TITLE: A Multicenter Phase 1/2a, Open-Label Study of SQ3370 in Patients with Advanced Solid Tumors

PROTOCOL NUMBER: SQ3370-001

INVESTIGATIONAL PRODUCT: SQ3370

IND NUMBER: 137024

SPONSOR: Shasqi, Inc
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San Francisco, CA 94107, USA

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VERSION, DATE: Amendment 8 - Version 1.0, 2022-11-17
Amendment 7 - Version 1.0, 2022-07-25 (US only)
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Amendment 6 - Version 1.0, 2021-08-10
Amendment 5 - Version 1.0, 2021-03-05
Amendment 4 - Version 1.0, 2020-11-18
Amendment 3 - Version 1.0, 2020-04-28 (COVID-19 Updates)
Amendment 2 - Version 1.0, 2020-01-30 (FDA Updates)
Amendment 1 - Version 1.0, 2019-12-05 (AU HREC Updates)
Original Protocol - Version 1.0, 2019-08-30

PROTOCOL INVESTIGATOR SIGNATURE PAGE

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I have read this protocol, including all appendices. By signing this protocol signature page, I agree to conduct the clinical study, following approval by an Independent Ethics Committee/Institutional Review Board, in accordance with this protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this protocol and will receive all necessary instructions for performing the study according to the protocol.

_____
Principal Investigator's Name (print)

_____ _____
Principal Investigator's Signature **Date (DD-MMM-YY)**

Please retain the signed original of this form for your study files. Please return a ***copy*** to the Sponsor or designee.

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PROTOCOL SYNOPSIS

Sponsor/Company:
Shasqi, Inc.

Investigational Product:
SQ3370

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SQ3370-001

TITLE
A Multicenter, Phase 1/2a, Open-Label Study of SQ3370 in Patients with Advanced Solid Tumors

OBJECTIVES AND ENDPOINTS (Primary, Secondary and Exploratory)

Objectives	Endpoints
Primary	

Phase 1: Dose Escalation
• Assess the safety and tolerability of SQ3370, 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
 	
Phase 2a: Expansion Groups
• Further investigate the safety and tolerability of SQ3370 in anthracycline naïve patients with:
  • Group 1: Patients with extremity Soft Tissue Sarcoma (STS)
  • Group 2: Patients with unresectable, locally advanced or metastatic STS.
  • Group 3:
  ○ 3a) Patients with relapsed or metastatic squamous-cell head and neck cancer
	Phase 1: Dose Escalation
	• 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
	
	Phase 2a: Expansion Groups
	• Frequency of AEs and SAEs, as well as changes from baseline in vital signs, clinical laboratory parameters, physical examination findings, ECHO/MUGA, and electrocardiogram (ECG) results across all groups and treatment cycles

Secondary	
Phase 1: Dose Escalation • Characterize the PK profile of SQP33 protodrug and active doxorubicin (Dox) following SQ3370 treatment • Assess preliminary signals of SQ3370 anti-tumor activity	*Phase 1: Dose Escalation* • Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Phase 2a: Expansion Groups
• Assess preliminary signals of SQ3370 anti-tumor activity
• Characterize the PK profile of SQP33 protodrug and active Dox following SQ3370 treatment.
	• Plasma concentration and pharmacokinetics (PK) parameters for SQP33 protodrug and active Dox following SQ3370 treatment
	
	Phase 2a: Expansion Groups
	• <u>General for all Expansion Groups</u>
	  • Objective response rate (ORR) per RECIST v1.1
	  • Overall survival (OS)
	  • Plasma concentration and PK parameters for SQP33 protodrug and active Dox following SQ3370 treatment
	  • Time from enrollment to first subsequent therapy (TFST)
	• <u>Group 1: Extremity STS</u>
	  • Histopathological Response
	  • Surgical outcome amputation/limb-salvage vs planned
	  • Disease-free survival
	  • Local recurrence-free survival
	  • Distant recurrence-free survival
	  • Symptomatic disease control
	• <u>Group 2: Unresectable STS</u>
	  • Compare safety and tolerability of two infusion schedules of SQP33 (3-day vs 5-day)
	  • Pharmacokinetic comparison of the two infusion schedules (3-day vs 5-day)
	  • Duration of Response (DOR) per RECIST v1.1
	  • Progression Free Survival (PFS) per RECIST v1.1
	  • Disease Control Rate (DCR) per RECIST v1.1
	• <u>Group 3a: Head and Neck</u>
	  • Duration of Response (DOR) per RECIST v1.1
	  • Progression Free Survival (PFS) per RECIST v1.1
	  • Time to local-regional progression or distant progression per RECIST v1.1
	  • Local-regional control per RECIST v1.1
	  • Disease Control Rate (DCR) per RECIST v1.1

Exploratory	

Phase 1: Dose Escalation
• 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
 	
Phase 2a: Expansion Groups
• 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
	Phase 1: Dose Escalation
	• 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.
	
	Phase 2a: Expansion Groups
	• <u>General for all Expansion Groups</u>
	  • 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

OVERALL DESIGN

This multicenter, Phase 1/2a, first-in-human, single-arm, open-label, dose-escalation study will be conducted in 2 stages including a dose escalation to evaluate the safety and tolerability, PK, and preliminary efficacy of SQ3370 in patients with locally advanced or metastatic solid tumors, and a secondary Phase 2a to compare differing tumor types.

<u>Phase 1: Dose Escalation</u>

The Phase 1 dose-escalation portion of the study will initially consist of an accelerated titration design and then switch to a 3+3 (Rolling 6) design. Patients will receive specific dose levels of SQP33 protodrug assigned according to the dose escalation design described in section 3.2 Phase 1 Dose Escalation.

20 mL SQL70 Biopolymer (from Cycle 1) Cohort: To evaluate the administration of 20 mL of SQL70 biopolymer in one or two lesions starting at Cycle 1, patients will be enrolled in a separate cohort at a dose level of SQP33 protodrug that is lower than the current dose level being evaluated (see section 3.2.3 Phase 1: 20 mL SQL70 Biopolymer (from Cycle 1) Cohort). The sponsor may choose doses up to or less than the RP2D to include in the 20 mL polymer group or may discontinue dose escalation within this group at any point in the study after enrollment of the initial 20 mL cohorts.

<u>Phase 2a: Expansion Groups</u>

Patients will be enrolled in the Phase 2a expansion groups (further defined below) to study the preliminary activity and gain additional SQ3370 safety data, dosing schedule comparisons, as well as PK and immune changes in blood and tumor tissue (see section 3.3 Phase 2A Expansion Groups).

STUDY POPULATION

Phase 1: Dose Escalation

This study will enroll male or female patients ≥ 18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and adequate organ function.

- A key exclusion criteria is prior lifetime exposure to >300 mg/m^2 of Dox HCl or DOXIL / CAELYX® or 600 mg/m^2 of epirubicin HCl or 600 mg/m² daunorubicin prior to study dosing.
- All patients must have a histologically or cytologically confirmed cancer or desmoid tumor.
- All patients must be either refractory to or relapsed following standard of care or ineligible for standard of care therapy

Phase 2: Dose Expansion will treat <u>anthracycline naïve patients</u>

- Group 1: 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 histologies.
- Group 2: unresectable, locally advanced or metastatic STS with predefined anthracycline sensitive histologies
- Group 3:
    - 3a: relapsed or metastatic squamous-cell head and neck cancer (R/M HNSCC)

Phase 1 & 2a Tumor Requirements

The injected local or metastatic solid tumor must meet all the following criteria:

- A tumor type that is defined in where clinical evidence suggests that anthracyclines have favorable clinical activity. An injectable tumor defined as:
    - measurable per RECIST v1.1 at Baseline
    - palpable or able to be injected percutaneously with imaging guidance (i.e., ultrasound)
    - excluding the following organs/structures: pancreas and extrahepatic biliary tract, central nervous system, or heart and great vessels
    - accessible by repeated intra and/or peritumoral injection with a 18- to 22-gauge needle
- Phase 1 additional criteria for the 20 mL SQL70 biopolymer (from Cycle 1) Cohort:
    - Have at least two injectable tumors or, based on investigator clinical judgement documented in the medical record, a sufficiently large single lesion that can be injected with a 20 mL volume (i.e., 5 cm or larger).
- Anthracycline sensitive tumors for Phase 2a Groups 1 & 2 include:
    - Angiosarcomas
    - Leiomyosarcoma
    - Liposarcoma
    - Synovial sarcoma
    - Adult fibrosarcoma
    - Undifferentiated pleomorphic sarcoma

TREATMENT GROUPS AND REGIMENS

Phase 1: Dose Escalation

SQ3370 consists of 2 components: SQP33, a Dox protodrug, and SQL70, a biopolymer. SQL70 biopolymer is injected on Day 1 of each 21-day cycle into a lesion or lesions followed by 5 consecutive daily infusions of SQP33 protodrug (Day 1-5). No more than 2 lesions may be injected during the treatment cycle with the exception of a “regional cluster of lesions”.

Patients may continue to receive treatment for up to 12 cycles. Treatment for more than 12 cycles requires approval by the Medical Monitor. All lesions should continue to be injected until either:

- they are no longer injectable (as determined by the investigator): this includes lesions that are resolved, no longer clearly seen on scan, no longer palpable, cannot continue to be safely injected, or are either suspected or confirmed on biopsy to no longer contain viable tumor. At this point the area of the tumor bed, if possible, should be treated for a minimum of at least two additional cycles.
- they have progressed per RECIST v1.1
- or other treatment discontinuation criteria are met (see section 3.1.5 End of Treatment)
- See APPENDIX G – Schedule of Assessments – Phase 1 Dose Escalation for details.

Phase 2: Expansion Groups

- Group 1: Extremity STS
  - Subjects with soft tissue sarcomas of the extremity AJCC Stage III OR IV (> 5 cm injectable tumors) locally advanced and or metastatic, not amendable to primary surgical intervention, according to the consensus of a multidisciplinary treatment team, determined prior to screening.
  - Group 1 will be conducted in 2 phases with a possible expansion phase. The group will open with a) the initial phase safety run-in of 6 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, and b) 31 additional patients initial adaptive design phase.
  - Patients will enroll at the RP2D of SQ3370. It is anticipated that the size of tumors given the stage and inclusion criteria eligible for enrollment will be potentially larger than in Phase 1, this group will receive a fixed dose of SQL70 (20 mL). 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 initial 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). (See APPENDIX H – Schedule of Assessments – Expansion Group 1: Extremity STS for details).
  - 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. Note that the study will allow up to 4 additional cycles, at which point all patients should undergo exploratory surgery and or tumor resection.
  - If a patient with Stage III had a radiological and surgical complete response (CR) they may receive up to 4 additional cycles, but no patient may exceed 12 cycles within the study. Stage IV patients may continue post op chemotherapy. Any patient group III or IV must have accessible lesions or the primary tumor that is deemed adequate for post operative intratumoral injection. If a patient receives post-operative radiation which is allowed on study, they meet End of Treatment criteria and will not receive further SQP3370 (see section 3.1.5 End of Treatment).
  - Any patient at any point who has been determined to have progressive disease has reached end treatment and will proceed to a definitive surgical treatment, note pre-operative radiation is allowed for patients with progressive disease pre-operatively on study at this point.
    - Subjects will be treated with the RP2D of SQ3370 every 21 days (1 cycle) up to 12 cycles or until other treatment discontinuation criteria are met (see section 3.1.5 End of Treatment). On Day 1 of each cycle, the subject will receive an injection of SQL70 biopolymer into the tumor (20 mL), followed by 5 days of SQP33 infusion starting 3 hours ± 30 min after the SQL70 biopolymer injection.

- Group 2: Unresectable STS locally advanced or metastatic.
    - Patients will enroll at the RP2D of SQ3370, maintaining the total dose per cycle constant and compare 2 different infusion schedules a 3-day vs a standard 5-day schedule. The 3-day cycle will administer the same dose on Day 1 as the 5-day cycle and 2x the doses on days 2 and 3 of the cycle. (See APPENDIX I – Schedule of Assessments – Expansion Group 2: Unresectable STS (5 day) and APPENDIX J – Schedule of Assessments – Expansion Group 2: Unresectable STS (3 Day) for details).
    - Eleven (11) patients per group. Subjects will be treated with the RP2D of SQ3370 every 21 days (1 cycle) up to 12 cycles or until other treatment discontinuation criteria are met (see section 3.1.5 End of Treatment). On Day 1 of each cycle, the subject will receive an injection of SQL70 biopolymer into the tumor (10 mL) followed by 3 or 5 days of SQP33 infusion starting 3 hours ± 30 min after the SQL70 biopolymer injection.
- Group 3a: Head and Neck
    - Patients with histologically or cytologically confirmed relapsed or metastatic squamous-cell carcinoma of the head and neck (R/M HNSCC), who have exhausted curative intent therapies or patients with distant metastases who may have received one or less chemotherapy regimen.
    - This will follow a Simon 2-stage design. Thirteen (13) patients will be initially treated with the RP2D of SQ3370 every 21 days (1 cycle) up to 12 cycles or until other treatment discontinuation criteria are met (see section 3.1.5 End of Treatment). On Day 1 of each cycle, the patient will receive a 10 mL injection of the SQL70 biopolymer into the tumor, followed by five (5) days of SQP33 infusion starting 3 hours ± 30 min after the SQL70 biopolymer injection. If ≥ 4 patients have a response (CR or PR), then 13 additional patients will be enrolled. (See APPENDIX K – Schedule of Assessments – Expansion Group 3A: Head and Neck for details).

Sample Size

Phase 1: Dose Escalation: Sample size for the dose-escalation portion of the study is not predefined. Total enrollment will depend on the DLTs observed and number of escalation cohorts.

Phase 2a: Expansion Groups 1 and 3a will be utilizing a Simon 2-stage (optimal) design to determine sample size (see below) based on historical objective responses per indication. Expansion Group 2 will utilize the Continuous Reassessment Method (CRM) design.

