before the first date of dosing of the first cycle. For this protocol, screening days are from Day -28 to -1.
    - There will be no Study Day 0.
    - “Study Day x” (where x>0) refers to the number of days from first dosing date in Cycle 1. For example, Study Day 1 is Cycle 1 Day 1.
- Visit Nomenclature: Nominal visits nomenclature on the CRFs and the scheduled visit will be used for summary tables.
    - Scheduled visits for the Treatment Period are: “Screening”, “Cycle x Day 1” (where x = 1, 2, 3, … 9), Days 1, 2, 3, 4, 5, 10, 17, etc.
    - Safety follow-up visit is 28-34 days after the last dose of study drug and on-site.
    - Long Term follow-up visits are every 12 weeks (on or off site).

- Assessment for response and tumor burden is planned every 6 weeks and at Safety follow-up and long-term follow-up.
- The objective response rate (ORR): Percentage of subjects whose best objective response recorded from the start of the treatment until disease progression/recurrence is a CR or PR according to RECIST 1.1 criteria.
- Best Overall Response (BOR) is defined as the best response recorded in the case report form after the start of the study treatment.
- The Maximum Tolerated Dose (MTD) is defined as the dose level of SQP33 protodrug in 2 or more subjects experiencing a DLT during Cycle 1 of treatment across all subjects treated (up to 6). An SQP33 protodrug MTD may be determined for both groups the 10 mL and 20 mL doses of SQL70 biopolymer.
- A determination of the recommended Phase 2 dose (RP2D) will be based on the safety and tolerability from every cycle of treatment, not just Cycle 1. The RP2D will be determined based on all available data, including PK/PD analysis, tolerability that will include the incidence and severity of DLTs, other AEs and the evidence for biological activity at each dose level tested. The RP2D can be defined by an SQP33 protodrug dose and a SQL70 biopolymer volume.
- Dose Limiting Toxicity (DLT). AE and serious adverse event (SAE) severity is based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. A DLT is defined as an AE that is at least possibly related to study treatment, occurs during the subject's first cycle of treatment (21 days; also known as the DLT window), and is a:
    - Hematologic toxicity
        - Febrile neutropenia
        - Grade ≥ 3 thrombocytopenia associated with clinically significant bleeding
        - Grade 4 neutropenia or thrombocytopenia lasting >7 days

or

- Grade ≥ 3 non-hematologic toxicity except for:
    - Grade ≥ 3 isolated asymptomatic laboratory abnormalities or laboratory abnormalities that resolve within 72 hours
    - Grade 3 nausea/vomiting/anorexia controlled by maximal medical management that does not persist for greater than 3 days
    - Grade 3 fatigue/asthenia that does not persist for more than 7 days
    - Grade 3 diarrhea or constipation that resolves to ≤ Grade 1 or baseline within 72 hours with maximal medical management
    - Grade 3 or 4 elevation of amylase or lipase not associated with pancreatitis
    - Grade 3 infusion reaction returning to ≤ Grade 1 in < 6 hours
    - Grade 3 tumor lysis syndrome that is successfully managed and resolves within 7 days without end-organ damage

- Hepatic abnormalities that resolve within 7 days.

If a subject experiences a DLT, both SQP33 protodrug and SQL70 biopolymer should be temporarily interrupted.

- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 month = 30.4375 days. Month is calculated as (days / 30.4375) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 pound = 0.454 kg and 1 kg = 2.2 pounds
- 1 inch = 2.54 cm and 1 cm = 0.3937 inches
- Body mass index (BMI) calculated as [weight (lbs) / height $(in)^2$] x 703.
- Age will be calculated in years relative to the date of study consent based on the following SAS statement: Age = ([Consent Date - Date of Birth] / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- Doxorubicin equivalent: 1 g of SQP33 protodrug is equivalent to 0.7153 g of doxorubicin hydrochloride.

9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The listings, figures and summary tables for the disposition, baseline characteristics, study drug administration, safety, and efficacy data will be the responsibility of the study Biostatistician at Vantage Data Designs.

The currently supported version of SAS software (9.4 or later) will be used to perform all data analyses. The actual SAS version used will be presented in the Clinical Study Report.

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by type of dosing schedule, dose level cohort, subject number, and assessment date/time.

Unless otherwise stated, continuous variables will be summarized using descriptive statistics including number of non-missing observations, mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized with frequency counts and percentages. The population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented.

In general, only data from nominal protocol scheduled visits will be included in the summary tables. They will be used in summary tables which are not ‘time specific’, for example,

summaries of first, last, minimum, maximum, and average post dose values. Data from unscheduled visits will not be included in the summary tables but will be included in the listings.

The Efficacy Evaluable analysis set will be the primary basis for the efficacy analysis and the Safety analysis set for the safety summaries.

9.1 Multicenter Studies

Data from all participating sites will be pooled for the analysis.

9.2 Other Strata and Covariates

Not applicable for this study.

9.3 Examination of Subgroups

For the Phase 1 dose escalation portion of this study, there are no pre-defined exploratory subgroup analyses planned. However, if the data warrant (high ORR, etc.), subgroup analyses may be performed and will be discussed fully in the clinical study report. For the Phase 2a Expansion part of this study where detecting efficacy signals is the objective, exploratory subgroup will be performed and will be discussed in the Phase 2a SAP.

9.4 Multiple Comparisons and Multiplicity

Not applicable for this study.

9.5 Missing Data and Dropouts

The issue of how to handle missing data caused by dropouts in clinical studies is a research topic that is still under development in the statistical literature. As has been noted in the ICH-E9 guideline, “no universally applicable method of handling missing values can be recommended”. The best approach is to minimize the chance of dropouts at the design stage of the clinical study and during study monitoring. Every effort will be made to collect data for all timepoints.

In general, data will be analyzed as received from the clinical database. Hence, missing values will not be replaced by imputed values except for the following situations:

9.5.1 Adverse Events

Adverse events with missing or partial dates will be handled such that in the absence of contradictory information an AE is classified as “treatment emergent”. So, for a missing start date (where the stop date is after the date of first study drug administration) the start date

will be imputed as the first study drug administration date. Similarly, for a missing stop date, the stop date will be imputed as the date of last visit.

- If a partial date is recorded, the following convention will be used to assign the AE: If a start date is missing the day information and the month/year is the same as the first study drug administration date, then use the first study drug administration date, else '01' will be used for the day. If a start date is missing the month and the year is the same as the first study drug administration date, then use the first study drug administration date, else 'January' will be used for the start month.
- If a stop date is missing the day information and month/year is the same as the last study date, then use the last study date, else the last day of the given month will be used for the stop day. If a stop date is missing the month and the year is the same as the last study date, then use the last study date, else 'December' will be used for the stop month.

9.5.2 Concomitant Medications

If the stop date of a concomitant medication is missing, then the medication will be treated as ongoing. If the start date of a medication is missing, the stop date will be used to determine whether or not it is concomitant. Medications with other incomplete start dates will be identified as concomitant using the same algorithm as above for TEAE, if the stop date information is insufficient for the determination.

If start date is missing, the medication will be considered to have started prior to the study. It may also be considered concomitant, depending on the stop date or lack thereof.

9.5.3 Other Situations

For subjects who are withdrawn from the study prior to study completion, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal.

Extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables but will be included in subject listings. They will be used in summary tables which are not 'time specific', for example, summaries of first, last, minimum, maximum, and average post dose values.

The original data will always be presented in the listings.

10. STUDY POPULATION

All disposition, baseline and demographic analyses will be conducted on both the safety and efficacy evaluable populations. Unless specified elsewhere, baseline is defined as the last recorded value prior to the administration of the first dose of study treatment (SQL70 Biopolymer).

10.1 Subject Enrollment

Subject enrollment will be presented for all enrolled subjects and will be summarized by investigative site, does cohort, and overall total based on:

- Number of subjects who were enrolled
- Number of subjects who qualified for the Safety Population
- Number of subjects who qualified for the Efficacy Evaluable Population
- Number of subjects who were enrolled but not treated with study drug (i.e., screen failures)

A listing of subject enrollment will be provided for all enrolled subjects. A listing of whether or not all inclusion and exclusion criteria were met and if not, which criteria were not met, by subject, will also be presented.

10.2 Subject Disposition

The subject disposition summary will be summarized by dose cohort and will include:

- Reasons for treatment discontinuation
- Number of subjects ongoing in the study
- Reasons for study discontinuation
- Summary of time on study described as the time in days from the first dose until the last recorded visit.

10.3 Protocol Violations or Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or Good Clinical Practice (GCP). The noncompliance may be either on the part of the subject, the investigator, or the study site staff. Capturing every specific protocol deviation was not part of the eCRF database. Protocol deviations will be identified and documented by Shasqi study monitors/project manager outside the eCRF database prior in an ongoing manner and finalized prior to database lock. All protocol deviations will be reviewed by Shasqi medical monitors in an ongoing fashion. Protocol deviations will be detailed in subject listings and discussed in the clinical study report.

10.4 Demographics

Demographic characteristics will include

- Age (years) (descriptive statistics)
- Age category (years)
  - ≥18 - < 66
  - ≥66 - < 75
  - ≥ 75
- Sex (male, female)
- Race
- Ethnicity

The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using mean, median, standard deviation, and range (maximum, minimum).

10.5 Baseline Characteristics

Baseline characteristics will include (but not limited to):

- ECOG performance status (0,1)
- Type of cancer e.g., liposarcoma
- Stage of disease at study entry (all cohorts)
  - Localized
  - Locally Advanced
  - Metastatic
- Primary location of disease
- Metastatic site locations
- Number of metastatic sites
- Response to most recent prior therapy
- Prior therapy received for cancer being studied
  - Systemic anti-cancer therapies (per Shasqi medical review)
  - Prior radiation
  - Prior surgery
  - Prior radiotherapy
- Prior therapy with an anthracycline

- Prior treatment with immuno-oncology therapies that could alter the body's immune response against cancer. This data will be identified by medical monitor review of prior lines of therapy
- Prior cumulative Dox received

10.6 Medical History

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Data will be descriptively summarized by the System Organ Class (SOC) and preferred terms (PT). The summary table will be sorted by overall frequency of recorded medical history and will show the number and percentage of subject's medical history by SOC and preferred term by dose cohort.

10.7 Concomitant Medications

Concomitant medications will be coded by WHODrug coding dictionary (September 2020). Data will be descriptively summarized by Anatomical Therapeutic Chemical (ATC) system Level 1, and drug preferred name. The summary tables will be sorted by overall frequency of recorded use and will show the number and percentage of subjects taking each medication by ATC Level 1 and preferred term by dose cohort. Subjects who take the same medication (in terms of the ATC Level 1 and preferred name) more than once will only be counted once for that medication. Medications with end dates prior to dosing will not be included in these summaries.

10.8 Study Drug Administration: Exposure and Modifications

Group 1 (10 mLSQP70): SQL70 biopolymer will be administered intra and/or peritumorally at a fixed 10 mL injection volume. During cycle 1, a single lesion (or regional cluster of lesions) will be injected on Day 1. For later cycles, Subjects on treatment who attain at least a 30% reduction in injected tumor size or have a tumor that is no longer injectable may have a second lesion injected with an additional 10 mL of SQL70 biopolymer.

The starting daily dose of SQP33 protodrug is 8 mg/m2/day (5.72 mg/m2/day Doxorubicin Molar Equivalent Dose (Dox Eq)) for the first accelerated dose cohort. SQP33 protodrug infusions are given daily on Day 1 through Day 5. The starting total dose per cycle of SQP33 will be 40 mg/m2/cycle (28.6 mg/m2/cycle Dox Eq). Higher doses will be converted to their doxorubicin hydrochloride molar equivalent (1 g of SQP33 protodrug is equivalent to 0.7153 g of doxorubicin hydrochloride). Dose escalation during stages 1 and 2 will take place after the SRC reviews Cycle 1 safety data.

Group 2 (20 mL SQL70): consists of a cohort of subjects to be evaluated following administration of 20 mL of SQL70 biopolymer in one or two lesions starting at Cycle 1. This cohort of subjects will be enrolled at an initial dose level of SQP33 protodrug that is lower than the dose level being evaluated in the standard dose escalation (Group 1) at the time of initiation of this cohort. This 20 mL SQL70 biopolymer (from cycle 1) cohort will follow the same 3+3 (Rolling 6) escalation design as used for the subjects described previously. The SRC will decide if another cohort of subjects should be enrolled at a higher SQP33 protodrug dose with the same 20 mL SQL70 biopolymer volume.

Study treatment (SQP33 and SQL70) received will be summarized as described below:

Study Drug Administration (Exposure):

- Number of cycles
- Duration of Therapy
- Average Duration of SQP33 Infusions
- Total SQP33 Cumulative Dose (mg/m2)
- Total SQL70 Cumulative Dose (mg/m2)
- Total Doxorubicin Equivalent Cumulative Dose (mg/m2)
- Highest SQP33 dose administered
- Highest Doxorubicin Equivalent dose administered

Dose Modifications:

1. SQL70 Biopolymer

    a. Injection interruption
    b. Dose increase of biopolymer (10 mL to 20 mL)

2. SQP33

    a. Dose interruption of infusion (bag change is not an interruption)
    b. Dose reduction (Y or N, and by summary units)
    c. Dose increase (Y or N, and by summary units)

Details concerning the derivation of these measures are below.

- Highest SQP33 Dose Administered = Defined as the largest (or maximum) SQP33 dose administered (mg/m2)
- Total SQP33 Cumulative Dose received (mg/m2) = Defined as the sum of all SQP33 doses (mg/m2) received

- Average Duration of infusion = As recorded on CRF, summarized using the average infusion duration in minutes
- Duration of therapy (median (min/max), mean) = As recorded on CRF, summarized using the time in days from first dose to last dose

These study drug administration and exposure parameters will be summarized using descriptive statistics. Continuous variables by the mean, standard deviation, median, minimum and maximum values. Categorical variables by the number and percentage of subjects in each category.

Additional information regarding study drug administration will be presented in the subject listings.

11. EFFICACY ANALYSIS

Since the primary objectives of this study are to determine the MTD and/or RP2D of SQ3370 treatment with 10 mL and/or 20 mL of SQL70 biopolymer, a formal efficacy analysis that includes hypothesis testing is not applicable for dose escalation. However, any objective response to treatment with SQ3370 will be noted using the RECIST v1.1 definitions of response (Appendix 20 of this SAP).

For the Dose Escalation portion of this study, the Efficacy Evaluable analysis set will be utilized for efficacy analyses. This analysis set consists of all subjects who receive at least 1 dose of SQL70 biopolymer and 1 dose of SQP33 protodrug and undergo at least 1 post baseline tumor evaluation. The efficacy endpoints will be assessed by the investigator assessed RECIST v1.1, and will be summarized in tables, listings and/or figures as outlined in the sections below.

Additional analyses may be performed to assist the Sponsor in planning future studies.

In addition to the summary tables, efficacy data will also be presented in the individual subject listings.

11.1 Objective Response Rate

Objective response rate (ORR) is defined as the number and percentage of participants with a best overall response (BOR) of confirmed CR or PR. BOR is defined as the best response designation, recorded between the date of enrollment and the date of the initial objectively documented tumor progression per RECIST v1.1, date of death from any cause, or the date of subsequent therapy, whichever occurs first. For participants without documented

progression or subsequent therapy, all available response designations will contribute to the BOR determination.

ORR will be summarized by presenting counts and percentage along with the corresponding two- sided 95% exact confidence interval (CI) by dose escalation cohort and overall. A swimmer's plot for all efficacy evaluable subjects will be constructed. This will depict time on study, CR/PR date, disease progression (and/or death) date, end of treatment/study date, etc. This swimmers plot will also help visualize the other efficacy endpoints described below (duration of response, disease control rate, and duration of stable disease).