Simon 2-Stage Optimal Design

- Expansion Group 1: Extremity STS- up to 15 locally advanced unresectable, or metastatic, intermediate, or high-grade soft-tissue sarcoma participants will be treated per study treatment in Stage 1
- Expansion Group 3a: Head & Neck- up to 13 R/M HNSCC participants will be treated per study treatment in Stage 1.

Simon 2-Stage Design Considerations

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

Continuous Reassessment Method

- Expansion Group 2: Unresectable STS locally advanced or metastatic
  - Sample sizes for Expansion Group 2 participants are guided by the Continuous Reassessment Method (CRM) design (Wheeler 2019). The indicated population for the Expansion 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 (see below). The participants will receive SQ3370 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.

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[3-5]	0.20
Minimum Efficacy proportion[3-5]	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.

Expansion Groups 1 and 3a will treat up to approximately 28 participants in Stage 1 and Expansion 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 cohort.

Safety/Tolerability

Electrocardiogram, vital signs, ECHO/MUGA and clinical laboratory data (observed and change from baseline) will be summarized by time point and treatment using descriptive statistics. The number and percentage of patients reporting any treatment-emergent AE will be summarized by system organ class and preferred term for each treatment (coded using Medical Dictionary for Regulatory Activities [MEDRA]). Treatment-emergent AEs will be further classified by severity and relationship to treatment.

Efficacy

Tumor dynamics will be summarized by dose, cycle, and overall follow-up. RECIST based tumor response such as ORR, DoR, PFS, DCR, BOR, Time to local-regional progression, and Local-regional control status will be summarized. Additionally, OS, TFST, TSST, histopathological response, disease-free survival, and surgical outcome will be summarized. Sub-set summaries will be performed on both injected and non-injected individual lesions.

Biomarkers

PK in tumor and plasma, markers of immune response in tumor and blood, and binary variable exploratory analyses will be described in the statistical analysis plan finalized before the database lock.

LIST OF ABBREVIATIONS

Abbreviation or Special Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
BOR	best objective response
BSA	body surface area
CHF	congestive heart failure
CNS	central nervous system
CI	confidence interval
CR	complete response
CRF	Case Report Form
CSF	colony-stimulating factor
CT	computed tomography
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DCR	disease control rate
DNA	deoxyribonucleic acid
DoR	duration of response
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
EC	endometrial cancer
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EU	European Union
FDA	Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HFS	Hand-foot syndrome
HIPAA	Health Insurance Portability and Accountability Act
HNSCC	Head and neck squamous cell carcinoma
HNSTD	highest non-severely toxic dose

Abbreviation or Special Term	Definition
HPV	Human papilloma virus
HR	Hazard ratio
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IS	Internal Standard
IV	intravenous(ly)
LFT	liver function test
LN	Lymph node
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MEDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NaHA	sodium hyaluronate
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect level
ORR	objective response rate
OS	overall survival
PR	partial response
PBMC	peripheral blood mononuclear cell
PD or DP	progressive disease or disease progression
PFS	progression-free survival
PLD	pegylated liposomal doxorubicin
PK or PK/PD	pharmacokinetic(s) or pharmacokinetic(s)/pharmacodynamics
RECIST	Response Evaluation Criteria in Solid Tumors
R/M	Relapsed or metastatic
RP2D	Recommended Phase 2 dose
SAE	serious adverse event
SC	subcutaneous
SCC	Squamous cell carcinoma
SD	stable disease
SQ3370	Shasqi's local drug activation technology combining SQP33 protodrug and SQL70 biopolymer
SQL70	tetrazine-modified sodium hyaluronate biopolymer that can activate SQP33 protodrug

Abbreviation or Special Term	Definition
SQP33	chemically modified protodrug of doxorubicin with attenuated activity
SRC	Safety Review Committee
STS	Soft Tissue Sarcoma
TCO	trans-cyclooctene
TFST	time from enrollment to first subsequent therapy
TNT	time to next treatment
TSST	time from enrollment to second subsequent therapy
ULN	upper limit of normal
US	United States

1. INTRODUCTION

1.1. DISEASE AND TREATMENT BACKGROUND

Cancer incidence and mortality are growing worldwide (Bray 2018). In 2018, the global incidence of new cancer diagnoses was estimated at over 18 million cases, and cancer-related deaths were estimated at over 9.6 million (Bray 2018). Of these cases, the vast majority were solid tumors (more than 16 million new cases and 8 million cancer deaths). For its part, soft tissue sarcoma (STS) is a heterogeneous group of aggressive malignant tumors. In the United States (US), it is estimated that over 12,000 people were diagnosed with STS in 2019, and that, of these diagnoses greater than 5,000 individuals will die from their cancer (Siegel 2019). In Australia, over 1500 new cases of STS were diagnosed in 2014 (Sarcoma Statistics 2019). Despite improvements in early detection and treatment protocols, most patients with solid malignancies die from metastatic burden (Chaffer & Weinberg 2011).

Anthracyclines are powerful, well-established anticancer agents and among the essential tools in the chemotherapy armamentarium of medical oncologists. Doxorubicin (Dox), a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius var. caesius*, has been used successfully to produce tumor regression in a variety of neoplastic conditions such as STS, acute lymphoblastic leukemia, acute myeloblastic leukemia, breast cancer, ovarian cancer, small cell lung cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, gastric cancer, transitional cell bladder cancer, neuroblastoma, Kaposi's sarcoma (Cooley 2007), thyroid cancer, Wilms' tumor, and bronchogenic carcinoma (in which the small cell histologic type is the most responsive compared with other cell types) (Arcamone 1969; McGowan 2017).

The antitumor activity of doxorubicin (Dox) is attributed to its interference of deoxyribonucleic acid (DNA) replication by inhibiting topoisomerase II enzyme. Despite its potent broad-spectrum antitumor activity, the extended use of conventional Dox in clinical practice is limited by life-threatening toxicities, with the most significant being largely irreversible and dose-dependent cardiotoxicity (Jain 2000). Cardiotoxicity includes short- and long-term toxic effects in the heart, ranging from alterations in myocardial structure and function, to severe cardiomyopathy and congestive heart failure (CHF). CHF was reported in > 4%, > 18%, or 36% of patients who had received cumulative conventional Dox doses of 500 to 550, 551 to 600, or > 601 mg/m^{2,} respectively (Lefrak 1973). Chronic cardiotoxicity occurred after prolonged administration of conventional Dox. Although the possibility of cardiotoxicity development is dose-dependent, it could occur even at lower doses due to individual patient variations (Lipshultz 1995). The exact causal mechanisms of Dox-induced cardiotoxicity remain elusive, making it difficult to predict or prevent its severe adverse events (AEs) in individual patients (Ghigo 2016; Whelan 2010; Chiong 2011). The most commonly used dose schedule of conventional Dox, as a single agent, is 60 to 75 mg/m^2 as a single intravenous (IV) injection every 3 weeks. The lower dosage is given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration (ADRIAMYCIN Australian Product Information; ADRIAMYCIN US Package Insert).

The cytotoxic activity of conventional Dox also affects normal cells with high turnover rates such as hematopoietic cells in the bone marrow, cells of the immune system and the gut, as well as skin and hair cells. This nonspecific cytotoxicity causes immune suppression (and associated

opportunistic infections), blood disorders, infertility, neuropathy, cognitive dysfunction, nausea, fatigue, pain, and hair loss (Liebner 2015). Bone marrow suppression is the most common acute dose-limiting toxicity (DLT) of conventional Dox; myelosuppression reaches its peak at 10 to 14 days after treatment with recovery usually occurring by the 21st day. Thrombocytopenia and anemia may also occur. Severe clinical consequences of myelosuppression include fever, infections, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death (ADRIAMYCIN Australian Product Information; ADRIAMYCIN US Package Insert). These cardiac and myelosuppressive toxicities limit the dose of conventional Dox and the combination of Dox with other antineoplastic agents.

The major side effects of conventional Dox are its narrow therapeutic window and limit the acute and lifetime doses in patients (Colombo 2015). Consequently, an unmet medical need exists for novel strategies to deliver chemotherapies such as Dox with improved safety, particularly with less cardiotoxicity and broader therapeutic windows (Frustaci 2001). Consequently, an unmet medical need exists for novel strategies to deliver chemotherapies such as Dox with improved safety, particularly with less cardiotoxicity and broader therapeutic windows (Frustaci 2001). SQ3370 has the potential to address this unmet medical need.

1.1.1. Soft-tissue Sarcoma

Soft tissue sarcomas are a rare group of heterogeneous malignancies with >50 histologic subtypes that have varying biological behavior and responsiveness to therapy. Surgery with radiotherapy is the most common treatment for localized disease when resection is possible, with associated 5-year overall survival of 55% (Seddon 2017). Survival outcomes for locally advanced or metastatic STS poor, with a median overall survival of 12.8-14.3 months after diagnosis (Verschoor 2020, Judson 2014).

With modern limb salvage techniques, amputation for extremity soft tissue sarcomas is now rare. A study that reviewed patients where amputation was used for local control compared to limb conservation showed the rates of systemic relapse and disease-specific survival were poorer in the amputation patients, with a 3 year overall survival of only 50.3% following curative amputation, while those patients undergoing limb salvage had a greater than 75% overall survival. Of the 59 patients with localized disease at the time of amputation, 29 developed metastatic disease (49.2%), with a median time to first metastasis of 10 months (Smith 2017). Amputation patients are a high risk group of soft tissue sarcoma patients where improved treatments are needed.

Doxorubicin has been the mainstay of first-line treatment for locally advanced, unresectable, or metastatic STS for decades, achieving objective response rates of 0–20% (Seddon 2017, Chawla 2015, Tap 2017), median progression-free survival (PFS) of 23.3 weeks (Seddon 2017), and a median OS of 12.8 months (Verschoor 2020). More recent trials report slightly better median OS for doxorubicin monotherapy with 16.9 months (Ryan 2016), 17.6 months (Seddon 2017), and 19.0 months (Tap 2017) respectively (Ryan 2016). A randomized controlled Phase 3 trial (Judson 2014) comparing combination Dox and ifosfamide versus Dox alone showed a significant increase in PFS in the combination treatment group, but with no increase in OS. Further, in a recent retrospective database analysis of 2045 patients from 12 EORTC sarcoma trials (inclusion period 1980–2012) after completing 6-cycles of first line Dox monotherapy or

Dox plus ifosfamide at varied doses for locally advanced, unresectable, or metastatic STS, demonstrated that there was a significantly worse PFS in participants receiving Dox monotherapy vs. Dox + high dose ifosfamide. No significant difference of histology on PFS, and no significant difference of treatment regimen or histology on OS was observed (Verschoor 2020). Although the addition of ifosfamide to Dox-based regimens for STS is standard and generally improves response rates and PFS, OS is not improved and the incidences of Grade ≥3 myelosuppression, febrile neutropenia, and deaths from adverse events are markedly increased (Judson 2014).

Subsequently, two first-line phase 3 trials (Ryan 2016, Tap 2017) have combined doxorubicin with novel agents (doxorubicin and palifosfamide compared with doxorubicin and placebo, and doxorubicin and evofosfamide compared with doxorubicin alone), and neither study was able to show improved PFS or OS for the combination treatments. Thus, no regimen has proved to be unequivocally superior in efficacy or toxicity to doxorubicin monotherapy as first-line treatment for locally advanced, unresectable, or metastatic soft-tissue sarcoma. Patients who are beyond the 1st relapse with STS, the benefit of treatment in the third-line was very limited for most histologies, with a median time to next treatment (TNT) and OS ranging between 2.3 and 3.7 months and 5.4 and 8.5 months, respectively (Savina 2017). Therefore, better treatment options are needed in earlier lines of treatment while the tumors remain sensitive to treatment.

1.1.2. Head and Neck Cancer

The prognosis of patients with recurrent or metastatic head and neck squamous cell cancer is generally poor. The median survival in most series is 6 to 15 months depending on patient and disease-related factors (Pfirschke 2020). The median overall survival for recurrent or metastatic head and neck cancer (R/M HNSCC) remains less than 1 year despite modern chemotherapy and targeted agents. Palliative chemotherapy and the epidermal growth factor receptor inhibitor, cetuximab, constitute the backbone of treatment for patients with R/M HNSCC (Price 2012).

From an initial trial of patients with R/M HNSCC, 36 were treated with doxorubicin and cisplatin, the overall response rate (complete + partial) was 30%, with a median duration of response of 4 months (Sandler 1984). A Phase 2 trial of 36 patients with unresectable, recurrent, or metastatic squamous cell carcinoma arising from the upper respiratory or alimentary passages of the head and neck were accrued between April 1993 and February 1996, and treated with the drug combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) (Okuno 2002). The ORR over the first 4 cycles of treatment was 46%. Two of the 18 patients who responded had a complete response. Among the 22 patients with unresected residual or recurrent disease, the median time to progression was 11 weeks, and 1-year PFS was 14%, and median OS was 24 weeks, and the 1-year OS was 36%. Among the 13 patients with metastatic disease, the median time to progression was 26 weeks, and the 1-year PFS was 23%, the median OS was 54 weeks, and the 1-year OS was 54%.

Caelyx, a liposomal anthracycline, was administrated as 1 hr infusion every 3 weeks at doses of 35 mg/m^2 (group A) and then subsequently given at 45 mg/m^2 (group B). 26 patients received a total of 87 cycles. The median number of cycles was 3 (range 1–7). Four out of 24 evaluable patients (17%, 95% confidence interval (CI) 0.5–32%) showed significant evidence of antitumor

activity, with tumor necrosis being observed in 2 patients. Grade 3–4 neutropenia was observed in only 2 patients. Myelosuppression, particularly severe leukopenia, and thrombocytopenia was observed in 81% and 7% of the patients during the entire course of their treatment. One patient developed sepsis and died after 3-cycles of therapy secondary to chemotherapy-induced neutropenia.

Liposomal doxorubicin was administered up to 45 mg/m^2 to 24 evaluable patients with locally recurrent and/or metastatic squamous cell carcinoma of the head and neck, and 4 patients (17%) showed significant evidence of antitumor activity. The median number of cycles was 3. Toxicities included 2 patients with Grade 3-4 non-febrile neutropenia, 2 patients with Grade 3 allergic reaction, 1 patient with Grade 3 diarrhea, Grade 3 necrosis in 2 patients, and moderate bleeding in 2 patients (Faivre 2004).

1.2. SQ3370 BACKGROUND

SQ3370 is a novel Investigational Product (IP) that enables local targeting and activation of a cytotoxic protodrug without the need for specific molecular biomarkers. The therapeutic goal of SQ3370 is to enhance the antitumor efficacy of Dox by increasing its concentration at a specific tumor site while minimizing its systemic toxicity.

The SQ3370 IP consists of 2 components:

- SQL70 biopolymer made of tetrazine-modified sodium hyaluronate (NaHA). This biopolymer does not contain a therapeutically active ingredient. It functions by activating the SQP33 protodrug inside the body upon chemical reaction in situ that releases the active drug, Dox. Hence, SQL70 is considered to be an ‘activating article’.
- SQP33 protodrug, a trans-cyclooctene (TCO)-modified protodrug of Dox with attenuated cytotoxic activity. SQP33 is the active component.

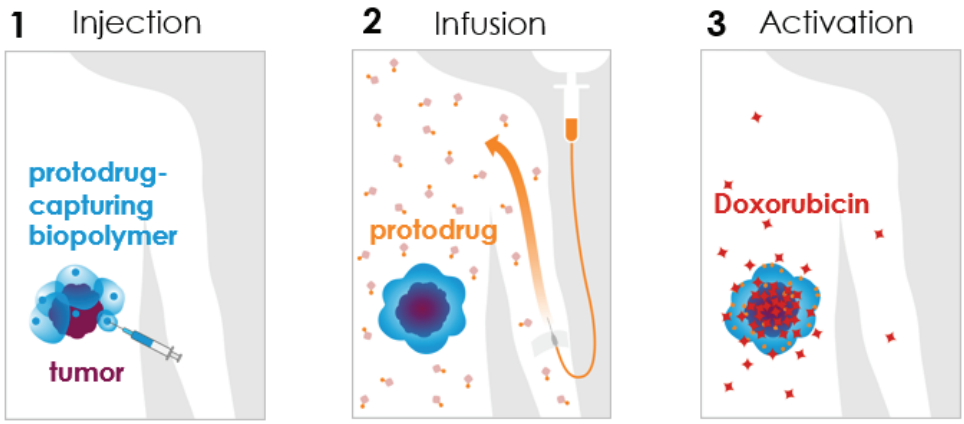


Figure 1: SQ3370 Local Drug Activation Approach

(1) SQL70 biopolymer is locally injected at the tumor site and (2) SQP33 protodrug is infused systemically. (3) SQP33 protodrug is captured by SQL70 biopolymer at the tumor site through a rapid covalent reaction between tetrazine and trans-cyclooctene moieties, followed by chemical rearrangement to release active dox.

SQL70 biopolymer is locally injected at the tumor site and followed by IV infusions of SQP33 protodrug. At the tumor site, SQL70 biopolymer selectively and rapidly captures SQP33 protodrug via an irreversible covalent reaction between tetrazine and TCO (bioorthogonal chemical groups), followed by the release of active Dox (Figure 1).

SQ3370 is being developed for the treatment of adult patients with solid tumors for which an anthracycline-containing regimen is appropriate and who have an injectable localized tumor or metastatic lesion.

Several key attributes make SQ3370 a suitable treatment for solid tumors: Favorable reaction kinetics ensure rapid capture of SQP33 protodrug by SQL70 biopolymer at the tumor site. SQP33 protodrug activation is dependent only on the chemical reaction with SQL70 biopolymer and is independent of native biological processes or biomarkers. A single injection of SQL70 biopolymer can capture multiple doses of SQP33 protodrug. SQP33 protodrug has attenuated activity compared with conventional Dox, minimizing off-target effects. As a result, it is hypothesized that the SQ3370 Investigational Product can result in higher local concentrations of active Dox at the tumor site.

1.2.1. Summary of Nonclinical Experience

In support of the first-in-human (FIH) trial, a series of nonclinical studies have been conducted with SQ3370 and different prototypes (made of the same type of materials as SQ3370 and with analogous local drug activation functions). The nonclinical safety of Dox hydrochloride (Dox HCl) and various formulations such as liposomal Dox (e.g., DOXIL, CAELYX) have been extensively studied. As the clinical development program proceeds, those studies will supplement the nonclinical studies conducted with SQ3370.

The types of DLTs observed with SQ3370 are consistent with those reported for conventional Dox; however, SQ3370 allows a significantly higher dose of cytotoxic therapy to be given safely.

Nonclinical Pharmacology

Published in vitro results show that a prototype of the SQP33 protodrug, without SQL70 biopolymer, is 57-fold less toxic than conventional Dox to human fibrosarcoma cells in culture (Mejia Oneto 2016). In a syngeneic mouse tumor model (MC38), SQ3370 enhanced overall survival and tumor growth inhibition of both injected and non-injected tumors compared with conventional Dox treatment. This technology also enabled a sustained antitumor response upon rechallenge with MC38 tumor cells, without additional treatments. At 2 weeks post SQ3370 treatment, there was an increase in total T-cell infiltration in both injected and non-injected tumors compared with saline treatment. Together, these effects indicate that the antitumor efficacy observed in non-injected and/or rechallenged tumors was likely due to immune activation by SQ3370.

Nonclinical Pharmacokinetics

Pharmacokinetic (PK) studies in mice, rats, and dogs confirm that SQL70 biopolymer captures SQP33 protodrug and removes it from circulation, followed by the release of active Dox. In mice, a fluorescently labeled version of SQL70 biopolymer remained detectable at the local injection site for approximately 2 months, with suggested clearance by lymphatic, hepatic, and renal routes. In a separate study in mice, 7 days after the last dose of SQP33 protodrug, active

Dox was detected at the local site. In rats, SQL70 biopolymer rapidly captured and rendered SQP33 protodrug undetectable in plasma samples within 30 minutes of administration, with measurable conversion to active Dox. SQP33 protodrug was stable in vivo, showing minimal nonspecific conversion to active Dox in the absence of SQL70 biopolymer, based on plasma exposure levels. Plasma exposure to active Dox was highest when SQP33 protodrug was given between 1 to 24 hours after SQL70 biopolymer injection. Liver exposure to active Dox peaked when SQP33 protodrug was given 24 hours after SQL70 biopolymer injection. Plasma and liver exposure to active Dox decreased drastically when SQP33 protodrug was given 96 hours (Day 5) after SQL70 biopolymer injection. Active Dox concentrations at the SQL70 biopolymer site suggest local conversion of systemic SQP33 protodrug to active Dox even 5 days after SQL70 biopolymer injection.

A Good Laboratory Practice (GLP)-compliant study in dogs showed that a single 10 mL local injection of SQL70 biopolymer could continue to capture 26.5% of the SQP33 protodrug given systemically on the fifth day of a 5-day regimen. In a separate GLP bridging study in dogs, plasma samples (collected up to 3 days after the animals received a single local SQL70 biopolymer injection) and liver samples (collected on Day 6) reacted with a TCO-containing internal standard (IS), suggesting the presence of SQL70 biopolymer in the plasma and the liver. Plasma samples collected on Day 4 and 5 did not react with the IS.

In summary, the studies suggest that a fraction of the locally injected SQL70 biopolymer circulates in the plasma from Day 1 to Day 3, leading to active Dox exposure that peaks in the plasma between Day 1 and 2, and peaks in the liver around Day 2. Active Dox exposure in the plasma and liver decrease markedly by Day 4 and 5. SQL70 biopolymer at the local site continues to transform systemic SQP33 protodrug into active Dox at least until Day 5 following local SQL70 biopolymer injection.

Toxicology

SQ3370 is less toxic than conventional Dox in rodent and dog models, enabling higher doses to be administered safely. In a GLP study (5 days of dosing and 23 days of recovery) in dogs administered with a single 10 mL SQL70 biopolymer volume and 5 daily SQP33 protodrug doses, the no-observed-adverse-effect level (NOAEL) was 0.72 mg/kg/day (3.6 mg/kg/cycle) Dox HCl equivalents (Dox Eq); the highest non-severely toxic dose (HNSTD) was 1.79 mg/kg/day (8.9 mg/kg/cycle) Dox Eq. The DLTs observed at the HNSTD level were consistent with those reported for conventional Dox and included bone marrow hypocellularity and decreased hematopoiesis. All side effects showed evidence of reversibility in the recovery phase. When SQP33 protodrug was administered at the HNSTD level without SQL70 biopolymer, no AEs were reported, highlighting the attenuated activity of the protodrug. Available safety findings do not support a vesicant effect for SQP33 when SQL70 is administered subcutaneous (SC). Other injection routes for SQL70 such as intramuscular (IM), do not indicate different safety profiles to date, with additional studies ongoing.

The tolerability of SQL70 biopolymer alone was also evaluated. In a GLP dog study, SQL70 biopolymer-related clinical pathology effects were reversible, and magnitudes of change were similar for the affected groups regardless of the dose administered. Injection site reactions were consistent with an inflammatory response to a foreign material and inconsistent with notable tissue irritation. An earlier study with a prototype of SQL70 biopolymer demonstrated that 41%

of the injected material remained at the injection site for ~2.5 months with no evidence of inflammatory changes on histopathology.

Overall, side effects of SQ3370 were consistent with the well-known side effect profile of conventional Dox and did not lead to any unique or new DLTs. In particular, no evidence of liver injury was noted in nonclinical studies. Further details are available in the Investigator's Brochure.

1.2.2. Summary of Clinical Experience

The current study, SQ3370-001, is the first-in-human clinical trial to evaluate SQ3370. Therefore, aside from this ongoing SQ3370-001 study, no previous clinical data are available.

1.3. STUDY RATIONALE

1.3.1. Experimental Doxorubicin-Based Therapeutics

Local drug activation approaches have been developed in which systemic Dox-based therapeutics are activated by inherent biological differences between cancerous and healthy tissue, such as pH (Mita 2015), oxygen level (Tap 2017), or protein expression (Schöffski 2017). Several of these Dox- based drugs have been developed by modifying the aminoglycoside portion of Dox with peptides, designed to be cleaved by proteases elevated in cancerous cells: 1) L-377202 (Merck; DeFeo-Jones 2002; DiPaola 2002), 2) DTS-201 (CPI-0004Na) (Diatos; Schöffski 2017), and 3) "Compound 5" (Bristol-Myers Squibb; Albright 2005). The main benefit of cancer-activated therapeutics is that they may eliminate cancerous cells while sparing healthy tissue from the cytotoxic effects. However, the extensive biological differences between cancerous and healthy tissue, as well as interpatient variabilities, are major limitations to these approaches.

SQ3370 is unique in that drug activation occurs through a bioorthogonal chemical reaction independent of differences in specific molecular markers between cancerous and healthy tissues. Activating agents in the locally injected SQL70 biopolymer enable the local activation of systemically administered SQP33 protodrug. SQ3370 is less susceptible to inherent differences in biomarker expression between healthy and tumor tissue and between different patients, which should lead to less off-target effects and less interpatient variability. A comparison of the tolerability of SQ3370 with several other Dox-based treatments is presented below. The MTD of SQ3370 in mice was 19.1-times higher than the MTD of conventional Dox therapy; no side effects were observed in mice receiving this dose of SQ3370. In dogs, SQ3370 treatment at a dose of 8.9-times higher than the veterinary clinical dose of conventional Dox was chosen as the highest non-severely toxic dose (SQ3370-TOX-108). To date, in human patients, SQ3370 has been dosed at 15 times the standard clinical dose of Dox (75 mg/m^2); although an MTD has not yet been reached, the MAD (maximum administered dose) is 15x in the Phase 1 clinical trial (Study SQ3370-001).

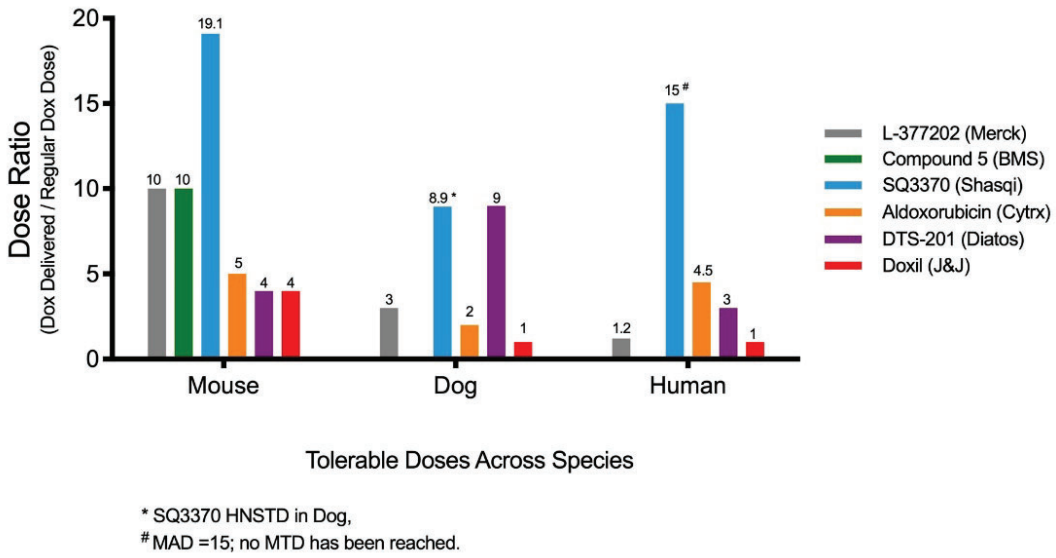


Figure 2: Tolerability of Various Dox Products in Mouse, Dog, and Human

The MTD of conventional Dox for mice is defined as 8.1 mg/kg (Bristol-Myers Squibb; Albright 2005). The standard clinical dose is defined as 1 mg/kg for dogs and as 75 mg/m^2 for humans (endpoint is dose-limiting toxicity). The MTD of SQ3370 in mice was 19.1 times the MTD of conventional Dox. In dogs, the HNSTD of SQ3370 treatment was established at 8.9-times higher than the veterinary clinical dose of conventional Dox (SQ3370-TOX-108). In human patients, SQ3370 has been dosed at 15-times the standard clinical dose of Dox (75 mg/m^2); the MAD is 15x and the study defined DLT was not established. Doxil (Johnson and Johnson; Working 1996) and aldoxorubicin (Kratz 2007; Unger 2007) are not referenced in text but are included in this figure for further illustration of the tolerable doses (safety) of SQ3370 (Figure 2).