11.2 Duration of Response

Duration of Response (DoR) is defined as the time from documentation of tumor response to disease progression or death and will be calculated as:

Date of Disease Progression or Death or Censoring – Date of First PR or CR + 1

By definition, the DoR analysis will only include those patients achieving a CR or PR. Responders who were lost to follow-up or had not progressed or died on study will be censored on the date of their last disease assessment or end-of-study visit (whichever is earliest) and will be calculated as:

Date of last response assessment or end-of-study visit (whichever is earliest) – Date of first study drug dose + 1

Kaplan-Meier methods will be used for the analysis of duration of response. Median (with corresponding 2-sided 95% CI), quartiles (25th and 75th percentiles), minimum, and maximum duration of response time will be displayed. A Kaplan- Meier figure of duration of response will be provided as standard for time-to-event endpoints.

11.3 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of subjects whose BOR is CR or PR or SD (≥60-days).

The disease control rate (DCR) will be summarized with the number and percentage of subjects by dose escalation cohort and overall.

11.4 Duration of Stable Disease

Duration of stable disease is defined as the time recorded between the date of first dose of study drug to the date of the initial objectively documented tumor progression per RECIST v1.1, date of death from any cause, or the date of subsequent therapy, whichever occurs first and will be calculated as:

Date of Disease Progression or Death Date or Date of Subsequent Therapy – Date of First Study Drug + 1

Subjects who were lost to follow-up or had not progressed/died on study or not taken new therapy will be censored on the date of their last disease assessment or end-of-study visit (whichever is earliest) and will be calculated as:

Date of last response assessment or end-of-study visit (whichever is earliest) – Date of first study drug dose + 1

Kaplan-Meier methods will be used for the analysis of duration of stable disease. Median (with corresponding 2-sided 95% CI), quartiles (25th and 75th percentiles), minimum, and maximum duration of response time will be displayed. A Kaplan- Meier figure will be provided as standard for time-to-event endpoints.

11.5 Target Lesions

Change in size of target lesion(s) including both injected, and non-injected tumors (if available) will be defined as the best percent change from baseline in the sum of diameters. This will be represented by a standard waterfall figure that is typically used to portray this efficacy parameter.

12. SAFETY ANALYSIS

Safety and tolerability will be summarized using AEs, SAEs, DLTs, deaths, events of special interest, events leading to dose reductions/modifications, discontinuation, and laboratory parameters.

All treatment-emergent AEs will be summarized by system organ class and preferred terms within a system organ class for each treatment group and Grade per NCI-CTCAE (version 5). Only treatment-emergent AEs will be summarized in the tables. Treatment-emergent AEs are those that occur after the first dose of Investigational Product is given. Each preferred term will be counted only once for a given subject. The severity (intensity) and the relationship to study medication will be summarized by system organ class and preferred term within a system organ class for each treatment group. For severity, if a subject has multiple occurrences of the same preferred term, the highest severity will be assumed.

Changes from baseline through the end of study will be descriptively summarized for the following: vital signs, ECG, ECHO/MUGA, coagulation, urinalysis, hematology, and clinical chemistry parameters. Tolerance and toxicity of SQ3370 treatment regimen will be assessed through evaluation of physical examinations, vital signs, laboratory parameters, AEs

including DLTs, and all causes of mortality. The baseline definition for safety assessment is either at screening or prior to receiving the first dose of study drug; whichever is latest.

The Safety Analysis set defined as all subjects who received at least 1 dose of SQL70 biopolymer and/or SQP33 protodrug will be utilized for all safety analyses.

In addition to the summary tables, safety data will also be presented in the individual subject listings.

12.1 Treatment Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as all AEs that begin on or after the date of the first administration of study drug. Related AEs are those reported as possibly related to SQL70 bipolymer, related to SPQ33 protodrug, and related to SQ3370 (both SQL70 and SQP33). The verbatim terms of the TEAEs will be coded to preferred terms (PT) and system organ classes (SOC) per the Medical Dictionary for Regulatory Activities (MedDRA®) Version 24.1.

All reported AEs (including non-TEAEs) will be listed, documenting all information collected on the eCRF including verbatim term, MedDRA preferred term, MedDRA system organ class, start date, stop date, severity and relationship to SQ3370 treatment, relationship to SQL70 biopolymer, relationship to SQP33 protodrug, action taken, and outcome.

The TEAEs will be graded by the Investigator in terms of:

- Severity graded 1-5 according to CTCAE v5.0:
    - 1=Mild, 2=Moderate, 3=Severe, 4= Life Threatening, 5=Fatal.
- Relation to SQ3370:
    - 'Related' includes events where the causality was reported as related to SQL70 bipolymer, related to SPQ33 protodrug, related to SQ3370 treatment (both SQL70 and SQP33), or where the relationship was not reported on the eCRF.
    - 'Not Related' includes events where the study drug causality was reported 'Not Related' on the eCRF.

All TEAE summary tables will be presented with the number and percentages of subjects in the Safety population. Incidence rates of treatment-emergent adverse events (TEAEs) will be summarized within each dose level at the Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class levels and preferred term. Subjects may be counted under multiple system organ class (SOC) and preferred terms (PT), but for each SOC and PT category, subjects are only counted once. If a subject has the same AE on multiple

occasions, the highest severity grade (fatal > life threatening > severe > moderate > mild) or drug relationship (related > not related) recorded for the event will be summarized.

This list includes:

- All TEAEs
- All TEAEs graded severity
- All Related TEAEs to SQ3370 treatment
- All Related TEAEs to SQ3370 treatment graded by severity
- All Related TEAEs to SQL70 biopolymer
- All Related TEAEs to SQL70 biopolymer graded by severity
- All Related TEAEs to SQP33 protodrug
- All Related TEAEs to SQP33 protodrug graded by severity
- Serious TEAEs
- Adverse Event of Special Interest (AESI)
- Dose Limiting Toxicity (DLT)
- TEAEs leading to discontinuation from study
- TEAEs resulting in death.

Separate subject listings will be provided for all SAEs, AEs leading to study discontinuation, DLTs, AESIs, and deaths.

12.2 Serious Adverse Events

Incidence rates of serious TEAEs will be summarized within each dose level at the Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class levels and preferred term A listing of subjects who reported a serious adverse event will be presented. The data will be obtained from the AE dataset where ‘Is this adverse event serious? is checked ‘Yes’.

12.3 Adverse Events Leading to Discontinuation from Study

Incidence rates of TEAEs leading to discontinuation from study will be summarized within each dose level at the Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class levels and preferred term. A listing of subjects and the adverse events which led to study discontinuation from the study will be included. The specific AE will be identified from the AE dataset where ‘Discontinued Study’ is checked or has data within in.

12.4 Deaths Due to Adverse Event

Incidence rates of TEAEs leading to death will be summarized within each dose level at the MedDRA primary system organ class levels and preferred term. A listing of subjects who

died on study will be included. The specific AE leading to death will be identified from the AE dataset where 'Did the adverse event result in death? is checked 'Yes'. Other possibilities are Outcome=Fatal and/or CTCAE Grade=5.

12.5 Adverse Event of Special Interest (AESI)

Incidence rates of TEAEs of special interest will be summarized within each dose level at the MedDRA primary system organ class levels and preferred term. All AESIs will be listed by dose cohort and subject.

AESIs will be defined as DLTs and the preferred terms of potential myocardial toxicity, pregnancy, COVID-19 infections, and AEs due to overdose. The specific AESI will be identified from the AE dataset where AESI is checked.

12.6 Dose Limiting Toxicity (DLT)

For dose escalation the protocol defined DLT for a 21-day cycle (Cycle 1) using the protocol dose escalation DLT definitions and criteria following review by the Safety Review Committee (SRC), incidence rates of dose limiting toxicities will be summarized within each dose level at the MedDRA primary system organ class levels and preferred term. All DLTs will be listed by dose cohort and subject. The specific DLT will be identified from the AE dataset where AEDLT is checked.

12.7 Clinical Laboratory Tests

Safety laboratory assessments will be conducted on as specified in Schedule of Assessments (Section 18).

All laboratory tests, values, units, normal ranges, flags collected in the clinical database (i.e., results that are outside the normal ranges will be flagged with "L" (below normal range) or "H" (above normal range)) will be included in the-subject listings for further medical review.

For laboratory analysis, baseline will be defined as either the screening visit or the Cycle 1 Day 1 visit; whichever is the closest visit prior to the administration of study treatment.

12.7.1 CTCAE Grading

For the hematology laboratory tests of interest where CTCAE [version 5.0] severity criteria are specified, CTCAE severity grades will be assigned. These laboratory tests include:

Panel	Test	CTCAE grade directions
Hematology	ANC	Decrease
	Hemoglobin	Decrease / Increase

	Platelet Count	Decrease
	White Blood Cell (WBC) count	Decrease
	Lymphocyte Count	Decrease

Analyses will be performed using “shift tables” of CTCAE toxicity grades relative to the baseline (pre-treatment) toxicity grade. The number and proportion of subjects with directional shifts of the “worst” CTCAE toxicity grade post-baseline and CTCAE toxicity grade of the last post-baseline visit relative to the baseline (pre-treatment) toxicity grade will be summarized for the selected hematology and chemistry parameters.

The CTCAE toxicity grading algorithms for the appropriate laboratory analytes are detailed in Section 19.

12.7.2 Hematology

Hematology laboratory tests are planned to include Hemoglobin, Hematocrit, MCV, Platelets, Absolute White Blood Count, Absolute Neutrophil Count, Absolute Lymphocyte Count, Absolute Monocyte Count, Absolute Eosinophils Count, Absolute Basophils Count, % Neutrophils, % Lymphocyte, % Monocytes, % Eosinophils, and % Basophils.

Due to the large number of laboratory visits, the data will be summarized by these post-baseline timepoint descriptors: First post-baseline, Last post-baseline value, Minimum post-baseline value, Maximum post-baseline value, and Average post-baseline value.

These hematology laboratory test results are measured on a continuous scale and the observed values as well as changes from baseline values will be summarized for each dose cohort using n, mean, standard deviation, median, minimum and maximum values.

12.7.3 Chemistry

Chemistry laboratory tests are planned to include Sodium, Potassium, Glucose, Calcium (Total), Creatinine, Protein (Total), Albumin, Bilirubin (Total), Bilirubin (Direct), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Lipase, Amylase.

Due to the large number of laboratory visits, the data will be summarized by these post-baseline timepoint descriptors: First post-baseline, Last post-baseline value, Minimum post-baseline value, Maximum post-baseline value, and Average post-baseline value.

These chemistry laboratory test results are measured on a continuous scale and the observed values as well as changes from baseline values will be summarized for each dose cohort using n, mean, standard deviation, median, minimum and maximum values.

12.7.4 Coagulation

Coagulation laboratory tests are planned to include Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), Thrombin Time (TT) and INR.

Due to the large number of laboratory visits, the data will be summarized by these post-baseline timepoint descriptors: First post-baseline, Last post-baseline value, Minimum post-baseline value, Maximum post-baseline value, and Average post-baseline value.

These coagulation laboratory test results are measured on a continuous scale and the observed values as well as changes from baseline values will be summarized for each dose cohort using n, mean, standard deviation, median, minimum and maximum values.

12.7.5 Urinalysis

All Urinalysis test results (Protein, Blood, Specific Gravity, Glucose) will be presented in the subject listings.

12.8 Vital Signs and Weight

The vital sign tests to be collected include:

- Blood pressure (systolic and diastolic [mmHg])
- Heart rate (beats per minute [bpm]
- Respiratory rate (bpm)
- Temperature (c)
- Weight (lbs) once per cycle
- Height (in) at screening only.

See Schedule of Assessments (Section 18) for specific vital sign data collection timepoints.

Vital sign assessments measured on a quantitative scale will be summarized in a descriptive manner by calculating the n, mean, standard deviation, median, and range at the baseline timepoint (defined as either the screening visit or the Cycle 1 Day 1 visit; whichever is the closest visit prior to the administration of study treatment) and subsequent post-baseline timepoint, and by dose cohort. Mean change from baseline will also be presented in the same manner.

Due to the large number of vital sign visits, the data will be summarized by these post-baseline timepoint descriptors:

- First post-baseline, Last post-baseline value, Minimum post-baseline value, Maximum post-baseline value, and Average post-baseline value.
- Height will only be summarized at baseline.

All vital sign tests will be included in subject listings for further medical review.

12.9 12-Lead Electrocardiogram (ECG)

The 12-Lead ECG assessments include:

- Heart Rate
- QT interval
- PR interval
- QRS interval
- QTcF interval

See Schedule of Assessments (Section 18) for specific ECG data collection timepoints. In summary they include:

- Screening.
- On Day 1 of each cycle ECGs will be performed both pre and post SQP33 protodrug infusion.
- On Days 2-5 of Cycle 1 ECGs will be performed post SQP33 protodrug infusion only.

Quantitative Analysis:

ECG assessments measured on a quantitative scale will be summarized in a descriptive manner by calculating the n, mean, standard deviation, median, and range at the baseline timepoint (defined as either the screening visit or the Cycle 1 Day 1 visit; whichever is the closest visit prior to the administration of study treatment) and subsequent post-baseline timepoint, and by dose cohort. Mean change from baseline will also be presented in the same manner.

Categorical Analysis:

Additionally, QTcF results will also be categorized according to their values into the categories as defined in ICH E14:

- ≤ 450 ms
- > 450 ms to ≤ 480 ms
- > 480 ms to ≤ 500 ms
- >500 ms

and categorized according to their change from baseline into the categories:

- ≤ 30 ms,
- > 30 ms to ≤ 60 ms
- > 60 ms

The categories described above will be summarized in frequency tables using number of subjects (n) and percentages at each post-dose timepoint for each dose cohort

A separate analysis of the overall ECG interpretation (categorical: Normal, Abnormal Not Clinically Significant, and Abnormal Clinically Significant) will be performed using "shift tables" relative to the baseline (screening) interpretation. The number and proportion of subjects with directional shifts of ECG interpretation categories post-baseline relative to the baseline (screening) will be summarized.

All ECG results will be included in subject listings for further medical review. Of specific interest would be the interpretation of Abnormal, Clinically Significant ECG panel.

12.10 ECOG Performance Status

ECOG performance status will be assessed at Screening, and Week 3 (Day 17+-2 days) at Cycles 1-4, Day 1 of Cycles 5+, and 28 days Safety Follow-up. The ECOG performance status categories (6-point scale) are as follows:

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

ECOG will be summarized by dose cohort using shifts from screening to the subject's "worst" (i.e., highest number) ECOG score during the post-baseline study period and the last ECOG score taken post-baseline.

ECOG assessments will be included in subject listings.

12.11 Echocardiogram (ECHO) or Multigated acquisition (MUGA)

From the ECHO or MUGA scans, the LVEF (%) results are reported for the following time points:

- Screening.
- Treatment: An ECHO or MUGA scan (whichever was performed during screening) should be reported for 7 days from Cycle 3 Day 1, Cycle 5 Day 1 and Day 1 of every cycle thereafter

- Safety Follow-Up: An ECHO or MUGA scan (whichever was performed during screening) should be reported for the Safety Follow-Up visit if not performed in the previous 14 days.
- Long Term Follow Up (if applicable): An ECHO or MUGA scan (whichever was performed during screening) should be reported for each Long-Term Follow-Up visit.

Ejection Fraction percentages, LVEF (%), will be provided in table format by timepoint and by change from baseline summaries using descriptive summary statistics (n, mean, SD, median, range).

ECHO or MUGA test results to assess left ventricular ejection fraction (LVEF) will be presented in the subject listings.

12.12 Physical Examination

A physical examination should include a review of the following body systems: constitutional, skin, HEENT (head, eyes, ears, nose, and throat), neck, chest and lungs, cardiovascular, abdomen, neurological, and musculoskeletal, and genitourinary and gynecologic if indicted by the Investigator.

Symptom directed examinations should include an examination of organ systems related to subject symptoms for potential AEs. Any new post-baseline abnormal physical examination findings assessed as clinically significant should be recorded as an AE or SAE.

Physical examinations results will be displayed in subject listings.

12.13 Pregnancy Test

Individual subject data listings will be displayed for pregnancy test results.

13. PHARMACOKINETIC (PK) ANALYSIS

PK data analysis will be performed by the Shasqi R&D group and/or sponsor PK consultant and is not part of this SAP.

14. BIOMARKER ANALYSIS

Biomarker data analysis will be performed by the Shasqi R&D group and/or sponsor consultant and is not part of this SAP.

15. COMMITMENT TO GOOD STATISTICAL PRACTICE

15.1 Definition of Good Statistical Practice

International Conference on Harmonisation (ICH) Guidance on Statistical Principles for Clinical Trials (ICH E9) implicitly defines good statistical practice. Good statistical practice includes both appropriate statistical designs to minimize bias and to maximize precision of analysis plus operational excellence to assure credibility of results. The scientific design associated with any clinical trial is found in the protocol and in a more detailed pre-specified statistical analysis plan such as this one.

15.2 Data Management and Use of CDISC Standards

Data standards for clinical development of drugs have been defined and are maturing under various initiatives through the Clinical Data Interchange Standards Consortium (CDISC).

Shasqi will use third party vendors for clinical data collection and data analysis. Clinical data will be managed by Novotech (Australian based CRO). and will be captured in electronic case report form (eCRF) by the Medidata RAVE platform. The “raw” data contained in the eCRF clinical database will then be converted into Study Data Tabulation Model (SDTM) datasets per CDISC standards by Novotech. The SDTM datasets will then be utilized in statistical data analysis as the source to create Analysis Data Model (ADaM) datasets. These ADaM data conversions and data analysis will be conducted by Vantage Data Designs.

Other applicable standards include regulatory guidance’s from the Food and Drug Administration (FDA), ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3), and ICH Guidance for Good Clinical Practice (ICH E6).

15.3 Testing/Validation Plan and Software System

Statistical Analysis Software (SAS) version 9.4 or later will be used to analyze the data, create summary tables, subject data listings, and graphical representation of the data. All SAS computer programs will be validated using industry standard validation procedures including independent quality control programming.

16. STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL

The analyses described are based on the final clinical study protocol SQ3370-101 Amendment 7 dated July 25, 2022. This SAP supersedes the statistical considerations identified in the protocol. The following table summarizes changes in the SAP versus the protocol:

SAP	Protocol	Reason
N/A	N/A	N/A

17. REFERENCES

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18. SCHEDULE OF ASSESSMENTS

Phase 1 Dose Escalation, Cycles 1-4

		Screening		Cycles 1 - 4 Treatment			
Study Day		Day -28 to Day -1	Day 1 [K]	Day 2 / 3 / 4	Day 5	Day 10 ± 2 days	Day 17 ± 2 days
			Week 1			Week 2	Week 3
		On-Site	On-Site	On-Site	On-Site	Telephone or On-Site [A]	On-Site
Screening	Informed consent [B]	X					
	Medical history	X					
	Review Inc/Exc Criteria	X					
	Confirm Eligibility		X				
Safety	Physical Exam	X					
	Symptom-Directed PE		X [C]				Cycle 1 only
	Vital Signs	X	X	X	X		X
	ECHO or MUGA	X	Cycle 3 only [D]				
	Triplicate 12-Lead ECG	X	X [C, E]	Cycle 1 only	Cycle 1 only		Cycle 1 only
	ECOG	X					X
	AE Review		X	X	X	X	X
	Conmed Review	X	X	X	X	X	X
Labs	Hematology & Chemistry	X	X [C]	Cycle 1 only	X	Cycle 1 only [C]	X [C]
	Coagulation & Urinalysis	X					X [C]
	Pregnancy Test	X [F]	X				
	Serology	X					
	Plasma PK		X	X	X		
	PBMC		Cycle 1, 2, 3 only				
	Tumor Biopsy [G]		X [J]				
Tumor Evaluation	CT / MRI & RECIST	X	Every 6 weeks [D]				
IP [H]	Administer SQL70 Biopolymer		X				
	Administer SQP33 Protodrug		X [I]	X	X		

Investigator can perform unscheduled labs, ECGs and physical exams as needed / clinically indicated.

Notes:

A - Day 10 visit may be performed via telephone (using a lab closer to a patient's home) or on-site.

B - Written informed consent must be obtained prior to any study-specific procedures.

C - May be performed up to 3 days before the visit.

D - May be performed up to 7 days prior to projected every 6 weeks from C1D1 date.

E - ECG to be performed pre and post dose.

F - To be collected ≤ 7 days prior to Cycle 1 Day 1 for women of child-bearing potential.

G - Collect biopsy unless the tumor is considered too small to be biopsied; optional biopsy at Cycle 4 per investigator discretion
H - IP administration is the last procedure for each visit (aside from post-dose vitals, ECG, and PK draws).
I - SQP33 protodrug infusion occurs within 2 hrs ± 30 mins after receiving SQL70 biopolymer injection.
J - Biopsy can be performed during screening and up to 4 days prior to Day 1 for other cycles
K - Day 1-5 is typically Monday through Friday, however if the site can accommodate protocol procedures on the weekends Day 1 may start on any day of the week.

Phase 1 Dose Escalation, Cycles 5+, Safety Follow Up and Long Term Follow Up.

		Cycles 5+ Treatment			SFTY FU	LTFU
Study Day		**Day 1 [A]**	**Day 2 / 3 / 4**	**Day 5**	28-34 days after last dose of IP	every 12 weeks (± 7 days)
		On-site	**On-site**	**On-site**	**On-site**	**Variable [J]**
Safety	Symptom-Directed PE	X **B**			X	
	Vital Signs	X	X	X	X	
	ECHO or MUGA	X **C**			X **I**	
	Triplicate 12-Lead ECG	X **B, D**			X	
	ECOG	X **B**			X	
	AE Review	X	X	X	X	
	Conmed Review	X	X	X	X	
Labs	Hematology & Chemistry	X **B**		X	X **B**	
	Coagulation & Urinalysis	X **B**			X **B**	
	Pregnancy Test	X **B**			X **B**	
	Optional Tumor Biopsy	X **H**			X **J**	
Tumor Evaluation	CT / MRI & RECIST	Every 6 weeks **[E]**			X **K**	X **M**
IP [F]	Administer SQL70 Biopolymer	X				
	Administer SQP33 Protodrug	X **G**	X	X		
Survival	Vital Status [L]					X

Investigator can perform unscheduled labs, ECGs and physical exams as needed / clinically indicated
Notes:
A - Day 1-5 is typically Monday through Friday, however if the site can accommodate protocol procedures on the weekends Day 1 may start on
any day of the week.
B - May be performed up to 3 days before the visit.
C - May be performed up to 7 days before the visit.
D - ECG to be performed pre and post dose.
E - May be performed up to 7 days prior to the projected every 6 weeks from C1D1 date.
F - IP administration is the last procedure for each visit (aside from post-dose vitals and ECG).
G - SQP33 protodrug infusion occurs within 2 hrs
± 30 mins after receiving SQL70 biopolymer injection.
H - Optional biopsy per investigator discretion; can be performed up to 4 days prior to Day 1.
I - ECHO or MUGA not required at the Safety Follow-Up visit if performed in the previous 14 days.
J - Optional tumor biopsy if the patient only completed one cycle, as second biopsy for comparison

will not be collected at Cycle 2.
K - CT / MRI & RECIST not required at the Safety Follow-Up visit if performed in the previous 6 weeks.
L – for up to 2 years after treatment end; collected during routine clinic visits, telephone or e-mail with the subjects/caregivers or referring physician offices.
M – Until disease progression per RECIST; May be performed up to 14 days before the visit

19. CTCAE TOXICITY LABORATORY GRADING CHART

Panel	Analyte	Type	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v5.0)
Hematology	WBC count	WBC with differential	10^9/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 3.0 × 10^9/L Grade 2: < 3.0 – 2.0 × 10^9/L Grade 3: < 2.0 – 1.0 × 10^9/L Grade 4: < 1.0 × 10^9/L
Hematology	ANC	WBC with differential	10^9 cells/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 1.5 × 10^9/L Grade 2: < 1.5 – 1.0 × 10^9/L Grade 3: < 1.0– 0.5 × 10^9/L Grade 4: < 0.5 × 10^9/L
Hematology	Lymphocyte count	WBC with differential	10^9cells/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 0.8 × 10^9/L Grade 2: < 0.8 – 0.5 × 10^9L Grade 3: < 0.5 – 0.2 × 10^9/L Grade 4: < 0.2 × 10^9/L
Hematology	Hemoglobin	Erythrocytes and Platelets	g/L	Increase	Grade 0: ≤ ULN Grade 1: > 20 g/L + ULN Grade 2: > 20 – 40 g/L +ULN Grade 3: > 40 + ULN Grade 4: Not defined
			g/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 100 g/L Grade 2: < 100 – 80 g/L Grade 3: < 80 Grade 4: Not defined
Hematology	Platelet count	Erythrocytes and Platelets	10^9/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 75 × 10^9/L Grade 2: < 75 – 50 × 10^9/L Grade 3: < 50 – 25 × 10^9/L Grade 4: < 25 × 10^9/L

LLN=lower limit of normal. ULN=upper limit of normal.

The LLN and ULN for each analyte will be determined from the normal range of the local laboratory facility.

20. RECIST VERSION 1.1 RESPONSE CRITERIA

Below is a summary of the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 guidelines as it relates to the categorization of overall response. Further detail and clarification can be obtained from the referenced European Journal of Cancer article authored by Eisenhauer et al. or viewed on-line at the following website:

https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	**CR**
CR	Non-CR/non-PD	No	**PR**
CR	Not evaluated	No	**PR**
PR	Non-PD or not all evaluated	No	**PR**
SD	Non-PD or not all evaluated	No	**SD**
Not all evaluated	Non-PD	No	**NE**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, inevaluable.

Time Point Response: Patients with Nontarget Disease Only

Non Target Lesions	New Lesions	Overall Response
CR	No	**CR**
Non-CR/non-PD	No	**Non-CR/non-PD**
Not all Evaluated	No	**NE**
Unequivocal PD	Yes or No	**PD**
Any	Yes	**PD**

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009. 45(2):228-247.

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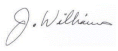
Jim Williams jim@shasqi.com Medical Monitor Shasqi Security Level: Email, Account Authentication (Required)	 Signature Adoption: Uploaded Signature Image Signature ID: 73D93686-AB41-41F6-A2A3-20ED0DA3631C Using IP Address: 70.176.72.143 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10/27/2022 8:44:53 AM Viewed: 10/27/2022 8:45:03 AM Signed: 10/27/2022 8:45:49 AM
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STATISTICAL ANALYSIS PLAN

Study Title:	A Multicenter Phase 1/2a, Open-Label Study of SQ3370 in Patients with Advanced Solid Tumors
Sponsor	Shasqi Inc 665 3rd Street Suite 501 San Francisco, CA 94107 USA
Protocol Number	SQ3370-001 Amendment 8 (17Nov2022)
IND Number	137024
Investigational Product	SQ3370
Phase of Development	Phase 1 / 2a
Analysis Plan Version	Final Version 1.0
Analysis Plan Date	July 19, 2023

STATISTICAL ANALYSIS PLAN APPROVAL

AUTHORS:

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William D. Mikrut Digitally signed by William D. Mikrut
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APPROVED BY:

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADaM	Analysis data model
AE	Adverse event
AESI	Adverse event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AV	Atrioventricular
BP	Blood pressure
BSA	Body surface area
CAPAC™	Click Activated Protodrugs Against Cancer
CBC	Complete blood count
CHF	Congestive heart failure
CNS	Central nervous system
CS	Clinically significant
CSF	Colony-stimulating factor
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
Dox	Doxorubicin
Dox Eq	Doxorubicin hydrochloride molar equivalent (1 g of SQP33 protodrug is equivalent to 0.7153 g of doxorubicin hydrochloride)
Dox HCl	Doxorubicin hydrochloride
DOXIL/CAELYX	Liposomal doxorubicin
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
eCRF	Electronic case report form
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HNSTD	Highest non-severely toxic dose
ICF	Informed consent form
IRB	Institutional Review Board
IV	Intravenous(ly)
LFT	Liver function tests
LVEF	Left ventricular ejection fraction
MAD	Maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUFA	Multigated acquisition

N/A	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria
NOAEL	No-observed-adverse-effect level
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cell
PK	Pharmacokinetic(s)
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE SOC SRC	Serious adverse event
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the data analysis specifications for Shasqi, Inc protocol SQ3370-001 titled: "*A Multicenter Phase 1/2a, Open-Label Study of SQ3370 in Patients with Advanced Solid Tumors (Amendment 8)*. It details the inferential statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical study protocol.

This version of the SAP was prepared in accordance with the protocol SQ3370-001 Amendment 8 dated November 17, 2022. Other related documents are the annotated subject case report forms and the corresponding Medidata RAVE electronic data capture (EDC) data dictionary.

This SAP will be finalized prior to the Phase 2 dose expansion database lock data availability and describes the statistical analysis as it was planned when the study was approved. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the approved SAP after database lock data availability, reasons for such deviations, and all alternatives or additional statistical analyses that may be performed will be described in the final clinical study report. This SAP supersedes the statistical considerations identified in the protocol.

NOTE: This SAP will focus on the Phase 2 Dose Expansion stage of this study. A separate SAP (dated October 13, 2022) was written and executed for Phase 1 Dose Escalation.

2. OVERVIEW OF STUDY TREATMENT AND STUDY DESIGN

2.1 Study Treatment

SQ3370 is a novel Investigational Product that enables local targeting and activation of a cytotoxic protodrug without the need for specific molecular biomarkers. SQ3370 utilizes Shasqi's proprietary Click Activated Protodrugs Against Cancer (CAPAC™) platform where mutually reactive click chemistry groups release doxorubicin (Dox) at the tumor site minimizing systemic exposure.

The therapeutic goal of SQ3370 is to enhance the antitumor efficacy of doxorubicin by increasing its concentration at a specific tumor site while minimizing its systemic toxicity.

The SQ3370 Investigational Product consists of 2 components:

(1) Intratumoral injection of a protodrug activating biopolymer (SQL70: 10 mL or 20 mL).

(2) Five (or three) consecutive days of intravenous (IV) infusions of a trans-cyclooctene (TCO)-modified protodrug of Dox with attenuated cytotoxic activity (SQP33) for a 21-day cycle.

An individual cycle of treatment is defined as a 3-week (21-day) period wherein the SQL70 biopolymer is injected into a lesion or lesions on Day 1 followed by 3-5 consecutive daily infusions of SQP33 protodrug (Day 1-5 or in Phase 2a Group 2 subset will receive Day 1-3). In Phase 1 subjects assigned to receive 20 mL SQL70, no more than 2 lesions may be injected (10 mL each) during the treatment cycle with the exception of a “regional cluster of lesions” defined as tumors that are contiguous, in apposition to each other, or are within 5 cm of each other. If there is a question whether a lesion or lesions are appropriate for injection, the Medical Monitor should be consulted.