1.3.2. Doxorubicin and the Immune System

Cytotoxic agents such as Dox are known to induce immunogenic cell death (Bezu 2015) and enhance tumor responsiveness to immune checkpoint blockade therapies (Pfirschke 2020; Zitvogel 2013). Addition of Dox-based therapies to anti-PD-1 and anti-CTLA-4 monoclonal antibodies in pre-clinical experiments resulted in significantly improved antitumor response compared to antibodies alone (Rios Doria 2015). Conventional Dox treatment improved tumor antigen–specific CD8 T-cell proliferation in tumor-draining lymph nodes and promoted tumor infiltration of interferon-γ–producing cytotoxic T lymphocytes in mice (Mattarollo 2011). Tumors such as STS that are accessible by injection can have microenvironments that are poorly immunogenic and are consequently poorly responsive to checkpoint inhibition therapies (Cancer Genome Atlas Research Network 2017). We hypothesize that SQ3370 can deliver higher concentrations of active Dox to the tumor, enhancing local immune response, while minimizing systemic immunosuppression associated with conventional Dox.

1.4. BENEFIT-RISK ASSESSMENT

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH), Good Clinical Practice (GCP), and applicable regulatory guidelines.

Because this is the first study to evaluate SQ3370 in humans, its clinical benefits and safety are not fully known; however, both the SQL70 biopolymer and SQP33 protodrug are based on approved products with well-established safety profiles, and conventional Dox has demonstrated anticancer activity across a range of tumor types. Thirty-nine patients were enrolled and treated in the Phase 1, and thirty-eight patients are evaluable for safety as one patient's treatment was halted day 2 due to COVID-19. Thirty-two of the thirty-nine patients are sarcomas. Thirty patients were treated on the dose expansion protocol with escalating doses of SQP33 from 0.38x to 15x Dox equivalent dose. Eight patients were treated in the 20 mL SQL70 biopolymer cohort, five at the 4x Dox equivalent and three patients at the 6x doxorubicin equivalent dose of SQP33. One patient was treated at the low dose/fragile cohort at 8x Dox equivalent dose of SQP33. Note that patients remain on study treatment at the time of this update. In the Phase 1 the MAD was 15x while the study defined DLT was not established. The sponsor in consultation with the investigators decided not to continue dose escalations. The treatment was well tolerated as published in the ESMO Congress 2022 Poster 1499P, with the most frequent treatment emergent adverse events (TEAEs) being nausea, fatigue, diarrhea or constipation, and decreased appetite. Hematologic toxicities were neutropenia, anemia, and thrombocytopenia. As of 9/27/2022, an analysis of Grade 3 or greater TEAEs was performed through Cohort 8 (12x Dox equivalent). In the 20 mL SQL70 biopolymer group, TEAEs >10% of the total and in >1 patient showed worsening anemia in 3 patients (37.5%) and neutropenia in 2 patients (25%). In the 10 mL SQL70 biopolymer dose expansion, grade 3 or greater TEAEs >10% of the total and in >1 patient showed **worsening anemia** in 4 patients (16.7%). The totality of available data supports the continuation of the study and opening of the Phase 2a. Nonetheless, SQ3370 is a new treatment and there may be both unexpected risks and benefits not previously associated with conventional Dox or NaHA treatments. See the Investigator's Brochure for additional details.

2. OBJECTIVES AND ENDPOINTS

In this study patients will be enrolled into a series of SQP33 protodrug dose escalation cohorts. Following completion of the dose escalation cohorts, the study will evaluate SQ3370 in three expansion groups. The study will also evaluate the administration of 10 mL and/or 20 mL of SQL70 biopolymer.

2.1. PHASE 1 DOSE ESCALATION

2.1.1. Objectives

2.1.1.1. Primary Objective

- Assess the safety and tolerability of SQ3370, including determination of the MTD and/or RP2D of SQP33 protodrug administered with 10 mL and/or 20 mL of SQL70 biopolymer.

2.1.1.2. Secondary Objectives

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

2.1.1.3. 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.

2.1.2. Endpoints

2.1.2.1. Primary Endpoint

- Frequency of AEs, SAEs and DLTs, as well as changes from baseline in vital signs, clinical laboratory parameters, physical examination findings, ECHO/MUGA, and ECG results.
- Establish RP2D (see section 3.2.5 Recommended Phase 2 Dose for details)

2.1.2.2. Secondary Endpoints

- Plasma concentration and PK parameters for SQP33 protodrug and active Dox following SQ3370 treatment.
- ORR per RECIST v1.1.

2.1.2.3. 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.

2.2. PHASE 2A EXPANSION GROUPS

2.2.1. Objectives

2.2.1.1. 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 3:
    - 3a) Patients with relapsed or metastatic squamous-cell head and neck cancer

2.2.1.2. Secondary Objective

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

2.2.1.3. 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.

2.2.2. Endpoints

2.2.2.1. Primary Endpoints

- Frequency of AEs and SAEs, as well as changes from baseline in vital signs, clinical laboratory parameters, physical examination findings, ECHO/MUGA, and ECG results across all treatment cycles and groups.

2.2.2.2. Secondary Endpoint

- ORR per RECIST v1.1.
- 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/m^2 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

2.2.2.3. 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.

3. STUDY DESIGN

3.1. OVERVIEW

This multicenter, Phase 1/2a, first-in-human, single-arm, open-label, dose-escalation study will evaluate the safety and tolerability, PK, and preliminary efficacy of SQ3370 in patients with locally advanced or metastatic solid tumors. The Screening, Treatment, Safety Follow Up and Long Term Follow Up schedules for both the escalation and Phase 2a groups in the study can be found in the Schedules of Assessments.

3.1.1. Phase 1 Dose Escalation

Patients will receive specific dose levels of SQP33 protodrug, assigned according to the dose escalation design described in section 3.2 Phase 1 Dose Escalation.

20 mL SQL70 Biopolymer (post-Cycle 1) Cohort:
Patients *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, thereby receiving a total of 20 mL of SQL70 biopolymer (see section 3.1.4.4 Phase 1: 20 mL SQL70 Biopolymer (post-Cycle 1) Cohort).

20 mL SQL70 Biopolymer (from Cycle 1) Cohort:
To evaluate the administration of 20 mL of SQL70 biopolymer in one or two lesions starting at Cycle 1, patients will be enrolled in a separate cohort at a dose level of SQP33 protodrug that is lower than the current dose level being evaluated.

Also see the Schedule of Assessments Appendix G.

3.1.2. Phase 2a Expansion Groups

Patients will be enrolled in expansion groups to further study the preliminary activity and safety of SQ3370, dosing schedules, as well as PK and immune changes in blood and tumor tissue (see section 3.3 Phase 2A Expansion).

3.1.3. Screening

Screening is up to 28 days prior to starting treatment (Day -28 to Day -1). Procedures performed per standard of care during the screening period, but prior to informed consent may be used rather than repeating procedures (see section 6.2 Screening and Re-Screening).

3.1.4. Treatment

3.1.4.1. Treatment Cycles

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.

Phase 2a Groups Specific Treatment Cycles

All patients treated at the RP2D in all groups within the Phase 2a will not be treated beyond 12 cycles or approximately 8 months.

The table below provides an overview of the SQL70 volume administered per lesion, number of potential lesions to inject, number of SQP33 timepoints per cycle and the dose to be administered each day.

Table 1: Expansion Group SQ3370 Administration Overview

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

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

Patients will enroll at the RP2D of SQP33 given over 5 days 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 (PD) 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, have achieved a clinical benefit may defer surgery at this point, and the study will allow up to 4 additional pre-op cycles, at which point patients should undergo exploratory surgery and or tumor resection. It is recommended that the surgical team place markers at the tumor margins to direct SQL70 dosing post resection. Post operatively subject with good responses may receive up to 4 additional cycles but not to exceed 12 cycles within the study. Surgical markers will be used to indicate the tumor bed for injection with SQL70.

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 for patients with PD pre-operatively on study at this point. It is encouraged to keep subjects on study and to evaluate surgical specimens as per planned biomarker and pathological assessments. See Schedules of Assessments Appendix H.

Group 2: Unresectable Soft Tissue Sarcoma with a Comparison of the RP2D of SQP33 administered over 3 vs 5 days

Patients will enroll at the RP2D of SQP33 given over 3 or 5 days and will receive a fixed dose of SQL70 (10 mL) on Day 1 of each cycle.

To compare safety and tolerability of the RP2D in two infusion schedules of SQP33 (3-day vs 5-day) in locally advanced, unresectable, each treatment group will maintain the total dose of SQP33 per cycle and compare two different infusion schedules while receiving the same dose and timing of SQL70. All subjects will commence treatment with SQP33 within 3 hours ± 30 minutes.

Table 2: Group 2 SQP33 Protodrug RP2D (% Administered) Per Day

	Day 1	Day 2	Day 3	Day 4	Day 5
5-Day Administration	20%	20%	20%	20%	20%
3-Day Administration	20%	40%	40%	**NO Treatment**	**NO Treatment**

See Pharmacy Manual for additional details.

Any patient at any point who has been determined to have progressive disease has reached the end of treatment, any subject completing 12 cycles of treatment will also have been deemed to have reached the end of treatment. See Schedules of Assessments Appendix I and Appendix J.

Group 3a: Head and Neck

Patients will enroll at the RP2D of SQP33 given over 5 days and will receive a fixed dose of SQL70 (10 mL) on Day 1 of each cycle, except for patients with a secondary lymph node lesion. These patients may receive an additional 10 mL in that lesion for a total of 20 mL of SQL70 injection. All subjects will commence treatment with SQP33 within 3 hours ± 30 minutes.

Any patient at any point who has been determined to have progressive disease has reached the End of Treatment, any subject completing 12 cycles of treatment will have been deemed to have reached the end of treatment. See Schedule of Assessments Appendix K.

Note: All patients in Phase 2a expansion groups who are no longer on treatment should begin Long Term Follow Up per the Schedule of Assessments.

3.1.4.2. Treatment Delays

Cycles of treatment should be administered consecutively. Consult with the Medical Monitor regarding any unexpected delays in a patient starting their next cycle. Ideally, delays between cycles should not be more than 3 weeks, i.e., at most, the patient's next cycle should start on the 4th week following the end of the previous cycle. Please consult the medical monitor to discuss patients that need to delay their next cycle for more than 3 weeks.

3.1.4.3. Treatment Duration

Patients may continue to receive treatment for up to 12 cycles (approximately 8 months). Treatment for more than 12 cycles requires approval by the Medical Monitor.

Lesions should continue to be injected until they have progressed per RECIST v1.1.

- In rare instances where the treating physician believes the patient is clearly benefiting from SQ3370 therapy despite modest radiographic progression of less than 20% that would not meet PD definition per RECIST v1.1, and following a discussion between the Medical Monitor and the treating physician, documentation in the medical record of continuation of therapy duration and criteria for continuation
- or other treatment discontinuation criteria are met (see section 3.1.5 End of Treatment)

In the Phase 2a study all patients may receive up to 12 cycles.

3.1.4.4. Phase 1: 20 mL SQL70 Biopolymer (post-Cycle 1) Cohort

For patients who have received treatment cycles with 10 mL of SQL70 biopolymer in Phase 1 Dose Escalation:

If the injected lesion is considered no longer injectable by the Investigator (see section 3.1.4.3 Treatment Duration) then the area of the tumor bed, if possible, should be treated for two additional cycles. Additional lesion(s) may be treated with a further 10 mL of SQL70 biopolymer (for a total of 20 mL SQL70 biopolymer maximum administered per cycle) as considered appropriate by the investigator.

The administration of the additional 10 mL SQL70 biopolymer for patients already on study as described above is a separate group of patients from the cohort that will receive 20 mL SQL70 biopolymer beginning at Cycle 1 (see section 3.2.3 Phase 1: 20 mL SQL70 Biopolymer (from Cycle 1) Cohort).

3.1.5. End of Treatment

The patient, Investigators, and/or the Sponsor may decide to end a patient's treatment at any time. The Safety Follow-Up Visit should be performed approximately 30 days after the last dose of study drug (see section 3.1.6 Safety Follow-Up Visit).

Reasons that the patient, Investigators, and/or the Sponsor may decide to end (discontinue) a patient's treatment include:

- Radiographic progression of disease per RECIST v1.1
- Unacceptable AE(s)
- Initiation of radiotherapy or non-protocol tumor directed treatment
- Any medical condition or treatment that the Investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Patient noncompliance with study procedures
- Patient inability to attend visits (e.g., patient moves, change in caregiver)

- Patient withdrawal of consent to treatment
- Patient withdrawal of consent to treatment and follow-up
- Investigator decision
- Sponsor decision
- Lost to follow-up
- Death

3.1.6. Safety Follow-Up Visit

The Safety Follow-Up visit is either:

- within 28 to 34 days after the patient's last dose of SQL70 biopolymer or SQP33 protodrug, whichever was last administered
- or prior to the start of a new anticancer treatment

3.1.7. Long Term Follow-Up

Long Term Follow-Up visits commence after the patient's last cycle of treatment, every 12 weeks (±7 days) for up to two years. See Schedule of Assessments for the list of procedures performed at the visits.

All patients that discontinue treatment will be followed for information on progression, if treatment discontinuation was not RECIST 1.1 progression, and overall survival. Additional information will be obtained for next line of treatment and survival status.

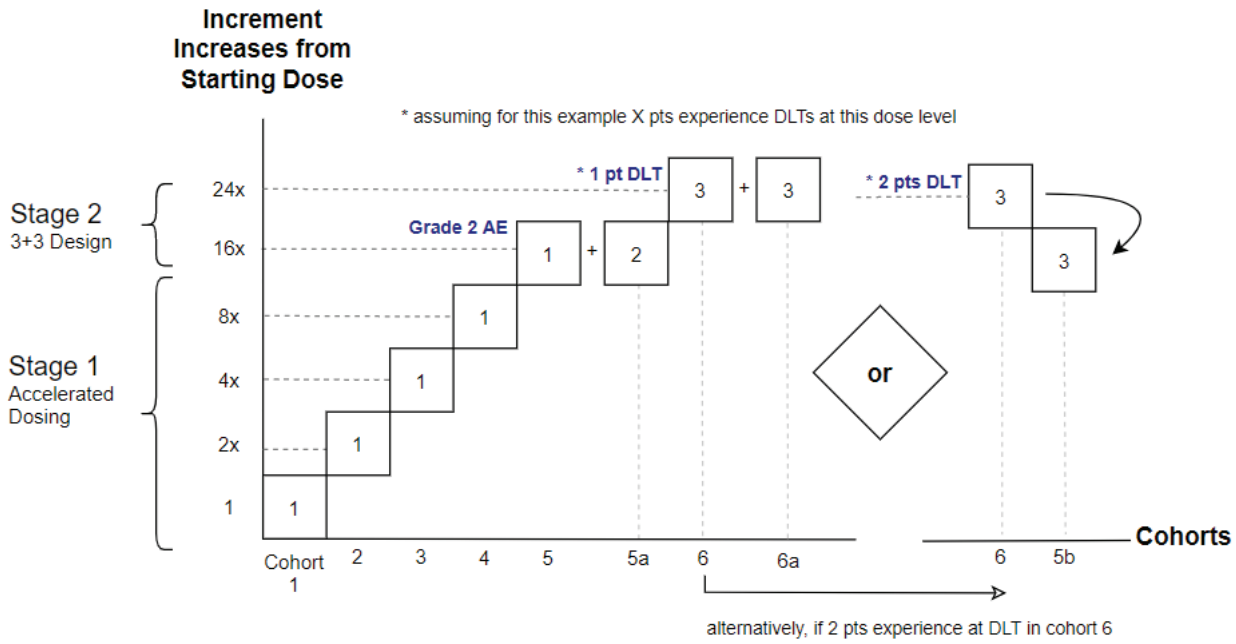
This long term follow-up information will be gathered during routine clinic visits, other study site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices.

If the study is closed, Long Term Follow-Up visits will stop.

3.2. PHASE 1 DOSE ESCALATION

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) as illustrated in Figure 3 below. This design is appropriate for cytotoxic therapies to minimize patient 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).

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



The SRC (see section 3.2.7 Safety Review Committee) 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 patients 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.

3.2.1. Accelerated Titration (Stage 1)

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 patient 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 (see section 3.2.6 Dose-Limiting Toxicity), or
- any Grade ≥2 AE considered to be at least possibly related to study drug

3.2.2. 3+3 (Rolling 6) Design (Stage 2)

The 3+3 (Rolling 6) design stage includes 3-6 patients enrolled per cohort and utilizes a modified Fibonacci scale to determine the dose level increase and minimum number of patients enrolled per dose level (Table 3). In the Rolling 6 design, a minimum of three, and up to six patients 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 patients enrolled in the Stage 2 dose escalation portion will be at the same dose level as the highest evaluated Stage 1 dose level; an example of this is shown in Figure 3. This will ensure that any dose level resulting in a DLT is tested in additional patients prior to continued dose escalation. If 2 patients experience 1 or more DLTs in any cohort, no additional patients will be enrolled at that dose level and further patients 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.

Table 3: 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

DLT = dose-limiting toxicity; MAD = maximum administered dose.

3.2.3. Phase 1: 20 mL SQL70 Biopolymer (from Cycle 1) Cohort

During the Phase 1 portion of the study, to evaluate the administration of 20 mL of SQL70 biopolymer in one or two lesions starting at Cycle 1, patients will be enrolled in a separate cohort at an initial dose level of SQP33 protodrug that is lower than the dose level being evaluated in the standard dose escalation 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 and DLT rules with 3-6 patients enrolled in the cohort. A per cohort SRC meeting will convene following the same guidelines as utilized for the SQP33 protodrug escalation. The SRC will decide if another cohort of patients should be enrolled at a higher SQP33 protodrug dose with the same 20 mL SQL70 biopolymer volume.

See section 4.1 General Inclusion/Exclusion Criteria for further details on the eligibility criteria for this cohort.

The 20 mL SQL70 biopolymer cohort described above is a unique and separate set of patients (see section 3.1.4.4 Phase 1: 20 mL SQL70 Biopolymer (post-Cycle 1) Cohort).

3.2.4. Maximum Tolerated Dose

The MTD is defined as the dose level of SQP33 protodrug in which a total of 6 patients are treated at that dose level with ≥ 2 patients experiencing a DLT during Cycle 1 of treatment across all 6 patients. An SQP33 protodrug MTD may be determined for both groups the 10 mL and 20 mL doses of SQL70 biopolymer.

3.2.5. Recommended Phase 2 Dose

A determination of the 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 will be defined by an SQP33 protodrug dose and a SQL70 biopolymer volume.

3.2.6. Dose-Limiting Toxicity

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 patient'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 patient experiences a DLT, **both SQP33 protodrug and SQL70 biopolymer should be temporarily interrupted** (see section 7.6.3 SQ3370 Treatment Interruptions). See section 3.1.5 End of Treatment if discontinuation of Investigational Product is permanent.

3.2.7. Safety Review Committee (Dose Escalation and Phase 2a)

The SRC will 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 patients 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

Phase 2a Responsibility

In Phase 2a, 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.

Table 4: Phase 2a Safety Evaluation Timing

Group	Run-in Evaluation N= (timing)	Simon 2 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

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 (see Table 4).

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.

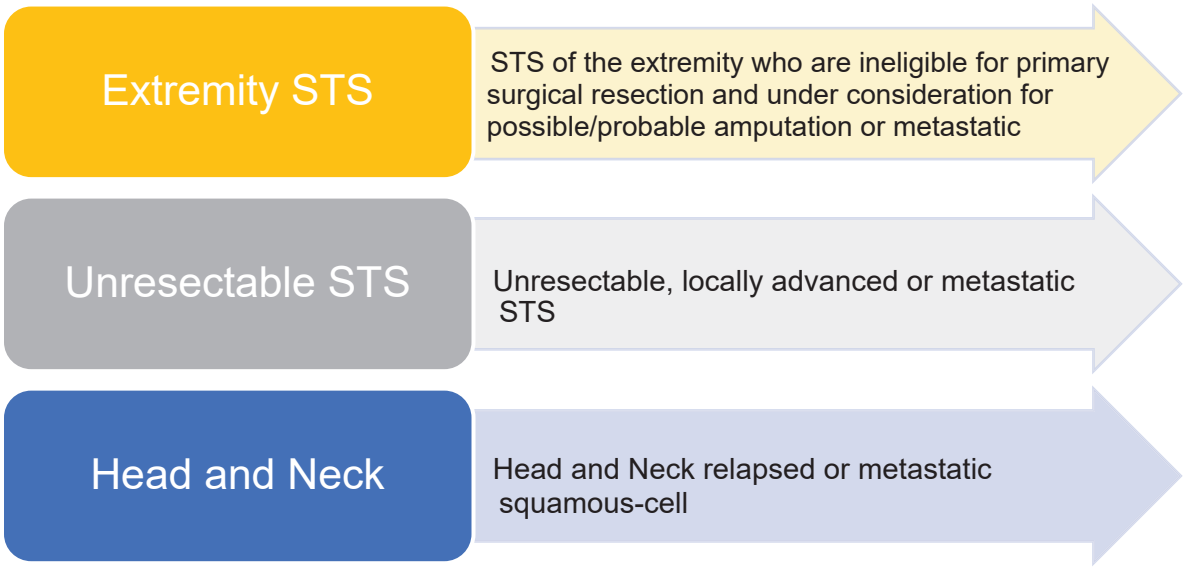
3.3. PHASE 2A EXPANSION GROUPS

The Phase 2a Dose Expansion groups include approximately 94 patients:

Phase 2: Expansion Groups

- Group 1: Extremity STS
  - Anthracycline naïve patients with soft tissue sarcomas of the extremity AJCC Stage III OR select IV (>5 cm injectable tumors) locally advanced and or metastatic disease not amendable to definitive surgical intervention at presentation, according to a multidisciplinary treatment team determined prior to screening. The following anthracycline sensitive histologies are allowed: angiosarcomas, leiomyosarcoma, liposarcoma, synovial sarcoma, adult fibrosarcoma, and undifferentiated pleomorphic sarcoma.
- Group 2: Unresectable STS
  - Anthracycline naïve patients with locally advanced or metastatic, unresectable, STS with defined anthracycline sensitive (expected historical ORR ~20%) histologies angiosarcomas, leiomyosarcoma, liposarcoma, synovial sarcoma, adult fibrosarcoma, and undifferentiated pleomorphic sarcoma.
- Group 3a: Head and Neck
  - Anthracycline naïve patients with histologically or cytologically confirmed relapsed or metastatic squamous-cell carcinoma of the head and neck, not suitable for further radical local treatment or patients with distant metastases who are treatment naïve or may have received two or less systemic therapies (chemotherapy and/or immunotherapy).

Figure 4: Phase 2a Dose Expansion Groups



3.4. STUDY-WIDE TREATMENT INTERRUPTION RULES

The study may be interrupted or stopped at any time based upon the Sponsor's and/or the SRC's review of the safety data. The study may resume once assessment by the SRC is complete, and an acceptable corrective action plan is implemented by the sponsor.

If the study is temporarily interrupted or permanently terminated, the Sponsor will inform study sites, the Institutional Review Board (IRB) / Independent Ethics Committee (IEC), and the appropriate regulatory bodies.

3.5. RATIONALE FOR STUDY DESIGN AND DOSE

3.5.1. Rationale for Study Design and Objectives

This is a first-in-human, Phase 1/2a study in patients with advanced solid tumors. Phase 1 will explore escalating doses of SQP33 protodrug and SQL70 biopolymer (see section 3.1 Overview) to identify the MTD and/or RP2D of SQP33 protodrug with 10 mL and/or 20 mL of SQL70 biopolymer. The accelerated titration and 3+3 (Rolling 6) design are being used to evaluate safety and tolerability of SQ3370. During the study, PK will be evaluated to determine the amount of systemic and localized active Dox following SQ3370 treatment.

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.

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 subjects enrolled in the lead-in will contribute to this phase of the study.

Patients will enroll at the RP2D of SQ3370 as anticipated that the size of tumors given the stage (≥ 2) will receive a fixed dose of SQL70 (20 mL). 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) of the extremity tumor.

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 subjects 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 subjects 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 subjects 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 subjects 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 the cohort, 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.

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 subject has PD, withdraws consent, Investigator decision, or death. 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. Sample sizes be guided by a Simon 2-stage (optimal) designs 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 subjects 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.

3.5.2. Rationale for Dose and Dosing Interval

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 in Phase 1 was explored for concurrent treatment of 2 lesions, or for a single larger lesion (see sections 3.1.4.4 Phase 1: 20 mL SQL70 Biopolymer (post-Cycle 1) Cohort and 3.2.3 Phase 1: 20 mL SQL70 Biopolymer (from Cycle 1) Cohort).

The dose volume of SQL70 biopolymer is expected to provide sufficient coverage for tumors of varying sizes and enable the local release of active Dox from escalating doses of SQP33 protodrug infusions, while taking into consideration practical limitations and historical precedent for local tumor injections.

High injection volumes of SQL70 biopolymer were performed in absolute terms (15 mL) in the GLP study SQ3370-TOX-108 in dogs and were well tolerated. The use of a single dose (10 mL) of SQL70 biopolymer was explored with escalating doses of SQP33 protodrug in SQ3370-TOX-108 and SQ3370-TOX-109. Based on allometric scaling by body surface area (BSA), this design introduces an extra margin of safety for human patients who have approximately 3.24-times the BSA of dogs but will still be injected locally with only 10 mL or 20 mL of SQL70 biopolymer.

The starting daily dose of SQP33 protodrug for this clinical study is 8 mg/m^2/day (5.72 mg/m^2/day Dox Eq).

The starting human dose of SQP33 protodrug with a fixed amount of SQL70 biopolymer was determined in accordance with ICH S9 guidelines, which propose using 1/6th of the human equivalent dose HNSTD taken from a GLP toxicology study in the relevant species.

The dose of SQP33 protodrug is rounded down from the suggested starting dose from the GLP toxicology study SQ3370-TOX-108 in dogs. SQP33 protodrug infusions are given daily on Day 1 through Day 5. The starting total dose per cycle of SQP33 protodrug will be 40 mg/m^2/cycle (28.6 mg/m^2/cycle Dox Eq).

This starting dose is anticipated to be well-tolerated, as the total dose per cycle is less than half of the 75 mg/m^2 recommended systemic clinical dose per cycle of Dox HCl. Additionally, the starting dose is less than half of the no-observed-adverse-effect level (NOAEL) found in the GLP toxicology study SQ3370-TOX-108.

No additional safety margins were included as conventional Dox and Dox-containing products are well-characterized agents with known risks. The nonclinical studies suggest that the clinical side effect profile of SQ3370 would be similar to that of conventional Dox, with myelosuppression as the expected major toxicity.

4. PATIENT POPULATION

All patients in all Phase 1 cohorts and Phase 2a expansion groups must meet the inclusion and exclusion criteria below.

4.1. GENERAL INCLUSION/EXCLUSION CRITERIA FOR PHASE 1 COHORTS AND PHASE 2A EXPANSION GROUPS

4.1.1. Inclusion Criteria

Patients are eligible to be included in the study only if all the criteria below apply.