For Phase 2a the treatment regimens are:

Group	SLQ70 Biopolymer (mL/Route)	SQP33 Protodrug RP2D IV	Daily % Dose
1: Extremity STS	20 mL intratumorally	x 5 days	20% daily x 5
2: Unresectable STS (SQP33 comparison 3 day vs 5 day)	10 mL intratumorally	x 5 days	20% daily x 5
		x 3 days	20% day 1 only 40% day 2 and 3 No Dosing on Day 4 or 5
3a: Head and Neck	10 mL intratumorally	x 5 days	20% daily x 5

2.2 Experimental Design

This multicenter, Phase 1/2a, first-in-human, single-arm, open-label, dose-escalation study will be conducted in two stages. This includes a dose escalation stage to evaluate the safety and tolerability, PK, and preliminary efficacy of SQ3370 in subjects with locally advanced or metastatic solid tumors for which an anthracycline-containing regimen is appropriate and who have an injectable tumor. The Phase 1 dose- escalation portion of the study was discussed in full within the Phase 1 Dose Escalation SAP. This SAP will focus on the Phase 2A Dose Expansion phase.

2.3 Phase 2a: Expansion Groups

Subjects will be enrolled in the Phase 2a expansion groups to study the preliminary activity and gain additional SQ3370 safety data, dosing schedules, as well as PK and immune changes in blood and tumor tissue. Phase 2a will utilize the RP2D determined in Phase 1. Three Expansion Groups will further explore the safety and preliminary efficacy of SQ3370 in different patient populations. The Phase 2a Dose Expansion groups include approximately 94 patients:

Group 1: Advanced High-risk Soft Tissue Sarcoma of the Extremity

Resectable is defined for the study as a primary surgical intervention that is thought to produce a surgical cure and maintain a good functional outcome of the affected extremity. The study will enroll patients with unresectable soft tissue sarcomas of the extremity AJCC III OR select IV (>5 cm injectable tumors) locally advanced and or metastatic that meet the preceding injectable tumor criteria not amendable to primary surgical intervention according to the consensus of multidisciplinary treatment team, determined prior to screening.

The study will be conducted in 2 phases with a Simon 2 stage design in the 2nd phase. The group will open with the initial phase safety run-in of patients to establish the safety and initial feasibility of a 12-week delay in definitive surgical resection in patients with high-risk STS of the extremity treated with SQ3370, after review by the safety steering committee the Simon 2 stage design will initiate patients enrolled in the lead-in will contribute to this phase of the study.

Patients will enroll at the RP2D of SQ3370 and will receive a fixed dose of SQL70 (20 mL). On Day 1 of each cycle, the subject will receive an injection of the SQL70 biopolymer into the tumor, followed by five (5) days of SQP33 infusion at the RP2D within 3 hours ±30 minutes. All patients are planned to receive 2 cycles of SQ3370 and undergo a disease reevaluation per RECIST 1.1. All patients without evidence of disease progression after 2 cycles will then undergo an additional 2 cycles of treatment and have a presurgical disease re-evaluation and proceed to definitive surgical procedure(s).

Only patients who have had objective evidence of response or whom in the opinion of the multidisciplinary treatment team determined to have achieved a clinical benefit may defer surgery at this point, the study will allow up to 4 additional cycles pre-operatively, at which point all patients should undergo exploratory surgery and or extremity tumor resection.

If a patient had a response, they may receive up to 4 additional cycles post operatively but not to exceed 12 cycles within the study. Surgical markers will be used to indicate the tumor

bed for injection with SQL3370 or if suitable for the metastatic patients, a metastatic lesion may be injected.

Any patient at any point who has been determined to have progressive disease has reached the end of treatment and will proceed to a definitive surgical treatment, note pre-operative radiation is allowed on study for patients with progressive disease preoperatively. It is encouraged to keep patients on study and to evaluate surgical specimens as per planned biomarker and pathological assessments.

Patients who undergo surgical resection and have had good response as defined by necrosis on histopathological resection may continue for additional treatment post-operatively. If post op radiation is administered the patients come off treatment (see 3.1.5 End of Treatment for details) and will remain on study in Long Term Follow-up.

Safety Monitoring: The Study will use a safety-run-in to evaluate the PK and tolerability when at least 6 patients have been enrolled and completed at least the planned Cycle 1. All available safety tolerability data will be presented and discussed at the SRC. If after the evaluation by the SRC the study proceeds after evaluation of the initial patients a second evaluation as defined in the statistical section. An evaluation of the totality of the data available to complete the planned 4 cycles and to review efficacy and histopathological response data and will provide the sponsor a recommendation as to proceed with expansion or to halt enrollment of the group.

Group 2: Comparison of the RP2D of SQP33 Administered Over 3 vs 5 Days

Compare safety and tolerability of the RP2D in two infusion schedules of SQP33 (3-day vs 5- day) in locally advanced, unresectable, STS who are anthracycline naïve and with defined anthracycline sensitive (expected historical ORR ~20%) histologies angiosarcomas, leiomyosarcoma, liposarcoma, synovial sarcoma, adult fibrosarcoma, and undifferentiated pleomorphic sarcoma.

Each treatment group will maintain the total dose of SQP33 per cycle constant and compare 2 different infusion schedules, a 3-day vs a 5-day schedule. The study will be guided by the Continuous Reassessment Method (CRM) design. The CRM model provides an indication of whether to alter the RP2D regimen (3-day dosing per 21-day cycle vs. 5-day dosing per 21-day cycle) based on a comparison of toxicity and efficacy data collected from participants enrolled. The participants will receive SQP33 at the RP2D administered IV as a 3-day dosing regimen per 21-day cycle or as a 5-day dosing regimen per 21-day cycle.

A toxicity rate at or above 15% for myelosuppression (Grade ≥3) related treatment emergent adverse events (TEAEs) (anemia and febrile neutropenia) would be considered unsafe for this expansion group, and enrollment would stop. If the 3-day infusion is not well tolerated that group will close, the study will continue with the RP2D and 5-day schedule with the initial adaptive design phase.

Safety Monitoring. All available safety tolerability data will be presented and discussed at the SRC. The maximum inefficacy and minimum efficacy rates are based on historical ORR, with <20% ORR being undesirable, and >35% ORR being desirable. Up to 11 participants per arm will be enrolled. After approximately half (n=6 per arm) of participants in Expansion Group 2 have been enrolled and observed for at least 2 cycles or approximately 6-weeks and have had at least one post- baseline tumor assessment, an evaluation of all available data (safety, efficacy, and PK from both the Expansion and Dose Escalation parts of the study) will be performed by the SRC. See Section 7.1 (Interim Analysis) for more information regarding the Group 2 safety run-in.

Group 3a: Head and Neck

The study will enroll patients with relapsed or metastatic head and neck tumors with advanced disease and historically poor outcomes and limited objective responses to currently available therapies. Patients will be selected with histologically or cytologically confirmed squamous-cell carcinoma of the head and neck who meet any of the following 1) confirmed relapsed squamous-cell carcinoma of the head and neck, 2) metastatic at initial presentation squamous- cell carcinoma of the head and neck, 3) patients with locally advanced head and neck cancer pretreated with surgery and/or radiotherapy and not suitable for further radical local treatment, 4) patients with distant metastases who may have received one or less chemotherapy regimen.

Patients will be treated with the RP2D of SQP33 with the SQL70 biopolymer dose fixed at 10 mL, every 21 days (1 cycle) up to 12 cycles or until the patient has PD, withdraws consent, Investigator decision, or death. On Day 1 of each cycle, the patient will receive an injection of the SQL70 biopolymer into the tumor, followed by five (5) days of SQP33 infusion at the RP2D. Sample sizes be guided by a Simon 2-stage (optimal) design based on historical objective responses (see statistical section for details). Enrollment will be continued after reaching the indicated number of participants at Stage 1 while the initial efficacy evaluation is ongoing.

Safety Monitoring: All available safety tolerability data will be presented and discussed at the SRC after 13 evaluable patients have been enrolled and a recommendation will be made to

the sponsor to continue or terminate the group enrollment based on ORR and totality of the data.

3. PHASE 2A EXPANSION OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives

Further investigate the safety and tolerability profile of SQ3370 in anthracycline naïve patients with:

- Group 1: Neo-adjuvant treatment of patients with STS of the extremity who are ineligible for primary surgical resection and under consideration for possible/probable amputation, with predefined anthracycline sensitive tumors.
- Group 2: Patients with unresectable, locally advanced or metastatic STS, with predefined anthracycline sensitive tumors and compare safety and tolerability of the RP2D in two infusion schedules of SQP33 (3-day vs 5-day).
- Group 3a Patients with relapsed or metastatic squamous-cell head and neck cancer

3.2 Secondary Objectives

- Assess preliminary signals of SQ3370 anti-tumor activity.
- Characterize the PK profile of SQP33 protodrug and active doxorubicin (Dox) following SQ3370 treatment.

3.3 Exploratory Objectives

- Assess the concentration of active Dox and SQP33 protodrug following SQ3370 treatment at the local site through analysis of tumor biopsies.
- Assess immune response through biomarker analysis of tumor biopsies and peripheral blood specimens.

3.4 Safety Endpoints

Frequency of adverse events (AEs), Serious Adverse Events (SAEs) and dose-limiting toxicities (DLTs), as well as changes from baseline in vital signs, clinical laboratory parameters, physical examination findings, ECHO/MUGA, and electrocardiogram (ECG) results.

3.5 Efficacy Endpoints

- Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Overall Survival (OS)
- Time from enrollment to first subsequent therapy (TFST)
- Plasma concentration and PK parameters for SQP33 protodrug and active Dox following SQ3370 treatment.
- Group 1: Advanced High-risk Soft Tissue Sarcoma of the Extremity
    - Histopathological Response
    - Surgical outcome amputation/limb-salvage vs planned
    - Disease-free survival
    - Local recurrence-free survival [Time Frame: 2 years]
    - Distant recurrence-free survival
    - Symptomatic disease control
- Group 2: Comparison of the RP2D of SQ33 total dose in mg/m2 administered every 21 days administered over 3 vs over 5 days
    - Compare safety and tolerability of two infusion schedules of SQP33 (3-day vs 5- day)
    - Pharmacokinetic comparison of the two infusion schedules
    - PFS per RECIST v1.1
    - DoR per RECIST v1.1
    - DCR per RECIST v1.1
- Group 3a: Head & Neck
    - DoR per RECIST v1.1
    - PFS per RECIST v1.1
    - Time to local-regional progression or distant progression per RECIST v1.1
    - Local-regional control per RECIST v1.1
    - DCR per RECIST v1.1

3.6 Exploratory Endpoints

- Assess the presence of SQP33 protodrug and active Dox in tumor tissue.
- Characterize immune response in blood and tumor tissue over time following treatment with SQ3370.

4. SAMPLE SIZE JUSTIFICATION

Groups 1 (Extremity STS) and 3a (Head and Neck)

Sample sizes are guided by Simon 2-stage (optimal) designs based on historical objective responses per indication. Because of the different participant populations (sarcoma and H&N cancers), different criteria are applied to determine the number of participants for each stage and the strength of the efficacy signal that would recommend proceeding to the next stage. Details are described in subsequent sections and in the following Simon 2-Stage Design table:

			Stage 1 responders/ Stage 1 n		Stage 2 responders/ Stage 2 n		
Group	Power	Historical ORR/Target ORR	Consider Futility	Go to Stage 2	Consider Futility	Consider Efficacy	Expected Sample Size
#1 Extremity Sarcoma	70%	20%/35%	≤3/15	≥4/15	≤13/46	≥14/46	25.91
#3 a H&N	85%	20%/45%	≤3/13	≥4/13	≤8/26	≥9/26	16.28

For sample size calculation and for simplicity of description, recommendations for stopping or progressing to the next stage are based on the number of objective responses observed.

However, since best overall response (BOR) does not necessarily capture the full extent of clinical benefit and since response can be delayed or of short duration, Shasqi will also review other aspects of clinical benefit that may better predict PFS or OS benefit, such as DOR, before making a final determination.

Enrollment will be continued after reaching the indicated number of participants at Stage 1 while the initial efficacy evaluation is ongoing. This will allow additional participants to enroll to account for unexpected trial impact, such as response non-evaluable participants due to early dropout, design parameter change (e.g., historical response rate update), etc. Although the sample size calculations are based on efficacy considerations, safety will also be continuously assessed and will be considered in the decision to continue or terminate a study treatment population.

Under the optimal Simon 2-stage design criterion:

Group 1 - Extremity STS: A sample size of 46 is required to test a null hypothesis of H_0: $\pi \leq 0.2$ (20%) versus an alternative hypothesis of H_1: $\pi \geq 0.35$ (35%) (Seddon 2017; Tapp 2017; Chawla 2015) with a one-sided significance level of 0.0498 and 70.5% power, where π is

the true proportion of successes. This design results in an expected sample size of 25.91 and a probability of early termination of 0.648. If the number of responses is less than or equal to 3 out of 15 participants in the first stage, then the trial will be stopped. If the trial proceeds to the second stage, 46 patients in total will be studied. If 13 or less responses are observed, then the drug is rejected.

Group 3a - Head & Neck: A sample size of 26 is required to test a null hypothesis of H_0: $\pi \leq 0.2$ (20%) versus an alternative hypothesis of H_1: $\pi \geq 0.45$ (45%) (Sandler 1984; Harrington 2001) with a one-sided significance level of 0.049 and 85.1% power, where π is the true proportion of successes. This design results in an expected sample size of 16.28 and a probability of early termination of 0.747. If the number of responses is less than or equal to 3 out of 13 participants in the first stage, then the trial will be stopped. If the trial proceeds to the second stage, 26 patients in total will be studied. If 8 or less responses are observed, then the drug is rejected.

Continuous Reassessment Method (CRM) design Group 2 (Unresectable STS)

Sample sizes for Group 2 participants are guided by the Continuous Reassessment Method (CRM) design (Wheeler 2019). The use of evaluating additional participants in the Expansion

Group 2 and the use of the CRM model provides an indication of whether to alter the RP2D regimen (3-day dosing per 21-day cycle vs. 5-day dosing per 21-day cycle) based on a comparison of toxicity and efficacy data collected from enrolled participants. The indicated population for the Group 2 participants is locally advanced or metastatic, unresectable, soft-tissue sarcoma of intermediate or high grade with evidence of disease progression and no prior anthracycline treatment, and thus the test statistics parameters for the CRM are based on historical toxicity and efficacy rates of said population (Table 10). The participants will receive SQP33 at the RP2D administered IV as a 3-day dosing regimen per 21-day cycle or as a 5-day dosing regimen per 21-day cycle. Participants may be replaced if they are enrolled into the study but do not receive (for reasons other than AEs/SAEs) the intended dose during Cycle 1. If Cycle 1 cannot be completed due to a COVID-19 infection, an additional patient may be enrolled in the group.

Continuous Reassessment Method Design Considerations

Parameters	Continuous Reassessment Method (CRM)
Historical Rates of Toxicity[2]	• Anemia: Grade ≥3- [8%] • Febrile neutropenia Grade ≥3- [~20%]
Acceptable threshold for toxicity	Grade ≥3 Related Myelosuppression TEAEs* • Anemia: Grade ≥3- <15% • Febrile neutropenia Grade ≥3- <15%
Maximum Inefficacy proportion[2-4]	0.20
Minimum Efficacy proportion[2-4]	0.35
Types I and II errors set at	0.05
Total number of pts per arm	11
Power	none

*Myelosuppression TEAES as per NCI-CTCAE v5.0- Anemia: Grade 3: Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated. Grade 4: Life-threatening consequences; urgent intervention indicated; Febrile Neutropenia: Grade 3-ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour. Grade 4: Life-threatening consequences; urgent intervention indicated.