1. Able to provide written informed consent and understand and comply with the requirements of the study.
2. Patients ≥ 18 years of age on the day of signing the Informed Consent Form (ICF).
3. Histologically or cytologically confirmed cancer or desmoid tumor. Confirmation is not required for each individual lesion, and it is not required for the tumor selected for injection.
   - *Additional Criteria for Phase 1 Dose Escalation Cohorts:* tumor is either refractory to or relapsed following standard of care or ineligible for standard of care therapy
4. There must be an injectable tumor defined as all the following:
   a. measurable per RECIST v1.1 at baseline
   b. palpable or able to be injected percutaneously
   c. not involving the following organs/structures: pancreas and extrahepatic biliary tract, central nervous system, or heart and great vessels
   d. accessible by repeated intratumoral or peritumoral injection with an 18- to 22-gauge needle
   - *Additional criteria the 20 mL SQL70 biopolymer cohorts in Phase 1 Cohort:*
     - Have at least two injectable lesions or, based on investigator discretion and Medical Monitor approval, a large single lesion (approximately 5 cm or larger).
5. Eastern Cooperative Oncology Group (ECOG) performance status score 0-1 (except for Group 3a, Head & Neck, where 0-2 is acceptable).
6. Adequate hematologic function[1] as defined by:
   a. absolute neutrophil count ≥ 1500 mL
   b. hemoglobin ≥ 9.0 g/dL
   c. platelet count ≥ 100,000/mL
7. Adequate hepatic function as defined by:
   a. total bilirubin ≤ 1.2 mg/dL (unless the elevation is due to Gilbert's Syndrome)

[1] This should reflect baseline hematological function and cannot be on growth factor supported agents, e.g. G-CSF, GM-CSF or erythropoietin stimulating.

b. aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x the upper limit of normal (ULN)

8. Adequate renal function as defined by creatinine clearance ≥ 45 mL/min according to the Cockcroft-Gault equation or a 24-hour urinary creatinine test.
9. Adequate coagulation function as defined by international normalized ratio ≤ 1.5 and a partial thromboplastin time ≤ 5 seconds above the ULN.
10. Resolution to Grade ≤ 1 AEs by the NCI-CTCAE v5.0 of all clinically significant toxic effects of prior locoregional treatment, surgery, chemoembolization, or other anticancer treatment. Exceptions to this are Grade ≥ 1 toxicities, which, in the opinion of the Investigator and the Sponsor, are stable, and should not exclude the patient (i.e., alopecia, neuropathy, and autoimmune complications of immunotherapy, such as well managed diabetes, hypothyroidism, or hyperthyroidism controlled on hormone replacement therapy).
11. Women of childbearing potential and sexually active males agree to use highly effective contraception for the duration of study participation and for 90 days after the last dose of study treatment

4.1.2. Exclusion Criteria

Patients are excluded from the study if any of the criteria below apply.

1. Prior lifetime exposure to >300 mg/m^2 of Dox HCl or DOXIL / CAELYX® or 600 mg/m^2 of epirubicin HCl or 600 mg/m² daunorubicin prior to study dosing.
2. CHF, severe myocardial insufficiency, or cardiac arrhythmia, including any one of the following:
    a. Echocardiogram (ECHO) or multigated acquisition (MUGA) scan with an actual left ventricular ejection fraction (LVEF) ≤ 45%, within 28 days prior to Cycle 1 Day 1.
    b. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II, and third-degree AV block).
    c. Conduction abnormalities that would prevent accurate diagnostic assessment of ventricular function, such as atrial fibrillation with rapid ventricular response.
    d. Symptomatic CHF.
    e. Screening QTc >470 msec and/or previous history of QT prolongation while taking other medications.
    f. History or signs of active coronary artery disease with or without angina pectoris within the last 6 months.
3. Any of the following within 28 days* prior to Cycle 1 Day 1 (i.e., Day -28 is the day after the last dose / procedure):
    a. Major surgery, as defined by the Investigator.
    b. Radiotherapy.

c. Chemotherapy, immunotherapy, and/or anticancer therapy. If the agent is a small molecule therapeutics, only 6 elimination half-lives are required before the patient is eligible.

d. An investigational product. If the agent is a small molecule investigational product, only 6 elimination half-lives are required before the patient is eligible.

e. Currently enrolled in a clinical study involving an investigational product, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

*1-2 days less may be allowed with Medical Monitor approval so as not to delay the start of SQ3370 treatment which, due to the 5 days of dosing, typically needs to begin on a Monday

4. Trastuzumab or trastuzumab emtansine dosed within 7 months prior to Cycle 1 Day 1.
5. Any transfusion within 14 days prior to Cycle 1 Day 1.
6. Pregnant or breast-feeding women.
7. Patients that are either positive for hepatitis B surface antigen (HBsAg) and/or detectable hepatitis B virus (HBV) DNA. HBcAb positivity will be allowed if one or both of the following is true: a) hepatitis B surface antibody is present or b) hepatitis B DNA testing is negative and the patient is receiving hepatitis B reactivation prophylaxis with entecavir, tenofovir, telbivudine or lamivudine.
8. Patients with hepatitis C; unless they have completed a course of antiviral therapy and have undetectable levels of HCV ribonucleic acid.
9. Has a known diagnosis of immunodeficiency or is receiving either chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to Day 1 Cycle 1, except in the case of central nervous system (CNS) metastases. The use of physiologic doses of prednisone 10 mg/day or its equivalent is permitted.
10. Patients with symptomatic concurrent conditions such as pleural effusion, ascites, or pericardial fluid requiring drainage.
11. Evidence of any active, uncontrolled bacterial, viral, parasitic, or systemic fungal infections within 1 week of the first dose of study drug.
12. Known active CNS metastases and/or carcinomatous meningitis or symptomatic brain metastasis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without any of the following:

    a. Evidence of progression for at least 4 weeks by repeat imaging,

    b. Steroid treatment or stereotactic radiosurgery for at least 14 days prior to Cycle 1 Day 1,

    c. Whole brain radiation therapy for at least 28 days prior to Cycle 1 Day 1.

13. Known or active other malignancies that have needed treatment (excluding palliative radiation) within 2 years prior to Cycle 1 Day 1 are excluded except for the following:

    a. Curatively resected non-melanomatous skin cancer

    b. Curatively treated cervical carcinoma in situ

c. Non-metastatic breast and prostate cancer patients with stable disease > 12 months

d. Other stable malignancies may be permitted based on Medical Monitor approval

14. Elective or a planned major surgery to be performed during the study.
15. History of allergic reactions attributed to Dox or other anthracyclines.
16. History of allergic reactions attributed to NaHA, hyaluronic acid, or gram-positive bacterial proteins.
17. Patients who have received a live vaccine within 28 days of Cycle 1 Day 1. See section 5.9.2 Prohibited Concomitant Treatment for examples. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.
18. History or evidence of a clinically unstable/uncontrolled disorder, condition, or disease (including but not limited to cardiopulmonary, renal, metabolic, hematologic, or neurologic) other than their primary malignancy, that in the opinion of the Investigator would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion.

4.2. SPECIFIC INCLUSION/EXCLUSION CRITERIA FOR PHASE 2A EXPANSION GROUPS

4.2.1. Expansion Group 1: Extremity STS

4.2.1.1. Inclusion Criteria

1. Patients with unresectable soft tissue sarcomas of the extremity AJCC III OR select IV (>5 cm injectable tumors) locally advanced and or metastatic, not amendable to primary surgical intervention according to the consensus of a multidisciplinary treatment team, determined prior to screening.
    - 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 assessment of resectability will be conducted by the multidisciplinary treatment team and study investigator and is typically defined by staging exams (CT scan of the chest, CT or MRI of the abdomen, MRI of the limb for extremity STS) and consultations with surgical oncology, radiology, and additional medical and surgical specialties as need.
2. High grade STS, Grade 2/3, with an assessable/injectable lesion of at least diameter >5 cm by RECIST 1.1 criteria
3. No prior chemotherapy for STS, or radiation to affected limb
4. Local disease candidates must meet one of the following criteria:
    a. Candidates for radical excision or removal of anatomic compartment
    b. Candidate for amputation where the gross total resection is considered to result in a non-functional limb

   c. Patients who refuse initial radical excision or amputation and who would prefer a neoadjuvant treatment approach
   d. Patients who are candidates for limb salvage radiation but decline radiation therapy
5. Patients who are candidates for neoadjuvant chemotherapy based on the location of the tumor and have clinical contraindications to standard of care or refuse neoadjuvant chemotherapy
6. Patients who have a recommendation from the multidisciplinary tumor board for single agent anthracycline
7. Only soft-tissue sarcomas of the following histologies are to be enrolled: leiomyosarcoma, liposarcoma, synovial sarcoma, adult fibrosarcoma, and undifferentiated pleomorphic sarcoma, angiosarcoma
8. Surgery can be deferred up to 12 weeks, in a clinically monitored patient on study

4.2.1.2. Exclusion Criteria

1. Uncontrolled pain related to tumor
2. Open wounds or tissue necrosis related to tumor mass
3. Compartment syndrome or impending compartment syndrome

4.2.2. Expansion Group 2: Unresectable STS

4.2.2.1. Inclusion Criteria

1. Locally advanced or metastatic, unresectable, soft-tissue sarcoma of intermediate or high grade with measurable disease.
2. Only soft-tissue sarcomas of the following histologies are to be enrolled: leiomyosarcoma, liposarcoma, synovial sarcoma, adult fibrosarcoma, angiosarcoma, and undifferentiated pleomorphic sarcoma.
3. Life expectancy >12 weeks (about 3 month)

4.2.2.2. Exclusion Criteria

1. Prior exposure to anthracyclines
2. Treatment naïve extremity tumors (as they would enroll in Group 1)

4.2.3. Expansion Group 3a: Head and Neck

4.2.3.1. Inclusion Criteria

1. Patients with histologically or cytologically confirmed squamous-cell carcinoma of the head and neck (HNSCC) who meet any of the following
   a. confirmed relapsed HNSCC

b. metastatic at initial presentation HNSCC

2. Patients who may have received two or less systemic regimens (therapies include chemotherapy and/or immunotherapy)
3. Biopsy-confirmed squamous-cell carcinoma (SCC) of the oral cavity, oropharynx, supraglottic larynx, or hypopharynx (archived biopsies are allowed)
4. For participants with oropharyngeal cancer, human papilloma virus (HPV) p16 status must be documented at screening
5. Has at least 1 tumor lesion that can be accurately measured by CT or MRI according to RECIST 1.1 and is amenable for intratumoral injection, as determined by the Investigator
6. The primary tumor itself must be injected, if amenable for intratumoral injection, and must be noted at screening and targeted for intratumoral injection
    a. A secondary lesion may be injected if, biopsy confirmed SCC that is eligible for intranodal injection*,
        - Secondary lesions may include metastasis eg, soft tissue mass or lymph node (LN) in the neck of ≥3 cm

    *No lesion with 180-degree or more encasement of the carotid artery on MRI or CT scan may be selected
7. ECOG performance status of 0 to 2
8. Life expectancy ≥ 6 months

4.2.3.2. Exclusion Criteria

1. Airway obstruction by tumor mass that requires clinical intervention
2. Prior treatment with anthracyclines or intratumorally directed treatment
3. Ulceration or other characteristics that may, in the opinion of the Investigator, increase the risk of severe tumor bleeding
4. SCC originating in the nasopharynx or paranasal sinus, from the salivary gland, or thyroid gland, or non-squamous histology (e.g., melanoma or neuroendocrine carcinoma), or SCC of unknown primary origin
5. Prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen

5. INVESTIGATIONAL PRODUCT

5.1. INVESTIGATIONAL PRODUCT FORMULATION AND PACKAGING

The SQ3370 Investigational Product (IP) is comprised of SQP33 protodrug and SQL70 biopolymer. There is only one active component or drug substance, SQP33 protodrug. SQL70 biopolymer is considered an activating article rather than a drug substance.

- The SQL70 biopolymer is considered an activating article in the SQ3370 Investigational Product and is made of NaHA that is chemically modified with tetrazine. It does not carry an active payload; rather, it captures the SQP33 protodrug upon chemical reaction *in* situ and releases the active drug, Dox.
- The SQP33 protodrug is a formulated protodrug of dox with attenuated activity for intravenous infusion composed of a novel trans-cyclooctene substituent conjugated to Dox.

SQ3370 is an IP only and has not been shown to be safe or effective in the treatment of human disease.

Drugs supplied for clinical investigation should be given personally or under the supervision of the Investigators throughout this study.

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

5.1.1. SQL70 Biopolymer Formulation and Packaging

SQL70 biopolymer for intratumoral and peritumoral injections is supplied as a sterile, fully-formulated liquid in single-use glass vials containing a 10 mL delivery volume. It is a light to dark pink clear aqueous solution of tetrazine-modified NaHA in sterile water for injection. It also contains sodium phosphate and sodium chloride as pharmaceutically-inert excipients to adjust the pH and osmolality respectively, within physiological ranges. SQL70 biopolymer is manufactured by Berkshire Sterile Manufacturing (Lee, MA, USA).

5.1.2. SQP33 Protodrug Formulation and Packaging

The drug product (SQP33 protodrug) is supplied in single-use vials as a sterile orange to red/brown lyophilized solid to be reconstituted in the clinic with sterile water prior to IV infusion. Dosage strength is expressed in terms of the active moiety, free acid form. It contains sucrose and citric acid as pharmaceutically inert excipients. SQP33 protodrug is manufactured by Curia Global (Glasgow, UK).

5.2. INVESTIGATIONAL PRODUCT STORAGE

Both components, SQL70 biopolymer and SQP33 protodrug, **must be stored refrigerated (at 2°C to 8°C/36°F to 46°F) and protected from light**.

The IP must be stored in accordance with the instructions in the protocol, study-specific Pharmacy Manual, Investigator's Brochure, and any other instructions provided by the Sponsor or designee.

Until dispensed to the patients, the IP must be stored **protected from light** in a temperature-monitored and securely locked area, accessible to authorized personnel only.

Unless prohibited by site policy, used IP, including residual solutions, should be retained for drug accountability but is not subject to the same temperature storage conditions. Used Investigational Product must still be stored in a securely locked area, accessible to authorized personnel only.

Report any temperature excursions to the Sponsor or designee immediately, as outlined in the study-specific Pharmacy Manual, and do not use impacted product unless written authorization is received from the Sponsor or designee.

5.3. INVESTIGATIONAL PRODUCT DOSAGE AND ADMINISTRATION

5.3.1. SQL70 Biopolymer Dosage and Administration

For reference, summary information is provided below. Details for study team members handling or administering IP are listed in the protocol-specific Pharmacy Manual.

SQL70 biopolymer is only administered on Day 1 of each cycle. SQL70 biopolymer should be administered 3 hours (± 30 min) prior to SQP33 protodrug infusion.

10 or 20 mL of SQL70 biopolymer should be injected per patient per cycle. Each vial contains 10 mL delivery volume and additional overfill. Vial(s) should be removed from refrigeration and kept protected from light for 60 minutes to warm up to room temperature passively (22 ºC to 28 ºC, not to exceed 28 ºC). The vial should NOT be warmed by placing in a microwave or in a hot water bath.

Once at room temperature, prior to use, the vial should be gently swirled to ensure the contents are homogenous. The vial should NOT be vigorously shaken.

For the intratumoral/peritumoral injection

A 14- to 18-gauge needle is attached to a 10- to 15-mL syringe. The liquid is gently withdrawn into the syringe until the syringe is filled with 10 mL and ANY excess overfill available in a vial to protect against leakage losses while changing needles.

For the intratumoral/peritumoral injection, a needle with a bore size between and including 18 to 22 gauge should be used. Great care should be taken to avoid any intravascular administration of SQL70 biopolymer.

Copies of redacted radiology reports and interventional radiology procedure notes may be obtained for assessing injection techniques and quality control.

Precautions: See section 7.5.1 Management of SQL70 Biopolymer Injection Reactions regarding injection site reactions.

5.3.2. SQP33 Protodrug Dosage and Administration

For reference, summary information is provided below. Details for study team members handling or administering IP are listed in the protocol-specific Pharmacy Manual.

SQP33 protodrug is administered once per day on Day 1 through 5 of each cycle (Expansion Group 2: Unresectable STS will also have a group receiving SQP33 protodrug once per day on Day 1 through 3 of each cycle). On Day 1, SQP33 protodrug infusion should start 3 hours (± 30 min) after SQL70 biopolymer injection. On Day 2 through 5, SQP33 protodrug infusion should start each day within ± 2 hours of the Day 1 infusion start time for that cycle.

SQP33 protodrug vials should be removed from refrigeration and kept protected from light for 60 minutes to warm up to room temperature passively (22 ºC to 28 ºC, not to exceed 28 ºC). The vial should NOT be warmed by placing in a microwave or in a hot water bath.

Once at room temperature, SQP33 protodrug is reconstituted with sterile water within each product vial. During reconstitution, the vial should be gently swirled to ensure full dissolution. The vial should NOT be vigorously shaken or inverted.

The reconstituted SQP33 protodrug solution is then added to saline IV bags at the appropriate concentration for IV infusion for the given dose level. One or more vials of SQP33 protodrug may be needed depending on the dose level.

Precautions: See section 7.5.2 Management of SQP33 Protodrug Infusion Reactions regarding infusion reactions.

5.4. INVESTIGATIONAL PRODUCT SUPPLY

The 2 components of the IP SQ3370, SQP33 protodrug and SQL70 biopolymer, will be provided by the Sponsor or designee. Instructions for requesting and confirming receipt of IP are specified in the study-specific Pharmacy Manual.

5.5. INVESTIGATIONAL PRODUCT DESTRUCTION

The Investigator must obtain written authorization from the Sponsor or designee each time prior to returning IP. The Investigator must store both used and unused IP according to section 5.2 Investigational Product Storage.

IP will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor or designee with the appropriate documentation. Additional details and documentation requirements are outlined in the study-specific Pharmacy Manual.

5.6. INVESTIGATIONAL PRODUCT ACCOUNTABILITY

IP accountability will be monitored throughout the study. Accurate records of IP received at, dispensed from, returned to, and disposed of/returned by the study site should be maintained by the Investigator.

The Investigator shall not make the IP available to any individuals other than to enrolled patients or allow the IP to be used in any manner other than that specified in this protocol.

Additional details and documentation requirements are outlined in the study-specific Pharmacy Manual.

5.7. INVESTIGATIONAL PRODUCT COMPLIANCE

IP compliance will be monitored throughout the study by review of records of study medication used, dosages administered, and intervals between visits.

5.8. POST-STUDY ACCESS TO INVESTIGATIONAL PRODUCT

At this time, the Sponsor does not plan to provide the IP, any other study treatments, or interventions to patients who have participated in the study once their participation ends.

5.9. CONCOMITANT THERAPY

Concomitant treatment includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 30 days prior to the start of screening through the patient's safety follow-up visit. All such medications should be reported to the Investigator and recorded on the Concomitant Medications Case Report Form (CRF). Note the use of herbal or homeopathic remedies, nutritional supplements should be discussed with the patient and wherever possible discontinued prior to treatment given the lack of data on the effects with SQ3370.

5.9.1. Permitted Concomitant Treatment

Necessary supportive measures for optimal medical care may be given throughout the study. Additional care will be administered as indicated by the treating physician and the patient's medical need.

Permitted treatment includes:

- IV antibiotics to treat infections
- Blood transfusions, except for Phase 1 Dose Escalation Cycle 1
- Anti-emetics
- Pain medications
- Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment is permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally
- Botanical/herbal medications or supplements are allowed unless there may be risk associated with their use. Patients should be encouraged to report all such agents so that they can be assessed for known or potential interactions with study treatments
- Routine prophylactic use of a colony-stimulating factor (G-CSF or GM-CSF) should be used according to regional approved label or guidelines i.e., the American Society of Clinical Oncology guidelines

- Erythropoietin is to be used according to regional approved label or guidelines
- Physiologic doses of prednisone 10 mg per day or its equivalent is permitted

5.9.2. Prohibited Concomitant Treatment

- No concomitant treatment, whether conventional or investigational, will be allowed to treat the tumor during this study
- No concomitant radiotherapy, except palliative therapy (Dose escalation only not permitted in Phase 2a), whether conventional or investigational, will be allowed during this study.
- No strong inhibitors and inducers of CYP3A4 and CYP2D6 will be allowed during this study. See Table 5 below.
- Chronic steroid use above physiologic doses is not permitted; however, a temporary course of steroids may be permitted with Medical Monitor approval.
- Live vaccines, including measles/mumps/rubella (MMR), varicella, measles/mumps/rubella/varicella (MMRV), herpes zoster, yellow fever, Ty21a oral typhoid, BCG, and rotavirus. (Advisory Committee on Immunization Practices (ACIP 2012)
- Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.

Table 5: Cytochrome p450 Strong Inducers and Inhibitors

CYP 3A4 Inducers	CYP 3A4 Inhibitors	CYP 2D6 Inducers	CYP 2D6 Inhibitors
barbiturates	clarithromycin	dexamethasone*	buproprion
brigatinib	indinavir	oritavancin	cinacalcet
carbamazepine	idelalisib	Rifampin	fluoxetine
efavirenz	itraconazole		paroxetine
enzalutamide	ketoconazole		quinidine
ethosuximide	nefazodone		ritonavir
glucocorticoids	nelfinavir		sertraline
modafinil	ribociclib		
nevirapine	ritonavir		
oxcarbazepine	saquinavir		
phenytoin	telithromycin		
pioglitazone			
rifabutin			
rifampin			
St. John's wort			
troglitazone			

* dexamethasone is permitted if administered as a temporary course of steroids with Medical Monitor approval, as stated earlier in this section.

Concomitant administration of certain agents may affect the toxicity or efficacy of Dox and/or the concomitantly administered agent, and so concomitant administration of the agents below are also prohibited:

- Calcium-channel blocking agents may potentiate Dox HCl-induced cardiotoxicity (amlodipine is an exception as it is likely cardioprotective)
- Live vaccines to immunosuppressed patients, including those undergoing cytotoxic chemotherapy, may be hazardous
- Phenobarbital may increase the elimination of Dox HCl (ADRIAMYCIN Australian Product Information; ADRIAMYCIN US Package Insert)
- Phenytoin levels may be decreased by Dox HCl (ADRIAMYCIN Australian Product Information; ADRIAMYCIN US Package Insert)
- Propranolol may inhibit cardiac mitochondrial CoQ10 enzyme (ADRIAMYCIN Australian Product Information)
- Progesterone may worsen neutropenia and thrombocytopenia (ADRIAMYCIN US Package Insert)

6. STUDY ASSESSMENTS

The schedules for all study assessments and procedures are outlined in Schedules of Assessments. The results of all assessments and procedures will be documented in the patient's medical record and in study documentation, including the CRF, as applicable.

6.1. INFORMED CONSENT

Content: The Sponsor's sample ICF will be provided to each Investigator. The Investigator or designee is responsible for the content of the study site-specific ICF, but the Sponsor or designee must review and approve any proposed deviations from the Sponsor sample ICFs, or any alternate consent forms proposed by the Investigator before IRB/IEC submission. Additionally, the study site-specific ICF must be approved by the IRB or IEC prior to use, and the approved document must be provided to the Sponsor or designee for regulatory purposes. The content of the ICF must comply with US Food and Drug Administration (FDA) regulations, Australian government's National Statement on Ethical Conduct in Human Research (2007) (National Statement (2007), and ICH guidelines. It should also include any additional information required by local laws relating to institutional review.

Language: The ICF must be in a language understandable to the study patient or to his or her representative.

Timing: The Investigator or designee is responsible for obtaining and documenting informed consent from each patient prior to participating in the study. Informed consent must be obtained from the patient before any screening activity or treatment is undertaken for the purpose of the study.

This includes, but is not limited to, the performance of diagnostic or therapeutic procedures, the discontinuation of any prohibited medications, and the administration of the first dose of Investigational Product.

Patients who have signed the ICF to begin screening procedures must be documented as screened patients.

Process:

The Investigator or designee is responsible for the informed consent process, which includes:

1. Reviewing and discussing the ICF document and any other applicable study information with the patient (or the patient's legally acceptable representative).
2. Obtaining written consent on the ICF document as demonstrated by the signature and date of the patient (or by the patient's legally acceptable representative) and the person who conducted the informed consent discussion.
3. Providing a signed and dated copy of the ICF to the patient (or to the patient's legally acceptable representative).
4. Documenting the **informed consent process** (not just filing the ICF document) in the patient's medical record/study documentation.

5. Storing the ICF document in a secure place (all signed and dated ICFs must remain in each patient's study file or in the study site file and must be available for verification by study monitors at any time).

Amendments: The ICF should be revised, and IRB/IEC approved whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. All patients on study must be re-consented in a timely manner to the most current version of the ICF (or significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised ICFs, the process described above should be followed to document that written informed consent was obtained using the updated/revised ICF for continued participation in the study.

Health Insurance Portability and Accountability Act (HIPAA; US Only): Each ICF may also include patient authorization to allow use and disclosure of personal health information in compliance with the US HIPAA of 1996. If the study site utilizes a separate authorization form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB/IEC review and approval may not be required per study site policies.

6.2. SCREENING AND RE-SCREENING

Number Allocation: The individual patient number for all patients will be assigned at screening, will be used to identify the patient throughout the study, and must be used on all study documentation related to the patient. An Interactive Voice/Web Response System will not be used in this study.

Screening Period Calculation: The calculation for the screening period (i.e., Day -28) begins the day the ICF is signed. The second day of screening is therefore Day -27 and so on. There is no Day 0 in this study. The patient must be enrolled by Day 1 (i.e., the day following Day -1).

Re-screening: A patient who fails the screening process may be re-screened up to 1 additional time or with approval from the Sponsor for additional re-screen attempts.

The individual patient number should be retained (a new patient number should not be assigned), and only the data from the final screening procedures that qualified the patient for the study should be included in the CRFs, although documentation should be retained at the study site for all study procedures from each screening attempt.

If the study site's current IRB/IEC-approved ICF is the same as the ICF that the patient signed for their previous screening attempt, re-consent is not required, unless as required by local study site/IRB/IEC policy. If a new IRB/IEC-approved ICF (or new safety data that requires immediate communication to the patient) is available, the patient should be re-consented using the new ICF (or informed of new safety data that requires immediate communication to the patient) prior to performing any re-screening procedures.

The re-screening period (i.e., Day -28) begins the day the ICF is signed (if applicable) or the first re-screening study procedure is performed if re-consent is not applicable.

6.3. ENROLLMENT

Patients are considered enrolled:

- Within 28 days of beginning screening
- After the results for all screening procedures have been received by the study site

and

- After the patient has met all inclusion and exclusion criteria and therefore is deemed eligible for the study by the Principal Investigator or designee

and

- After Sponsor approval is received and documented by signature per the agreed upon process
- The enrollment date is the date of the Sponsor's signature

6.4. MEDICAL HISTORY AND DEMOGRAPHIC DATA

Medical history and demographic data will be collected at screening. Special attention will be made to identify all prior cancer therapies, the response to therapy, and the duration of the response.

6.5. PHYSICAL EXAMINATION & DIRECTED MEDICAL HISTORY

A full physical examination will be done at screening, and a symptom-directed examination will be done at other time points. See Schedules of Assessments for specific time points.

Physical Examination: Should include, but is not limited to, 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 in addition to genitourinary and gynecologic if indicated by the Investigator.

Symptom-directed Physical Examinations: Should include an examination of organ systems related to patient symptoms to document potential AEs, AE severity, or AE resolution in addition to identifying any potential AE known or suspected to be associated with the treatment and procedures that the patient is receiving. Any new post-baseline abnormal physical examination finding(s) assessed as clinically significant should be recorded as an AE or SAE.

6.6. VITAL SIGNS

Vital signs include height (at screening only), weight (once per cycle), temperature, blood pressure (systolic and diastolic), heart rate, and respiratory rate. See Schedules of Assessments for specific time points. Post dose vital sign timings are based on the end time of the procedure (infusion / injection), not the start.