Test statistics parameters are based on historical toxicity and efficacy rates (Table 10). The acceptable threshold for toxicity is set at 15%, respectively. A toxicity rate at or above 15% for myelosuppression (Grade ≥3) related treatment emergent adverse events (TEAEs) (anemia and febrile neutropenia) would be considered unsafe for that group, and enrollment would stop. The maximum inefficacy and minimum efficacy rates are based on historical objective response rates (ORR), with <20% ORR being undesirable, and >35% ORR being desirable.

After approximately half (n=6 per arm) of participants in Group 2 have been enrolled and observed for at least 2 cycles or approximately 6-weeks and have had at least one post-baseline tumor assessment, an evaluation of all available data (safety, efficacy, and PK from both the Expansion and Dose Escalation) will be performed by the SRC, to determine whether to continue to enroll up to a total of 11 participants per arm or to stop enrollment of a group. See Section 7.1 (Interim Analysis) for more information regarding the Group 2 safety run-in.

Groups 1 and 3a will treat up to approximately 28 participants in Stage 1 and Group 2 will treat up to a total of 22 participants. For all Expansion Groups: Patients may be replaced if they are enrolled into the study but do not receive (for reasons other than AEs/SAEs) the intended dose during Cycle 1. If Cycle 1 cannot be completed due to a COVID-19 infection, an additional patient may be enrolled in the group.

5. RANDOMIZATION, BLINDING, AND REPLACEMENT OF PATIENTS

This is an open-label study with the identity of the treatment known to the patients, Investigators, and Sponsor; therefore, no randomization or blinding procedures will be performed.

All patients will receive SQ3370 treatment according to the expansion group in which they are enrolled. Patients will be enrolled from all participating centers if at all possible.

Patients who are lost to follow-up or withdraw consent for study participation prior to administration of study drug may be replaced, at sponsor's discretion.

6. DEFINITIONS OF PATIENT POPULATIONS TO BE ANALYZED

This study will have six analysis populations:

- Enrolled: All patients who sign consent.
- Treated / Full Analysis Set: All patients who receive at least 1 dose of SQL70 biopolymer and 1 dose of SQP33 protodrug.
- Efficacy Evaluable Analysis Set: All patients who receive at least 1 dose of SQL70 biopolymer and 1 dose of SQP33 protodrug and undergo at least 1 post baseline tumor evaluation.
- Safety Analysis Set: All patients who received at least 1 dose of SQL70 biopolymer and/or SQP33 protodrug.
- PK Analysis Set: All patients in the Safety Population who have the necessary Day 1 and on-study measurements to provide interpretable results for the specific parameters of interest.
- Biomarker Analysis Set: All patients with available biomarker data.

7. PLANNED ANALYSES

7.1 Interim Analysis

In Phase 2a, there will be two interim looks at the data:

1) run-in safety/tolerability and
2) Stage 1 of the Simon 2-stage design.

The SRC will utilize the same criteria to evaluate the safety and tolerability of all available safety data at the completion of timing for each group to determine the initial safety and monitor the groups throughout the study overall safety and tolerability.

Phase 2a Safety Evaluation Timing:

Group	Run-in Evaluation N= (timing)	Simon Design: Stage 1 evaluation	Final Assessment
1: Extremity STS	**N=6 (after cycle 1)**	**N=15**	**N=46**
2: STS unresectable	**N=12 (6 per arm; after cycle 2)**	**N.A.**	**N=22**
3a: Head and Neck	**N.A.**	**N=13**	**N=26**

N.A.=Not Applicable

Group 3a: A run-in is not planned for the Head & Neck group (Group 3a) since they will be receiving the RP2D and schedule of SQ3370 without modifications.

Group 1: will receive SLQ70 in a volume of 20 mL with the RP2D of SQP33 and therefore the safety lead-in to this group is warranted. The SRC may, after the planned initial review of any group, within its purview recommend additional monitoring to the sponsor.

The above table also describes the Stage 1 analysis of efficacy/safety based on the Simon 2 stage design parameters.

For the Group 2 safety run-in, after approximately half (n=12 total or n=6 per arm) of patients in Expansion Group 2 have been enrolled and observed for at least 2 cycles (or approximately 6-weeks) and have had at least one post- baseline tumor assessment, an evaluation of all available data (safety, efficacy, pk) will be performed by the SRC to determine whether to continue to enroll up to Group 2 final total n=22 (n-11 per arm) or to stop enrollment.

With respect to efficacy, the minimum number of responders needed to continue to full enrollment of Group 2 will be based on the stage 1 parameters of the Simon 2-stage design. The maximum inefficacy and minimum efficacy rates are based on historical ORR and are <20% ORR being undesirable, and >35% ORR being desirable. Assuming 70% power and one-sided significance level of 0.10, with 12 Group 2 patients in the safety run-in, if ≤ 2 patients achieve either a CR or PR, then the study is considered futile and will be stopped. If ≥3 responders in 12 patients, then the Group 2 enrollment may continue to enroll to n=22.

7.2 Final Analysis

The final tables, listings, graphs, and data analysis will be conducted once all study participants have completed the phase 2a of this study and the clinical database has been locked.

8. DATA PRESENTATION AND HANDLING

8.1 Table and Individual Patient Data Listing Considerations

Summary tables and listings will be prepared according to ICH Guideline E3 (as appropriate for a Phase 2A study).

In general, summary tables will be organized with respect to the Phase 2A expansion groups:

- Group 1: Extremity STS
- Group 2: Unresectable STS 3-Day Infusion
- Group 2: Unresectable STS 5-Day Infusion
- Group 3A: Head and Neck
- Total

Row entries in post text tables are made only if data exists for at least one patient (e.g., a row with all zeros will not appear). The only exception to this rule will apply to tables that summarize the study termination status of patients (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no patient satisfied. The summary tables will clearly indicate the number of patients to which the data apply and unknown or not performed are distinguished from missing data.

Summary tables for any concomitant medications will be coded according to the World Health Organization (WHO) Drug dictionary September 2020 (or later). Adverse event preferred terms and body/organ systems and medical history conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary Version 24.1 (or later).

Listings will also be sorted by expansion group (where applicable) and patient number. Listings will also include visit number, visit date/time and days relative to the initiation of study treatment.

In general, missing data will not be imputed unless otherwise specified. Any imputed or derived data will be flagged in the individual patient data listings. Imputed data will not be incorporated into any raw or primary datasets. These data will be retained in derived analysis datasets.

8.2 Format Considerations

The tables, figures and listings will be numbered using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with two digits per level (e.g., Table XX.YY.ZZ. …).

1. The first level number will be consistent with the corresponding Clinical Study Report (CSR) appendix in which the tables or listings will appear. For example, the post text tables will appear in Appendix 14 (and will be numbered 14.XX.YY) and the individual patient data listings will appear in Appendix 16 (and will be numbered 16.XX.YY). The patient disposition table will be first in the first section of the report and will be numbered Table 14.1. The supportive patient data listing will be Listing 16.1. Any subset table will have the number Table 14.1.2, etc.
2. Table numbering will follow ICH E3 for Phase I CSRs. Patient disposition, baseline and demography and prior and concomitant medications tables should appear as the second level number (Table 14.1 series). Efficacy tables will occupy the next sub-level (Table 14.2 series – 14.2.1, 14.2.2 and 14.2.3, respectively). Safety tables will follow next (Table 14.3 series). Similar conventions will be applied to the patient data listings.
3. Each table and listing title will be complete, accurate and concise. The last line of the title will provide the analysis group being summarized (e.g., Safety Population or Efficacy Evaluable Population).
4. If possible, variables being summarized, and statistics reported will appear in the left most column of a table. The next columns for dose expansion groups should report the data from left to right per group number (1, 2, 3A). .

8.3 Data Management

All data will be recorded by the site in individual source documents. An eCRF will be created by the data management vendor (Novotech) for recording of the required data in the study database. All eCRF information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be patient to data validation checks for consistency and completeness by the data management vendor

and sponsor. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

Database building, AE coding, medication coding, data cleaning will be conducted according to the Novotech (vendor clinical research organization) Data Management Plan for this specific study.

Derived datasets (including SDTM and ADaM) will be created using SAS® software. Data analyses and summary tables will be generated using the currently supported version at the time of data analysis (currently version 9.4).

8.4 Data Presentation Conventions

Continuous safety variables (e.g., clinical laboratory values and vital signs) will be listed to the same precision as the source data. Derived variables will be calculated and listed using the same precision as the value(s) from which they were derived.

For the tabular reporting of descriptive statistics:

- Continuous variables: the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD.
- Categorical/discrete variables: the frequency count and the percentage (of available data) for each class of the variable will be presented and will be displayed in the form XX (XX.X%) where the percentage is in parentheses. All percentages will be presented to 1 decimal place, unless otherwise specified. Percentages equal to 100 will be reported as 100% and percentages will not be presented for zero frequencies. Unless otherwise specified, percentages will be calculated based on the number of patients specified by the appropriate population definition.
- Date variables: formatted as DDMMMYYYY for presentation. Time will be formatted in military time as HH:MM for presentation.

Extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables but will be included in patient listings. They will be used in summary tables which are not ‘time specific’, for example, summaries of minimum maximum, first, last, average post dose values.

All tables, listings, figures will be produced in landscape orientation using Arial 9-point font. Output files will be created in rich text file (RTF) format.

Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 9.5).

The table, figures and listing shells and table of contents as part of this SAP provide the expected layout and titles of the tables, listings, and figures. Any changes to format, layout, titles, numbering, etc. will not necessitate a revision to the SAP, nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling (e.g., change in the population used, change from statistical method/assumption listed, transformation of data type [e.g., continuous data transformed to categorical], exclusion of planned analysis, etc.) or additional unplanned analyses will necessitate a revision to this SAP. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

8.5 Treatment Comparisons

The following labels for dose level will be used on all tabulations, in the following order:

Phase 2A Expansion				
Group 1 Extremity STS 5-Day Infusion (N=00)	Group 2 Unresectable STS 3-Day Infusion (N=00)	Group 2 Unresectable STS 5-Day Infusion (N=00)	Group 3A Head and Neck 5-Day Infusion (N=00)	Total (N=00)

8.6 Definitions, Computations, Derived Data

- Screening: Screening is defined as ≤ 28 days prior to Cycle 1 Day 1 prior to the first study drug administration.
- Baseline: Measurements taken at Screening or prior to receiving the first dose of study drug; whichever is latest.
- Study Day and Cycle Day follows the CDISC standard and is defined as:
    - On-study Assessment Days (Assessment date – First date of study drug dosing of the first cycle) + 1, where the assessment date is on or after the first date of dosing of the first cycle.
    - Screening Days (Assessment date – First date of study drug dosing of the first cycle), where the assessment date is before the first date of dosing of the first cycle. For this protocol, screening days are from Day -28 to -1.
    - There will be no Study Day 0.
    - “Study Day x” (where x>0) refers to the number of days from first dosing date in Cycle 1. For example, Study Day 1 is Cycle 1 Day 1.
- Visit Nomenclature: Nominal visits nomenclature on the CRFs and the scheduled visit will be used for summary tables.

  - Scheduled visits for the Treatment Period are: “Screening”, “Cycle x Day 1” (where x = 1, 2, 3, … 9), Days 1, 2, 3, 4, 5, 10, 17, etc.
  - Safety follow-up visit is 28-34 days after the last dose of study drug and on-site.
  - Long Term follow-up visits are every 12 weeks (on or off site).

- Assessment for response and tumor burden is planned every 6 weeks and at Safety follow-up and long-term follow-up.
- The objective response rate (ORR): Percentage of patients whose best objective response recorded from the start of the treatment until disease progression/recurrence is a CR or PR according to RECIST 1.1 criteria.
- Best Overall Response (BOR) is defined as the best response recorded in the case report form after the start of the study treatment.
- A determination of the recommended Phase 2 dose (RP2D) will be based on the safety and tolerability from every cycle of treatment, not just Cycle 1. The RP2D will be determined based on all available data, including PK/PD analysis, tolerability that will include the incidence and severity of DLTs, other AEs and the evidence for biological activity at each dose level tested. The RP2D can be defined by an SQP33 protodrug dose and a SQL70 biopolymer volume.
- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 month = 30.4375 days. Month is calculated as (days / 30.4375) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 pound = 0.454 kg and 1 kg = 2.2 pounds
- 1 inch = 2.54 cm and 1 cm = 0.3937 inches
- Body mass index (BMI) calculated as [weight (lbs) / height $(in)^2$] x 703.
- Age will be calculated in years relative to the date of study consent based on the following SAS statement: Age = ([Consent Date - Date of Birth] / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- Doxorubicin equivalent: 1 g of SQP33 protodrug is equivalent to 0.7153 g of doxorubicin hydrochloride.

9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The listings, figures and summary tables for the disposition, baseline characteristics, study drug administration, safety, and efficacy data will be the responsibility of the study Biostatistician at Vantage Data Designs.

The currently supported version of SAS software (9.4 or later) will be used to perform all data analyses. The actual SAS version used will be presented in the Clinical Study Report.

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by Phase 2A expansion group, patient number, and assessment date/time.

Unless otherwise stated, continuous variables will be summarized using descriptive statistics including number of non-missing observations, mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized with frequency counts and percentages. The population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented.

In general, only data from nominal protocol scheduled visits will be included in the summary tables. They will be used in summary tables which are not ‘time specific’, for example, summaries of first, last, minimum, maximum, and average post dose values. Data from unscheduled visits will not be included in the summary tables but will be included in the listings.

The Efficacy Evaluable analysis set will be the primary basis for the response efficacy endpoints and the Full Analysis Set for time-to-event endpoints (time-to-event has ‘censoring’ rules in place for missing data). The Safety analysis set will be used for the safety summaries.

9.1 Multicenter Studies

Data from all participating sites will be pooled for the analysis.

9.2 Other Strata and Covariates

Not applicable for this study.

9.3 Examination of Subgroups

For the Phase 2A dose expansion portion of this study, there are no pre-defined exploratory subgroup analyses planned. However, if the data warrant (high ORR, etc.), subgroup analyses may be performed and will be discussed fully in the clinical study report.

9.4 Multiple Comparisons and Multiplicity

Not applicable for this study.

9.5 Missing Data and Dropouts

The issue of how to handle missing data caused by dropouts in clinical studies is a research topic that is still under development in statistical literature. As has been noted in the ICH-E9 guideline, “no universally applicable method of handling missing values can be recommended”. The best approach is to minimize the chance of dropouts at the design stage of the clinical study and during study monitoring. Every effort will be made to collect data for all timepoints.

In general, data will be analyzed as received from the clinical database. Hence, missing values will not be replaced by imputed values except for the following situations:

9.5.1 Adverse Events

Adverse events with missing or partial dates will be handled such that in the absence of contradictory information an AE is classified as “treatment emergent”. So, for a missing start date (where the stop date is after the date of first study drug administration) the start date will be imputed as the first study drug administration date. Similarly, for a missing stop date, the stop date will be imputed as the date of last visit.

- If a partial date is recorded, the following convention will be used to assign the AE: If a start date is missing the day information and the month/year is the same as the first study drug administration date, then use the first study drug administration date, else ‘01’ will be used for the day. If a start date is missing the month and the year is the same as the first study drug administration date, then use the first study drug administration date, else ‘January’ will be used for the start month.
- If a stop date is missing the day information and month/year is the same as the last study date, then use the last study date, else the last day of the given month will be used for the stop day. If a stop date is missing the month and the year is the same as the last study date, then use the last study date, else ‘December’ will be used for the stop month.

9.5.2 Concomitant Medications

If the stop date of a concomitant medication is missing, then the medication will be treated as ongoing. If the start date of a medication is missing, the stop date will be used to determine whether or not it is concomitant. Medications with other incomplete start dates will be identified as concomitant using the same algorithm as above for TEAE, if the stop date information is insufficient for the determination.

If the start date is missing, the medication will be considered to have started prior to the study. It may also be considered concomitant, depending on the stop date or lack thereof.

9.5.3 Other Situations

For patients who are withdrawn from the study prior to study completion, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal.

Extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables but will be included in patient listings. They will be used in summary tables which are not 'time specific', for example, summaries of first, last, minimum, maximum, and average post dose values.

The original data will always be presented in the listings.

10. STUDY POPULATION

All disposition, baseline and demographic analyses will be conducted on both the safety and efficacy evaluable populations. Unless specified elsewhere, baseline is defined as the last recorded value prior to the administration of the first dose of study treatment (SQL70 Biopolymer).

10.1 Patient Enrollment

Patient enrollment will be presented for all enrolled patients and will be summarized by investigative site, expansion group and overall total based on:

- Number of patients who were enrolled.
- Number of patients who qualified for the Safety Population
- Number of patients who qualified for the Efficacy Evaluable Population
- Number of patients who were enrolled but not treated with study drug (i.e., screen failures)

A listing of patient enrollment will be provided for all enrolled patients. A listing of whether or not all inclusion and exclusion criteria were met and if not, which criteria were not met by patient, will also be presented.

10.2 Patient Disposition

The patient disposition summary will be summarized by expansion group and will include:

- Reasons for treatment discontinuation

- Number of patients ongoing in the study
- Reasons for study discontinuation
- Summary of time on study described as the time in days from the first dose until the last recorded visit.

10.3 Protocol Violations or Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or Good Clinical Practice (GCP). The noncompliance may be either on the part of the patient, the investigator, or the study site staff. Capturing every specific protocol deviation was not part of the eCRF database. Protocol deviations will be identified and documented by Shasqi study monitors/project manager outside the eCRF database prior in an ongoing manner and finalized prior to database lock. All protocol deviations will be reviewed by Shasqi medical monitors in an ongoing fashion. Protocol deviations will be detailed in patient listings and discussed in the clinical study report.

10.4 Demographics

Demographic characteristics will include

- Age (years) (descriptive statistics)
- Age category (years)
    - ≥18 - < 66
    - ≥66 - < 75
    - ≥ 75
- Sex (male, female)
- Race
- Ethnicity

The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using mean, median, standard deviation, and range (maximum, minimum).

10.5 Baseline Characteristics

Baseline characteristics will include (but not limited to):

- ECOG performance status (0,1)
- Type of cancer e.g., liposarcoma
- Stage of disease at study entry
    - Localized

  - Locally Advanced
  - Metastatic
- Primary location of disease
- Metastatic site locations
- Number of metastatic sites
- Response to most recent prior therapy
- Prior therapy received for cancer being studied
  - Systemic anti-cancer therapies (per Shasqi medical review)
  - Prior radiation
  - Prior surgery
  - Prior radiotherapy
-
- Prior treatment with immuno-oncology therapies that could alter the body's immune response against cancer. This data will be identified by medical monitor review of prior lines of therapy.

10.6 Medical History

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Data will be descriptively summarized by the System Organ Class (SOC) and preferred terms (PT). The summary table will be sorted by overall frequency of recorded medical history and will show the number and percentage of patient's medical history by SOC and preferred term by expansion group.

10.7 Concomitant Medications

Concomitant medications will be coded by WHO Drug coding dictionary (September 2020). Data will be descriptively summarized by Anatomical Therapeutic Chemical (ATC) system Level 1, and drug preferred name. The summary tables will be sorted by overall frequency of recorded use and will show the number and percentage of patients taking each medication by ATC Level 1 and preferred term by expansion group. Patients who take the same medication (in terms of the ATC Level 1 and preferred name) more than once will only be counted once for that medication. Medications with end dates prior to dosing will not be included in these summaries.

10.8 Study Drug Administration: Exposure and Modifications

The SQ3370 Investigational Product consists of 2 components:

(1) Intratumoral injection of a protodrug activating biopolymer (SQL70: 10 mL or 20 mL).

(2) Five (or three) consecutive days of intravenous (IV) infusions of a trans-cyclooctene (TCO)-modified protodrug of Dox with attenuated cytotoxic activity (SQP33) for a 21-day cycle.

An individual cycle of treatment is defined as a 3-week (21-day) period wherein the SQL70 biopolymer is injected into a lesion or lesions on Day 1 followed by 3-5 consecutive daily infusions of SQP33 protodrug (Day 1-5 or in Phase 2a Group 2 subset will receive Day 1-3). In Phase 1 patients assigned to receive 20 mL SQL70, no more than 2 lesions may be injected (10 mL each) during the treatment cycle with the exception of a “regional cluster of lesions” defined as tumors that are contiguous, in apposition to each other, or are within 5 cm of each other.

For Phase 2a the treatment regimens are:

- Group 1 Extremity STS: 20mL SQL70 Biopolymer + 250 mg/m2 (12x Dox Eq) SQP33 Protodrug on a 5 day infusion schedule
- Group 2 Unresectable STS :10mL SQL70 Biopolymer + 250 mg.m2 (12x Dox Eq) SQP33 Protodrug on a 5 day infusion schedule
- Group 2 Unresectable STS :10mL SQL70 Biopolymer + 250 mg.m2 (12x Dox Eq) SQP33 Protodrug on a 3 day infusion schedule
- Groups 3A Head and Neck:10mL SQL70 Biopolymer + 250 mg.m2 (12x Dox Eq) SQP33 Protodrug on a 5 day infusion schedule.

Study treatment (SQP33 and SQL70) received will be summarized as described below:

Study Drug Administration (Exposure):

- Number of cycles
- Duration of Therapy
- Average Duration of SQP33 Infusions
- Total SQP33 Cumulative Dose (mg/m2)
- Total SQL70 Cumulative Dose (mg/m2)
- Total Doxorubicin Equivalent Cumulative Dose (mg/m2)
- Highest SQP33 dose administered
- Highest Doxorubicin Equivalent dose administered

Dose Modifications:

1. SQL70 Biopolymer

    a. Injection interruption

b. Dose increase of biopolymer (10 mL to 20 mL)

2. SQP33

a. Dose interruption of infusion (bag change is not an interruption)
b. Dose reduction (Y or N, and by summary units)
c. Dose increase (Y or N, and by summary units)

Details concerning the derivation of these measures are below.

- Highest SQP33 Dose Administered = Defined as the largest (or maximum) SQP33 dose administered (mg/m2)
- Total SQP33 Cumulative Dose received (mg/m2) = Defined as the sum of all SQP33 doses (mg/m2) received
- Average Duration of infusion = As recorded on CRF, summarized using the average infusion duration in minutes
- Duration of therapy (median (min/max), mean) = As recorded on CRF, summarized using the time in days from first dose to last dose

These study drug administration and exposure parameters will be summarized using descriptive statistics. Continuous variables by the mean, standard deviation, median, minimum, and maximum values. Categorical variables by the number and percentage of patients in each category.

Additional information regarding study drug administration will be presented in the patient listings.

11. EFFICACY ANALYSIS

Time to event variables will be estimated using K-M methodology. Binary variables will be summarized by binomial response rates and their corresponding two- sided 95% exact CI. Categorical variables will be summarized using tables presenting counts and percentages for each category. Quantitative variables will be summarized using the mean, median, minimum, and maximum values, and standard deviation.

For the Dose Expansion portion of this study, the Treated/Full analysis set will be utilized for efficacy analyses. This analysis set consists of all patients who receive at least 1 dose of SQL70 biopolymer and 1 dose of SQP33 protodrug. The Efficacy Evaluable analysis set will also be utilized for comparison purposes. This analysis set consists of all patients who receive at least 1 dose of SQL70 biopolymer and 1 dose of SQP33 protodrug and undergo at least 1 post baseline tumor evaluation. The efficacy endpoints will be assessed by the

investigator assessed RECIST v1.1, and will be summarized in tables, listings and/or figures as outlined in the sections below.

Additional analyses may be performed to assist the Sponsor in planning future studies.

In addition to the summary tables, efficacy data will also be presented in the individual patient listings.

11.1 Objective Response Rate (Groups 1, 2, and 3a)

Objective response rate (ORR) is defined as the number and percentage of participants with a best overall response (BOR) of confirmed CR or PR. BOR is defined as the best response designation, recorded between the date of enrollment and the date of the initial objectively documented tumor progression per RECIST v1.1, date of death from any cause, or the date of subsequent therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination.

The overall response rate (ORR) will be summarized with the number and percentage of patients along with the corresponding two- sided 95% exact confidence interval (CI). by Phase 2a expansion group. In addition, a swimmer's plot will be constructed. This will depict time on study, CR/PR date, disease progression (and/or death) date, end of treatment/study date, etc. This swimmers plot will also help visualize the other efficacy endpoints using RECIST1.1 described below (i.e., duration of response, disease control rate, and disease control rate).

11.2 Duration of Response (Groups 1, 2, and 3a)

Duration of Response (DoR) is defined as the time from documentation of tumor response to disease progression or death and will be calculated as:

Date of Disease Progression or Death or Censoring – Date of First PR or CR + 1

By definition, the DoR analysis will only include those patients achieving a CR or PR. Responders who were lost to follow-up or had not progressed or died on study will be censored on the date of their last disease assessment or end-of-study visit (whichever is earliest) and will be calculated as:

Date of last response assessment or end-of-study visit (whichever is earliest) – Date of first study drug dose + 1

Kaplan-Meier methods will be used for the analysis of duration of response. Median (with corresponding 2-sided 95% CI), quartiles (25th and 75th percentiles), minimum, and

maximum duration of response time will be displayed by Phase 2a dose expansion group. A Kaplan- Meier figure of duration of response will be provided as standard for time-to-event endpoints.

11.3 Overall Survival (Groups 1, 2, and 3a)

Overall Survival (OS) is defined as the time between the date of first dose of study drug to the date of death from any cause and will be calculated as:

Date of Death or Censoring – Date of First Study Drug Dose + 1

Patients who were lost to follow-up or did not die on study will be censored on the last known date to be alive and will be calculated as:

Date of last response assessment or end-of-study visit or follow-up visit (whichever is latest) – Date of first study drug dose + 1

Kaplan-Meier methods will be used for the analysis of overall survival. Median (with corresponding 2-sided 95% CI), quartiles (25th and 75th percentiles), minimum, and maximum duration of response time will be displayed by Phase 2a dose expansion group. A Kaplan- Meier figure of OS will be provided as standard for time-to-event endpoints.

11.4 Disease Control Rate (Group 2 and 3a)

Disease control rate (DCR) is defined as the proportion of patients whose BOR is CR or PR or SD ≥60-days, BOR is defined as the best response designation, recorded between the date of enrollment and the date of the initial objectively documented tumor progression per RECIST v1.1, date of death from any cause, or the date of subsequent therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination.

The disease control rate (DCR) will be summarized with the number and percentage of patients along with the corresponding two- sided 95% exact confidence interval (CI).by Phase 2a expansion group.

11.5 Progression Free Survival (Groups 2 and 3a)

Progression Free Survival (PFS) is defined as the date of first dose of study drug to the date of the initial objectively documented tumor progression per RECIST v1.1 or date of death from any cause whichever occurs first and will be calculated as:

Date of Disease Progression or Death Date (whichever is earliest) – Date of First Study Drug + 1

Patients who were lost to follow-up or had not progressed/died on study will be censored on the date of their last disease assessment or end-of-study visit or subsequent therapy (whichever is earliest) and will be calculated as:

Date of last response assessment or end-of-study visit or subsequent therapy (whichever is earliest) – Date of first study drug dose + 1

NOTE: If a patient does not have post-baseline tumor assessment or clinically determined progression and have not died, then the PFS will be censored at Day 1;

Kaplan-Meier methods will be used for the analysis of duration of stable disease. Median (with corresponding 2-sided 95% CI), quartiles (25th and 75th percentiles), minimum, and maximum duration of response time will be displayed. A Kaplan- Meier figure will be provided as standard for time-to-event endpoints.

11.6 Time to First Subsequent Therapy (Groups 1, 2 and 3a)

Time to first subsequent therapy (TFST) is defined as the time between the date of first dose of study drug to the date of first new anti-cancer therapy (subsequent therapy). .

At this time, there is not enough information regarding this endpoint. The data collection and planned analysis of this endpoint will be discussed in the next version of this SAP after the safety run-in and/or Simon Stage 1 analysis. However, Kaplan-Meier methods will be utilized for data analysis of this endpoint.

11.7 Histopathologic Response (Group 1)

Patients will see their surgeon and medical oncologist after Cycle 4 to determine if the tumor(s) has shrunk enough for salvage surgery instead of amputation. The surgeon and medical oncologist may elect that the patient continue on therapy and have another consultation after additional cycles.

When the surgery does take place, a tumor section will be analyzed to determine if there is a pathological complete response or pathological partial response.

The histopathologic response categories (CR+PR) will be summarized with the number and percentage of patients along with the corresponding two- sided 95% exact confidence interval (CI).by Phase 2a expansion groups.

11.8 Surgical Outcome: Amputation / Limb Salvage vs. Planned (Group 1)

At this time, there is not enough information regarding this endpoint. The data collection and planned analysis of this endpoint will be discussed in the next version of this SAP after the safety run-in and/or Simon Stage 1 analysis.

11.9 Disease Free Survival (Group 1)

Disease-free survival is defined as the time between the date of first dose of study drug and the date of recurrence/relapse or death from any cause, whichever occurs first.

At this time, there is not enough information regarding this endpoint. The data collection and planned analysis of this endpoint will be discussed in the next version of this SAP after the safety run-in and/or Simon Stage 1 analysis. However, Kaplan-Meier methods will be utilized for data analysis of this endpoint.

11.10 Local Recurrence-Free Survival, Time Frame: 2 Years (Group 1)

Local-recurrence-free survival is defined as time between the date of enrollment and the date of local recurrence/relapse or death from any cause, whichever occurs first.

At this time, there is not enough information regarding this endpoint. The data collection and planned analysis of this endpoint will be discussed in the next version of this SAP after the safety run-in and/or Simon Stage 1 analysis. However, Kaplan-Meier methods will be utilized for data analysis of this endpoint.

11.11 Distant Recurrence-Free Survival (Group 1)

Distant-recurrence free survival is defined as time between the date of enrollment and the date of distant recurrence/relapse or death from any cause, whichever occurs first.

At this time, there is not enough information regarding this endpoint. The data collection and planned analysis of this endpoint will be discussed in the next version of this SAP after the safety run-in and/or Simon Stage 1 analysis. However, Kaplan-Meier methods will be utilized for data analysis of this endpoint.

11.12 Symptomatic Disease Control (Group 1)

At this time, there is not enough information regarding this endpoint. The data collection and planned analysis of this endpoint will be discussed in the next version of this SAP after the safety run-in and/or Simon Stage 1 analysis.

11.13 Time to Local-Regional or Distant Progression (Group 3a)

Time to local-regional progression or distant progression is defined as the time between the date of enrollment and the date of local recurrence/relapse or distant progression.

At this time, there is not enough information regarding this endpoint. The data collection and planned analysis of this endpoint will be discussed in the next version of this SAP after the safety run-in and/or Simon Stage 1 analysis. However, Kaplan-Meier methods will be utilized for data analysis of this endpoint.

11.14 Local-Regional Control pre RECIST v1.1 (Group 3a)

At this time, there is not enough information regarding this endpoint. The data collection and planned analysis of this endpoint will be discussed in the next version of this SAP after the safety run-in and/or Simon Stage 1 analysis.

11.15 Exploratory Analysis: Target Lesions

Change in size of target lesion(s) including both injected, and non-injected tumors (if available) will be defined as the best percent change from baseline in the sum of diameters. This will be represented by a standard waterfall figure that is typically used to portray this efficacy parameter.

11.16 Exploratory Analysis: Target Lesions

DoR of target lesion(s) (including both injected, if available, and non-injected tumors) is defined as the time recorded between the date of enrollment and the date of the initial objectively documented tumor progression per RECIST v1.1, date of death from any cause, or the date of subsequent therapy, whichever occurs first. DoR will be evaluated for responders (i.e., participants with confirmed CR or PR) only.

11.17 Exploratory Analysis: Landmark Analysis

Landmark analyses (e.g., overall survival at 12, 24 months) will be conducted as deemed appropriate given the data and indication. If conducted, this exploratory analysis will be discussed in the clinical study report.

12. SAFETY ANALYSIS

Safety and tolerability will be summarized using AEs, SAEs, DLTs, deaths, events of special interest, events leading to dose reductions/modifications, discontinuation, and laboratory parameters.

All treatment-emergent AEs will be summarized by system organ class and preferred terms within a system organ class for each treatment group and Grade per NCI-CTCAE (version 5). Only treatment-emergent AEs will be summarized in the tables. Treatment-emergent AEs are those that occur after the first dose of Investigational Product is given. Each preferred term will be counted only once for a given patient. The severity (intensity) and the relationship to study medication will be summarized by system organ class and preferred term within a system organ class for each treatment group. For severity, if a patient has multiple occurrences of the same preferred term, the highest severity will be assumed.

Changes from baseline through the end of study will be descriptively summarized for the following: vital signs, ECG, ECHO/MUGA, coagulation, urinalysis, hematology, and clinical chemistry parameters. Tolerance and toxicity of SQ3370 treatment regimen will be assessed through evaluation of physical examinations, vital signs, laboratory parameters, AEs including DLTs, and all causes of mortality. The baseline definition for safety assessment is either at screening or prior to receiving the first dose of study drug; whichever is latest.

The Safety Analysis set defined as all patients who received at least 1 dose of SQL70 biopolymer and/or SQP33 protodrug will be utilized for all safety analyses.

In addition to the summary tables, safety data will also be presented in the individual patient listings.

12.1 Treatment Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as all AEs that begin on or after the date of the first administration of study drug. Related AEs are those reported as possibly related to SQL70 bipolymer, related to SPQ33 protodrug, and related to SQ3370 (both SQL70 and SQP33). The verbatim terms of the TEAEs will be coded to preferred terms (PT) and system organ classes (SOC) per the Medical Dictionary for Regulatory Activities (MedDRA®) Version 24.1.

All reported AEs (including non-TEAEs) will be listed, documenting all information collected on the eCRF including verbatim term, MedDRA preferred term, MedDRA system organ class, start date, stop date, severity and relationship to SQ3370 treatment, relationship to SQL70 biopolymer, relationship to SQP33 protodrug, action taken, and outcome.

The TEAEs will be graded by the Investigator in terms of:

- Severity graded 1-5 according to CTCAE v5.0:
  - 1=Mild, 2=Moderate, 3=Severe, 4= Life Threatening, 5=Fatal.
- Relation to SQ3370:
  - ‘Related’ includes events where the causality was reported as related to SQL70 bipolymer, related to SPQ33 protodrug, related to SQ3370 treatment (both SQL70 and SQP33), or where the relationship was not reported on the eCRF.
  - ‘Not Related’ includes events where the study drug causality was reported ‘Not Related’ on the eCRF.

All TEAE summary tables will be presented with the number and percentages of patients in the Safety population. Incidence rates of treatment-emergent adverse events (TEAEs) will be summarized within each dose level at the Medical Dictionary for Regulatory Activities

(MedDRA) primary system organ class levels and preferred term. Patients may be counted under multiple system organ class (SOC) and preferred terms (PT), but for each SOC and PT category, patients are only counted once. If a patient has the same AE on multiple occasions, the highest severity grade (fatal > life threatening > severe > moderate > mild) or drug relationship (related > not related) recorded for the event will be summarized.

This list includes:

- All TEAEs
- All TEAEs graded severity
- All Related TEAEs to SQ3370 treatment
- All Related TEAEs to SQ3370 treatment graded by severity
- All Related TEAEs to SQL70 biopolymer
- All Related TEAEs to SQL70 biopolymer graded by severity
- All Related TEAEs to SQP33 protodrug
- All Related TEAEs to SQP33 protodrug graded by severity
- Serious TEAEs
- Adverse Event of Special Interest (AESI)
- Dose Limiting Toxicity (DLT)
- TEAEs leading to discontinuation from study
- TEAEs resulting in death.

Separate patient listings will be provided for all SAEs, AEs leading to study discontinuation, DLTs, AESIs, and deaths.

12.2 Serious Adverse Events

Incidence rates of serious TEAEs will be summarized within each dose level at the Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class levels and preferred term A listing of patients who reported a serious adverse event will be presented. The data will be obtained from the AE dataset where ‘Is this adverse event serious? is checked ‘Yes’.

12.3 Adverse Events Leading to Discontinuation from Study

Incidence rates of TEAEs leading to discontinuation from study will be summarized within each dose level at the Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class levels and preferred term. A listing of patients and the adverse events which led to study discontinuation from the study will be included. The specific AE will be identified from the AE dataset where ‘Discontinued Study’ is checked or has data within in.

12.4 Deaths Due to Adverse Event

Incidence rates of TEAEs leading to death will be summarized within each dose level at the MedDRA primary system organ class levels and preferred term. A listing of patients who died on study will be included. The specific AE leading to death will be identified from the AE dataset where 'Did the adverse event result in death? is checked 'Yes'. Other possibilities are Outcome=Fatal and/or CTCAE Grade=5.

12.5 Adverse Event of Special Interest (AESI)

Incidence rates of TEAEs of special interest will be summarized within each dose level at the MedDRA primary system organ class levels and preferred term. All AESIs will be listed by expansion group and patient.

AESIs will be defined as the preferred terms of potential myocardial toxicity, COVID-19 infections, and AEs due to overdose. The specific AESI will be identified from the AE dataset where AESI is checked.

12.6 Dose Limiting Toxicity (DLT)

Dose limiting toxicities are not part of the dose expansion part of this protocol. The Phase 1 dose escalation SAP contains details on DLTs. There should be no DLTs identified for Phase 2a dose expansion.

12.7 Clinical Laboratory Tests

Safety laboratory assessments will be conducted as specified in Schedule of Assessments (Section 18).

All laboratory tests, values, units, normal ranges, flags collected in the clinical database (i.e., results that are outside the normal ranges will be flagged with "L" (below normal range) or "H" (above normal range)) will be included in the-patient listings for further medical review.

For laboratory analysis, baseline will be defined as either the screening visit or the Cycle 1 Day 1 visit; whichever is the closest visit prior to the administration of study treatment.

12.7.1 CTCAE Grading

For the hematology laboratory tests of interest where CTCAE [version 5.0] severity criteria are specified, CTCAE severity grades will be assigned. These laboratory tests include:

Panel	Test	CTCAE grade directions
Hematology	ANC	Decrease
	Hemoglobin	Decrease / Increase
	Platelet Count	Decrease

	White Blood Cell (WBC) count	Decrease
	Lymphocyte Count	Decrease

Analyses will be performed using “shift tables” of CTCAE toxicity grades relative to the baseline (pre-treatment) toxicity grade. The number and proportion of patients with directional shifts of the “worst” CTCAE toxicity grade post-baseline and CTCAE toxicity grade of the last post-baseline visit relative to the baseline (pre-treatment) toxicity grade will be summarized for the selected hematology and chemistry parameters.

The CTCAE toxicity grading algorithms for the appropriate laboratory analytes are detailed in Section 19.

12.7.2 Hematology

Hematology laboratory tests are planned to include Hemoglobin, Hematocrit, MCV, Platelets, Absolute White Blood Count, Absolute Neutrophil Count, Absolute Lymphocyte Count, Absolute Monocyte Count, Absolute Eosinophils Count, Absolute Basophils Count, % Neutrophils, % Lymphocyte, % Monocytes, % Eosinophils, and % Basophils.

Due to the large number of laboratory visits, the data will be summarized by these post-baseline timepoint descriptors: First post-baseline, Last post-baseline value, Minimum post-baseline value, Maximum post-baseline value, and Average post-baseline value.

These hematology laboratory test results are measured on a continuous scale and the observed values as well as changes from baseline values will be summarized for each expansion group using n, mean, standard deviation, median, minimum and maximum values.

12.7.3 Chemistry

Chemistry laboratory tests are planned to include Sodium, Potassium, Glucose, Calcium (Total), Creatinine, Protein (Total), Albumin, Bilirubin (Total), Bilirubin (Direct), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Lipase, Amylase.

Due to the large number of laboratory visits, the data will be summarized by these post-baseline timepoint descriptors: First post-baseline, Last post-baseline value, Minimum post-baseline value, Maximum post-baseline value, and Average post-baseline value.

These chemistry laboratory test results are measured on a continuous scale and the observed values as well as changes from baseline values will be summarized for each

expansion group using n, mean, standard deviation, median, minimum and maximum values.

12.7.4 Coagulation

Coagulation laboratory tests are planned to include Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), Thrombin Time (TT) and INR.

Due to the large number of laboratory visits, the data will be summarized by these post-baseline timepoint descriptors: First post-baseline, Last post-baseline value, Minimum post-baseline value, Maximum post-baseline value, and Average post-baseline value.

These coagulation laboratory test results are measured on a continuous scale and the observed values as well as changes from baseline values will be summarized for each expansion group using n, mean, standard deviation, median, minimum and maximum values.

12.7.5 Urinalysis

All Urinalysis test results (Protein, Blood, Specific Gravity, Glucose) will be presented in the patient listings.

12.8 Vital Signs and Weight

The vital sign tests to be collected include:

- Blood pressure (systolic and diastolic [mmHg])
- Heart rate (beats per minute [bpm]
- Respiratory rate (bpm)
- Temperature (c)
- Weight (lbs) once per cycle
- Height (in) at screening only.

See Schedule of Assessments (Section 18) for specific vital sign data collection timepoints.

Vital sign assessments measured on a quantitative scale will be summarized in a descriptive manner by calculating the n, mean, standard deviation, median, and range at the baseline timepoint (defined as either the screening visit or the Cycle 1 Day 1 visit; whichever is the closest visit prior to the administration of study treatment) and subsequent post-baseline timepoint, and by expansion group. Mean change from baseline will also be presented in the same manner.

Due to the large number of vital sign visits, the data will be summarized by these post-baseline timepoint descriptors:

- First post-baseline, Last post-baseline value, Minimum post-baseline value, Maximum post-baseline value, and Average post-baseline value.
- Height will only be summarized at baseline.

All vital sign tests will be included in patient listings for further medical review.

12.9 12-Lead Electrocardiogram (ECG)

The 12-Lead ECG assessments include:

- Heart Rate
- QT interval
- PR interval
- QRS interval
- QTcF interval

See Schedule of Assessments (Section 18) for specific ECG data collection timepoints. In summary they include:

- Screening.
- On Day 1 of each cycle ECGs will be performed both pre and post SQP33 protodrug infusion.
- On Days 2-5 of Cycle 1 ECGs will be performed post SQP33 protodrug infusion only.

Quantitative Analysis:

ECG assessments measured on a quantitative scale will be summarized in a descriptive manner by calculating the n, mean, standard deviation, median, and range at the baseline timepoint (defined as either the screening visit or the Cycle 1 Day 1 visit; whichever is the closest visit prior to the administration of study treatment) and subsequent post-baseline timepoint, and by expansion group. Mean change from baseline will also be presented in the same manner.

Categorical Analysis:

Additionally, QTcF results will also be categorized according to their values into the categories as defined in ICH E14:

- ≤ 450 ms
- > 450 ms to ≤ 480 ms
- > 480 ms to ≤ 500 ms
- >500 ms

and categorized according to their change from baseline into the categories:

- ≤ 30 ms,
- > 30 ms to ≤ 60 ms
- > 60 ms

The categories described above will be summarized in frequency tables using number of patients (n) and percentages at each post-dose timepoint for each expansion group.

A separate analysis of the overall ECG interpretation (categorical: Normal, Abnormal Not Clinically Significant, and Abnormal Clinically Significant) will be performed using "shift tables" relative to the baseline (screening) interpretation. The number and proportion of patients with directional shifts of ECG interpretation categories post-baseline relative to the baseline (screening) will be summarized.

All ECG results will be included in patient listings for further medical review. Of specific interest would be the interpretation of Abnormal, Clinically Significant ECG panel.

12.10 ECOG Performance Status

ECOG performance status will be assessed at Screening, and Week 3 (Day 17+-2 days) at Cycles 1-4, Day 1 of Cycles 5+, and 28 days Safety Follow-up. The ECOG performance status categories (6-point scale) are as follows:

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

ECOG will be summarized by expansion group using shifts from screening to the patient's "worst" (i.e., highest number) ECOG score during the post-baseline study period and the last ECOG score taken post-baseline.

ECOG assessments will be included in patient listings.

12.11 Echocardiogram (ECHO) or Multigated acquisition (MUGA)

From the ECHO or MUGA scans, the LVEF (%) results are reported for the following time points:

- Screening.

- Treatment: An ECHO or MUGA scan (whichever was performed during screening) should be reported for 7 days from Cycle 3 Day 1, Cycle 5 Day 1 and Day 1 of every cycle thereafter
- Safety Follow-Up: An ECHO or MUGA scan (whichever was performed during screening) should be reported for the Safety Follow-Up visit if not performed in the previous 14 days.
- Long Term Follow Up (if applicable): An ECHO or MUGA scan (whichever was performed during screening) should be reported for each Long-Term Follow-Up visit.

Ejection Fraction percentages, LVEF (%), will be provided in table format by timepoint and by change from baseline summaries using descriptive summary statistics (n, mean, SD, median, range).

ECHO or MUGA test results to assess left ventricular ejection fraction (LVEF) will be presented in the patient listings.

12.12 Physical Examination

A physical examination should include a review of the following body systems: constitutional, skin, HEENT (head, eyes, ears, nose, and throat), neck, chest and lungs, cardiovascular, abdomen, neurological, and musculoskeletal, and genitourinary and gynecologic if indicted by the Investigator.

Symptom directed examinations should include an examination of organ systems related to patient symptoms for potential AEs. Any new post-baseline abnormal physical examination findings assessed as clinically significant should be recorded as an AE or SAE.

Physical examinations results will be displayed in patient listings.

12.13 Pregnancy Test

Individual patient data listings will be displayed for pregnancy test results.

13. PHARMACOKINETIC (PK) ANALYSIS

PK in tumor and plasma and binary variable exploratory analyses will be performed by the Shasqi R&D group and/or sponsor PK consultant and is not part of this SAP. A separate PK data analysis plan will be developed prior to the database lock.

14. BIOMARKER ANALYSIS

Immune response will be evaluated based upon summaries of the biomarker data collected as part of the tumor biopsies and by summarizing the PBMC data. These data will be summarized by dose (Phase 1), Expansion Group (Phase 2a), time point measured, and changes over time. Listings of the individual measures will also be provided. Biomarker data analysis will be performed by the Shasqi R&D group and/or sponsor consultant and a separate Biomarker data analysis plan will be developed prior to database lock. .

15. COMMITMENT TO GOOD STATISTICAL PRACTICE

15.1 Definition of Good Statistical Practice

The International Conference on Harmonisation (ICH) Guidance on Statistical Principles for Clinical Trials (ICH E9) implicitly defines good statistical practice. Good statistical practice includes both appropriate statistical designs to minimize bias and to maximize precision of analysis plus operational excellence to assure credibility of results. The scientific design associated with any clinical trial is found in the protocol and in a more detailed pre-specified statistical analysis plan such as this one.

15.2 Data Management and Use of CDISC Standards

Data standards for clinical development of drugs have been defined and are maturing under various initiatives through the Clinical Data Interchange Standards Consortium (CDISC).

Shasqi will use third party vendors for clinical data collection and data analysis. Clinical data will be managed by Novotech (Australian based CRO). and will be captured in electronic case report form (eCRF) by the Medidata RAVE platform. The “raw” data contained in the eCRF clinical database will then be converted into Study Data Tabulation Model (SDTM) datasets per CDISC standards by Novotech. The SDTM datasets will then be utilized in statistical data analysis as the source to create Analysis Data Model (ADaM) datasets. These ADaM data conversions and data analysis will be conducted by Vantage Data Designs.

Other applicable standards include regulatory guidance’s from the Food and Drug Administration (FDA), ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3), and ICH Guidance for Good Clinical Practice (ICH E6).

15.3 Testing/Validation Plan and Software System

Statistical Analysis Software (SAS) version 9.4 or later will be used to analyze the data, create summary tables, patient data listings, and graphical representation of the data. All

SAS computer programs will be validated using industry standard validation procedures including independent quality control programming.

16. STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL

The analyses described are based on the final clinical study protocol SQ3370-101 Amendment 8 dated November 17, 2022. This SAP supersedes the statistical considerations identified in the protocol. The following table summarizes changes in the SAP versus the protocol:

SAP	Protocol	Reason
N/A	N/A	N/A

17. REFERENCES

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7. International Federation of Pharmaceutical Manufacturers and Associations. Medical Dictionary for Regulatory Activities (MedDRA). Version 24.1. Reston, Virginia, USA; 2008.

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9. SAS Institute Inc. SAS Version 9.4. Cary, NC, USA; 2002-2003.
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18. SCHEDULE OF ASSESSMENTS

Expansion Group 1: Extremity STS

Study Day		Screening	Treatment				SFTY FU	LTFU
			Week 1			Week 2		
		Day -28 to Day -1	Day 1 [A]	Day 2 / 3 / 4	Day 5	Day 10 ± 2 days	28-34 days after last dose of IP	every 12 weeks (± 7 days)
		On-Site	On-Site	On-Site	On-Site	Telephone or On-Site [B]	On-site	Variable [M]
Screening	Informed consent [C]	X						
	Medical history	X						
	Review Inc/Exc Criteria	X						
	Confirm Eligibility		X					
Safety	Physical Exam	X						
	Symptom-Directed PE		X [D]				X	
	Vital Signs	X	X	X	X		X	
	ECHO or MUGA	X	Every other cycle [E]				X [K]	
	Triplicate 12-Lead ECG	X	X [D, F]	Cycle 1 Only	Cycle 1 Only		X	
	ECOG	X	Cycle 2+				X	
	AE Review		X	X	X	X	X	
	Conmed Review	X	X	X	X	X	X	
Labs	Hematology & Chemistry	X	X [D]	Cycle 1 Only	X	Cycle 1 Only [D]	X [D]	
	Coagulation & Urinalysis	X					X [D]	
	Pregnancy Test	X [G]	X [D]				X [D]	
	Serology	X						
	Plasma PK		Cycle 1 & 2 only; see separate PK Schedule					
	PBMC / ctDNA [O]		Cycle 1, 2, 3 only					
	Cardio Tox Biomarkers	X	Every other cycle [E]				X	
	Tumor Biopsy		Cycle 1, 2, 3 only [H]					
CT / MRI & RECIST		X	Every 6 weeks [I]				X [L]	X [N]
IP	Administer SQL70 Biopolymer		X					
	Administer SQP33 Protodrug		X [J]	X	X			
Survival	Vital Status							X

Notes For EXPANSION GROUP 1: EXTREMITY STS
A - Day 1-5 is typically Monday through Friday, however if the site can accommodate protocol procedures on the weekends Day 1 may start on any day of the week.

B - Day 10 visit may be performed via telephone (using a lab closer to a patient's home) or on-site.
C - Written informed consent must be obtained prior to any study-specific procedures.
D - May be performed up to 3 days before the visit.
E - ECHO/MUGA to be performed every other cycle starting at Cycle 3; may be performed up to 7 days before the visit. Serum sample for cardiotoxicity biomarker analysis is to be collected on the same day.
F - ECG to be performed pre dose and post dose +30 minutes.
G - To be collected ≤ 7 days prior to Cycle 1 Day 1 for women of child-bearing potential.
H - Collect biopsy unless the tumor is considered too small to be biopsied; biopsy can be performed during screening and up to 4 days prior to Day 1 for other cycles. Resected tumor samples should be collected at the time of surgery.
I - May be performed up to 7 days prior to the projected every 6 weeks from C1D1 date presurgical disease re-evaluation.
J - SQP33 protodrug infusion occurs within 3 hrs ± 30 mins after receiving SQL70 biopolymer injection.
K - ECHO or MUGA not required at the Safety Follow-Up visit if performed in the previous 14 days.
L - CT / MRI & RECIST not required at the Safety Follow-Up visit if performed in the previous 6 weeks.
M - For up to 2 years after treatment end; collected during routine clinic visits, telephone or e-mail with the subjects/caregivers or referring physician offices.
N - Until disease progression per RECIST; May be performed up to 14 days before the visit.
O - PBMC and ctDNA tubes are included in the same kit but are separate tubes. Collection is done on D1 of C1-3 only.
Reminder: Investigator can perform unscheduled labs, ECGs and physical exams as needed / clinically indicated

EXPANSION GROUP 2: UNRESECTABLE STS (5 DAY)

Study Day		Screening	Treatment				SFTY FU	LTFU
			Week 1			Week 2		
		Day -28 to Day -1	Day 1 [A]	Day 2 / 3 / 4	Day 5	Day 10 ± 2 days	28-34 days after last dose of IP	every 12 weeks (± 7 days)
		On-Site	On-Site	On-Site	On-Site	Telephone or On-Site [B]	On-site	Variable [M]
Screening	Informed consent [C]	X						
	Medical history	X						
	Review Inc/Exc Criteria	X						
	Confirm Eligibility		X					
Safety	Physical Exam	X						
	Symptom-Directed PE		X [D]				X	
	Vital Signs	X	X	X	X		X	
	ECHO or MUGA	X	Every other cycle [E]				X [K]	
	Triplicate 12-Lead ECG	X	X [D, F]	Cycle 1 Only	Cycle 1 Only		X	
	ECOG	X	Cycle 2+				X	
	AE Review		X	X	X	X	X	

	Conmed Review	X	X	X	X	X	X	
Labs	Hematology & Chemistry	X	X [D]	Cycle 1 Only	X	Cycle 1 Only [D]	X [D]	
	Coagulation & Urinalysis	X					X [D]	
	Pregnancy Test	X [G]	X [D]				X [D]	
	Serology	X						
	Plasma PK		See Separate PK Schedule					
	PBMC/ ctDNA		Cycle 1, 2, 3 [O]					
	Cardio Tox Biomarkers		Every other cycle [E]				X	
	Tumor Biopsy		Cycle 1, 2, 3 only [H]					
CT / MRI & RECIST		X	Every 6 weeks [I]				X [L]	X [N]
IP	Administer SQL70 Biopolymer		X					
	Administer SQP33 Protodrug		X [J]	X	X			
Survival	Vital Status							X

Notes For EXPANSION GROUP 2: UNRESECTABLE STS (5 DAY)

A - Day 1-5 is typically Monday through Friday, however if the site can accommodate protocol procedures on the weekends Day 1 may start on any day of the week.
B - Day 10 visit may be performed via telephone (using a lab closer to a patient's home) or on-site.
C - Written informed consent must be obtained prior to any study-specific procedures.
D - May be performed up to 3 days before the visit.
E - ECHO/MUGA to be performed every other cycle starting at Cycle 3; may be performed up to 7 days before the visit. Serum sample for cardiotoxicity biomarker analysis is to be collected on the same day.
F - ECG to be performed pre dose and post dose +30minutes.
G - To be collected ≤ 7 days prior to Cycle 1 Day 1 for women of child-bearing potential.
H - Collect optional biopsy unless the tumor is considered too small to be biopsied; biopsy can be performed during screening and up to 4 days prior to Day 1 for other cycles.
I - May be performed up to 7 days prior to the projected every 6 weeks from C1D1 date.
J - SQP33 protodrug infusion occurs within 3 hrs ± 30 mins after receiving SQL70 biopolymer injection.
K - ECHO or MUGA not required at the Safety Follow-Up visit if performed in the previous 14 days.
L - CT / MRI & RECIST not required at the Safety Follow-Up visit if performed in the previous 6 weeks.
M - Capture and report next line of therapy x1 then for up to 2 years after treatment end; collected during routine clinic visits, telephone or e-mail with the subjects/caregivers or referring physician offices.
N - Until disease progression per RECIST; May be performed up to 14 days before the visit.
O - In addition to Day 1 of Cycles 1, 2, and 3, plasma samples should be taken at the time of the CT / MRI scans for RECIST between Cycles 4 -12 (see footnote I). PBMC and ctDNA tubes are included in the same kit but are separate tubes.
Reminder: Investigator can perform unscheduled labs, ECGs and physical exams as needed / clinically indicated

EXPANSION GROUP 3: HEAD AND NECK

Study Day		Screening	Treatment				SFTY FU	LTFU
			Week 1			Week 2		
		Day -28 to Day -1	Day 1 [A]	Day 2 / 3 / 4	Day 5	Day 10 ± 2 days	28-34 days after last dose of IP	every 12 weeks (± 7 days)
		On-Site	On-Site	On-Site	On-Site	Telephone or On-Site [B]	On-site	Variable [M]
Screening	Informed consent [C]	X						
	Medical history	X						
	Review Inc/Exc Criteria	X						
	Confirm Eligibility		X					
Safety	Physical Exam	X						
	Symptom-Directed PE		X **D**				X	
	Vital Signs	X	X	X	X		X	
	ECHO or MUGA	X	Every other cycle [E]				X **K**	
	Triplicate 12-Lead ECG	X	X **D, F**	Cycle 1 Only	Cycle 1 Only		X	
	ECOG	X	Cycle 2+				X	
	AE Review		X	X	X	X	X	
	Conmed Review	X	X	X	X	X	X	
Labs	Hematology & Chemistry	X	X **D**	Cycle 1 Only	X	Cycle 1 Only [D]	X **D**	
	Coagulation & Urinalysis	X					X **D**	
	Pregnancy Test	X **G**	X D				X **D**	
	Serology	X						
	Plasma PK		See Separate PK Schedule					
	PBMC / ctDNA		Cycle 1, 2, 3 [O]					
	Cardio Tox Biomarkers	X	Every other cycle [E]				X	
	Tumor Biopsy		Cycle 1, 2, 3 only [H]					
CT / MRI & RECIST		X	Every 6 weeks [I]				X **L**	X **N**
IP	Administer SQL70 Biopolymer		X					
	Administer SQP33 Protodrug		X **J**	X	X			
Survival	Vital Status							X

Notes For EXPANSION GROUP 3A: HEAD AND NECK
A - Day 1-5 is typically Monday through Friday, however if the site can accommodate protocol procedures on the weekends Day 1 may start on any day of the week.
B - Day 10 visit may be performed via telephone (using a lab closer to a patient's home) or on-site.
C - Written informed consent must be obtained prior to any study-specific procedures.

D - May be performed up to 3 days before the visit.
E - ECHO/MUGA to be performed every other cycle starting at Cycle 3; may be performed up to 7 days before the visit. Serum sample for cardiotoxicity biomarker analysis is to be collected on the same day.
F - ECG to be performed pre dose and post dose +30 minutes.
G - To be collected ≤ 7 days prior to Cycle 1 Day 1 for women of child-bearing potential.
H - Collect optional biopsy unless the tumor is considered too small to be biopsied; biopsy can be performed during screening and up to 4 days prior to Day 1 for other cycles.
I - May be performed up to 7 days prior to the projected every 6 weeks from C1D1 date.
J - SQP33 protodrug infusion occurs within 3 hrs ± 30 mins after receiving SQL70 biopolymer injection.
K - ECHO or MUGA not required at the Safety Follow-Up visit if performed in the previous 14 days.
L - CT / MRI & RECIST not required at the Safety Follow-Up visit if performed in the previous 6 weeks.
M - Capture and report next line of therapy x1 then for up to 2 years after treatment end; collected during routine clinic visits, telephone or e-mail with the subjects/caregivers or referring physician offices.
N - Until disease progression per RECIST; May be performed up to 14 days before the visit.
O - In addition to Day 1 of Cycles 1, 2, and 3, plasma samples should be taken at the time of the CT / MRI scans for RECIST between Cycles 4 -12 (see footnote I). PBMC and ctDNA tubes are included in the same kit but are separate tubes.
Reminder: Investigator can perform unscheduled labs, ECGs and physical exams as needed / clinically indicated.

19. CTCAE TOXICITY LABORATORY GRADING CHART

Panel	Analyte	Type	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v5.0)
Hematology	WBC count	WBC with differential	10^9/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 3.0 × 10^9/L Grade 2: < 3.0 – 2.0 × 10^9/L Grade 3: < 2.0 – 1.0 × 10^9/L Grade 4: < 1.0 × 10^9/L
Hematology	ANC	WBC with differential	10^9 cells/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 1.5 × 10^9/L Grade 2: < 1.5 – 1.0 × 10^9/L Grade 3: < 1.0– 0.5 × 10^9/L Grade 4: < 0.5 × 10^9/L
Hematology	Lymphocyte count	WBC with differential	10^9cells/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 0.8 × 10^9/L Grade 2: < 0.8 – 0.5 × 10^9L Grade 3: < 0.5 – 0.2 × 10^9/L Grade 4: < 0.2 × 10^9/L
Hematology	Hemoglobin	Erythrocytes and Platelets	g/L	Increase	Grade 0: ≤ ULN Grade 1: > 20 g/L + ULN Grade 2: > 20 – 40 g/L +ULN Grade 3: > 40 + ULN Grade 4: Not defined
			g/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 100 g/L Grade 2: < 100 – 80 g/L Grade 3: < 80 Grade 4: Not defined
Hematology	Platelet count	Erythrocytes and Platelets	10^9/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 75 × 10^9/L Grade 2: < 75 – 50 × 10^9/L Grade 3: < 50 – 25 × 10^9/L Grade 4: < 25 × 10^9/L

LLN=lower limit of normal. ULN=upper limit of normal.

The LLN and ULN for each analyte will be determined from the normal range of the local laboratory facility.

20. RECIST VERSION 1.1 RESPONSE CRITERIA

Below is a summary of the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 guidelines as it relates to the categorization of overall response. Further detail and clarification can be obtained from the referenced European Journal of Cancer article authored by Eisenhauer et al. or viewed on-line at the following website:

https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	**CR**
CR	Non-CR/non-PD	No	**PR**
CR	Not evaluated	No	**PR**
PR	Non-PD or not all evaluated	No	**PR**
SD	Non-PD or not all evaluated	No	**SD**
Not all evaluated	Non-PD	No	**NE**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, inevaluable.

Time Point Response: Patients with Nontarget Disease Only

Non Target Lesions	New Lesions	Overall Response
CR	No	**CR**
Non-CR/non-PD	No	**Non-CR/non-PD**
Not all Evaluated	No	**NE**
Unequivocal PD	Yes or No	**PD**
Any	Yes	**PD**

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009. 45(2):228-247.