6.6.1. Phase 1 Dose Escalation

Routine Dosing Vitals: Vital signs as outlined below should be obtained on IP administration Days 1 to 5:

Routine Vital Time Points Dosing Days 1-5
Pre-infusion
15 min mid infusion (± 5 min)
Immediately post-infusion (+ 5 min)
15 min post-infusion (± 5 min)
30 min post-infusion (± 5 min)

Cycle 1 Day 1 Only Dosing Vital Signs: Vital signs as outlined below should be obtained on IP administration Cycle 1 Day 1 only:

Cycle 1 Day 1* Vital Signs Time Points	
In Relation to Administering	**Vitals Time Points**
SQL70 biopolymer	Pre-SQL70 injection
	15 min post-SQL70 injection (± 5 min)
SQP33 protodrug	Pre-SQP33 infusion
	15 min mid-SQP33 infusion (± 5 min)
	Immediately post-SQP33 infusion (+ 5 min)
	15 min post- SQP33 infusion (± 5 min)
	30 min post- SQP33 infusion (± 5 min)
	60 min post- SQP33 infusion (± 10 min)

*Day 2-5 of Cycle 1 vital signs time points should follow the routine dosing vitals

6.6.2. Phase 2a Expansion Groups

Routine Dosing Vitals: Vital signs as outlined below should be obtained on IP administration Days 1 to 5 (or Day 1 to 3 for the 3-day treatment Group 2 patients)

Routine Vital Time Points Dosing Days 1-5
Pre-infusion
Immediately post-infusion (+ 5 min)
Prior to Discharge from treatment site

Cycle 1 Day 1 Only Dosing Vital Signs: Vital signs as outlined below should be obtained on IP administration Cycle 1 Day 1 only:

Cycle 1 Day 1* Vital Signs Time Points	
In Relation to Administering	**Vitals Time Points**
SQL70 biopolymer	Pre-SQL70 injection
SQP33 protodrug	Pre-SQP33 infusion
	Immediately post-SQP33 infusion (+ 5 min)
	Prior to Discharge from treatment site

*Day 2-5 of Cycle 1 vital signs time points should follow the routine dosing vitals

6.7. BODY SURFACE AREA CALCULATION

The calculation of the dose per day of SQP33 protodrug will be based on the patient's body surface area (BSA) using the recommended Du Bois & Du Bois formula, however sites are allowed to use their institutional formula:

BSA (m^2) = 0.007184 x Height (cm)$^{0.725}$ x Weight (kg)$^{0.425}$

The BSA will be calculated at Cycle 1 Day 1 is to be used throughout the protocol. If there has been a significant (> 10%) weight change from the previous weight used for BSA calculation, then the BSA should be recalculated. Patient's BSA may be recalculated more frequently (at every cycle's Day 1 for example) if required by institutional policy.

Sites should follow their institutional policy on whether to round the BSA up or down. A weight measured up to 1 week prior to any Day 1 dose may be used to calculate the dose of SQP33 protodrug.

6.8. ECHOCARDIOGRAM/MULTIGATED ACQUISITION SCAN

ECHO/MUGA scans are included in the study given the cardiotoxicity risk associated with conventional Dox treatment. The frequency of the procedure increases after Cycle 5 to ensure heightened monitoring given the increased cumulative exposure to Dox.

Screening: An ECHO or MUGA scan should be performed during the screening period.

Treatment: An ECHO or MUGA scan (whichever was performed during screening) should be performed within 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 performed at the Safety Follow-Up visit if not performed in the previous 14 days.

6.9. ELECTROCARDIOGRAM

6.9.1. General Guidance

All ECGs for this study will be triplicate 12-lead ECGs, except for the screening ECG. Data collected will include heart rate, PR, QRS, QT, and QTc intervals as calculated using Fridericia's formula.

Day 1 pre-dose ECGs may be performed up to 3 days prior to the visit.

All post SQP33 protodrug infusion ECGs should be performed within + 30 minutes of the end of the infusion time.

ECGs will be reviewed, initialed, and dated by the Principal Investigator or designee within a timely manner. See Schedules of Assessments for specific time points.

6.9.1.1. Phase 1 Dose Escalation

- 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.

6.9.1.2. Phase 2a Expansion Groups

- On Day 1 of each cycle ECGs will be performed pre and post SQP33 protodrug infusion.

6.10. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

The ECOG performance status should be documented in the patient's medical record or study source documentation at applicable visits. A copy of the document is included in APPENDIX C – Eastern Cooperative Oncology Group Performance Status Assessment for reference. See Schedules of Assessments for specific time points.

6.11. ADVERSE EVENT REVIEW

Investigators should assess AEs at each visit. See section 7 ADVERSE AND SERIOUS ADVERSE EVENTS.

6.12. CONCOMITANT MEDICATION REVIEW

Investigators should assess concomitant medications at each visit.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted except as specifically prohibited (see section 5.9.2 Prohibited Concomitant Treatment). The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered within 30 days prior to the start of the screening period through the patient's final study visit will be recorded as a concomitant medication. Medications include not only physician-prescribed medications but also all over-the counter medications, herbal medications, and food or vitamin supplements, even if taken as a prophylaxis.

6.13. SAFETY LABORATORY SAMPLE COLLECTION

6.13.1. Phase 1 Dose Escalation

Safety laboratory sample collection includes the following:

- Hematology Panel: Includes complete blood count, including white blood cells with differential, hematocrit, hemoglobin, and platelets.
- Chemistry Panel: Includes sodium, potassium, calcium, creatinine, total protein, albumin, bilirubin (total, direct), AST/SGOT, ALT/SGPT, alkaline phosphatase, amylase, lipase, and glucose.
- Coagulation Studies: Includes prothrombin time, activated partial thromboplastin time and INR.
- Urinalysis: Includes protein, specific gravity, glucose, and blood. Can be performed by dipstick or laboratory analysis.

- Serology Test: Includes hepatitis B antigen and hepatitis C.
- Pregnancy Test: Women of childbearing potential must have a negative pregnancy test before starting study treatment and at the beginning of each cycle of treatment. Blood or urine pregnancy tests must have a minimum test sensitivity of at least 25 IU/L. Kits measuring either total human chorionic gonadotropin or the beta (β) fraction are acceptable.

6.13.2. Phase 2a Expansion Groups

Safety laboratory sample collection includes the following:

- Hematology Panel: Includes complete blood count, including white blood cells with differential, hematocrit, hemoglobin, and platelets.
- Chemistry Panel: Includes sodium, potassium, calcium, creatinine, total protein, albumin, bilirubin (total and/or direct), AST/SGOT, ALT/SGPT, alkaline phosphatase, and glucose.
- Coagulation Studies: Includes prothrombin time, activated partial thromboplastin time and INR.
- Urinalysis: Includes protein, specific gravity, glucose, and blood. Can be performed by dipstick or laboratory analysis.
- Serology Test: Includes hepatitis B antigen and hepatitis C.
- Pregnancy Test: Women of childbearing potential must have a negative pregnancy test before starting study treatment and at the beginning of each cycle of treatment. Blood or urine pregnancy tests must have a minimum test sensitivity of at least 25 IU/L. Kits measuring either total human chorionic gonadotropin or the beta (β) fraction are acceptable.

6.13.3. General Instructions for both Phase 1 and Phase 2a

See Schedules of Assessments for specific time points.

Throughout the study, safety laboratory results from the previous visit need to be available prior to each day of dosing, but safety labs drawn on the day of the visit do not need to be available prior to dosing that same day - they will be evaluated following the visit. For example, safety lab results from Day 2 need to be available prior to dosing on Day 3, but safety labs drawn on Day 3 do not need to be available prior to dosing on Day 3.

Safety laboratory data from screening will be used for study eligibility and the decision to move forward with dosing on Day 1; however, the Medical Monitor should be contacted if Day 1 laboratory data are significantly different or do not align with the eligibility criteria.

Day 1, Day 10 and Safety Follow Up safety laboratory tests may be collected up to 3 days prior to the visit so that the investigator may have the results available at the time of the patient's visit.

Safety laboratory data will be reviewed (to assess the clinical significance of any analyte that is outside the normal range), initialed, and dated by the Principal Investigator or designee within a timely manner. It will be the Investigator's responsibility to perform additional laboratory assessments more frequently if clinically indicated.

6.14. PHARMACOKINETIC LABORATORY SAMPLE COLLECTION

6.14.1. General Guidance

Plasma PK bioanalysis will be conducted using a validated liquid chromatography-mass spectrometry methods for SQP33 protodrug and active Dox, following SQ3370 treatment. PK parameters will then be calculated (as data permits) from plasma SQP33 protodrug concentration, including the following:

- C_{max}: maximum observed plasma concentration
- T_{max}: timepoint of maximum observed plasma concentration
- AUC_t: area under the plasma concentration-versus-time curve from time zero to the last measurable time point for individual days and/or complete cycles

See also APPENDIX F – PK Schedule

6.14.2. Phase 1 Dose Escalation

Blood (plasma) samples for determination of PK levels of SQP33 protodrug, SQL70 biopolymer and active Dox following SQ3370 treatment as well as to explore the kinetics of SQP33 protodrug degradation under pH, temperature, and other conditions to be collected from all patients during:

Cycle 1:

- Day 1 pre-infusion of SQP33 protodrug; at 5- and 30-minutes post-infusion; and at 1, 2, and 4 hours post-infusion.
- Days 2, 3, and 4 pre-infusion of SQP33 protodrug and at 5 and 30 minutes post-infusion.
- Day 5 pre-infusion of SQP33 protodrug; at 5- and 30-minutes post-infusion; and at 1, 2, and 4 hours post-infusion.

Cycles 2, 3 and 4:

- Day 1 pre-infusion of SQP33 protodrug; at 5- and 30-minutes post-infusion.
- Days 2, 3, 4 and 5 pre-infusion of SQP33 protodrug.

Note: Post dose PK timings are based on the end time of the SQP33 protodrug infusion, not the start.

6.14.3. Phase 2a Expansion Groups

Blood (plasma) samples for determination of PK levels of SQP33 protodrug, SQL70 biopolymer and active Dox following SQ3370 treatment as well as to explore the kinetics of SQP33 protodrug degradation under pH, temperature, and other conditions to be collected from patients in each of the Expansion Groups at the time points below:

Expansion Group 1: Extremity STS [Stage 1 Only]

Stage 1 Only

Cycle 1:

- Day 1 pre-infusion of SQP33 protodrug; at 15 minutes post-infusion; and at 2 and 4 hours post-infusion.
- Day 2, 3, and 4 pre-infusion of SQP33 protodrug and at 15 minutes post-infusion.
- Day 5 pre-infusion of SQP33 protodrug; at 15 minutes post-infusion; and at 2 and 4 hours post-infusion.

Cycle 2:

- Days 1, 3, and 5 pre-infusion of SQP33 protodrug and at 15 minutes post-infusion.

Note: Post dose PK timings are based on the end time of the SQP33 protodrug infusion, not the start.

Expansion Group 2: Unresectable STS

3-Day Infusion cohort

Cycle 1:

- Day 1 pre-infusion of SQP33 protodrug; at 15 minutes post-infusion; and at 2 and 4 hours post-infusion.
- Day 2 pre-infusion of SQP33 protodrug and at 15 minutes post-infusion.
- Day 3 pre-infusion of SQP33 protodrug; at 15 minutes post-infusion; and at 2 and 4 hours post-infusion.

Cycle 2:

- Day 1 pre-infusion of SQP33 protodrug and at 15 minutes post-infusion.
- Day 3 pre-infusion of SQP33 protodrug and at 15 minutes post-infusion.

5-Day Infusion cohort

Cycle 1:

- Day 1 pre-infusion of SQP33 protodrug; at 15 minutes post-infusion; and at 2 and 4 hours post-infusion.
- Day 2, 3, and 4 pre-infusion of SQP33 protodrug and at 15 minutes post-infusion.
- Day 5 pre-infusion of SQP33 protodrug; at 15 minutes post-infusion; and at 2 and 4 hours post-infusion.

Cycle 2:

- Days 1, 3, and 5 pre-infusion of SQP33 protodrug and at 15 minutes post-infusion.

Note: Post dose PK timings are based on the end time of the SQP33 protodrug infusion, not the start.

Expansion Group 3a: Head and Neck

Cycle 1:

- Days 1 and 5 pre-infusion of SQP33 protodrug; at 15 minutes post-infusion; and 2 and 4 hours post-infusion.

Note: Post dose PK timings are based on the end time of the SQP33 protodrug infusion, not the start.

6.15. PERIPHERAL BLOOD MONONUCLEAR CELLS AND CTDNA

For both Phase 1 and Phase 2a, PBMCs and ctDNA (Phase 2a only and is optional) will be collected, in separate tubes (both tubes included in the same kit), on Day 1 of Cycle 1, 2 and 3 (3-time points total) to assess immune response and minimal residual disease (MRD). In Phase 2a for Expansion Groups 2, and 3a, additional plasma samples (PBMCs and ctDNA [optional] will be collected every six weeks to coincide with the timing of the imaging scans, i.e. Cycle 4, 6, 8, 10, and 12 (5 time points). Collection on Day 1 will be prior to SQL70 biopolymer administration. See the Laboratory Manual for additional details on the collection process.

6.16. CARDIOTOXICITY BIOMARKERS FOR PHASE 2A EXPANSION GROUPS ONLY

6.16.1. General Guidance

Cardiotoxicity is the highest risk in cumulative doxorubicin doses with a lifetime dose should not exceed 450-550 mg/m^2 of body surface area (PDR.net). Cardiotoxicity has been defined as a decrease in the LVEF of greater than ten percentage points to a value below the average reference value (EF 53%). However, the LVEF measurements taken after doxorubicin exposure were not predictive of later cardiotoxicity (p=0.075) (Sawaya 2012). Combining ECHO, Troponin I and BNP serum levels have been used to monitor cardiotoxicity, i.e., elevated levels of troponin I (>30 pg/mL) and BNP (>100 pg/mL), and a decrease in LVEF from baseline (Skovgaard 2014).

- Other markers have been shown to have predictive values:
  - Serum topoisomerase 2b levels ≥0.5 ng/µg are associated with LVEF decline (p=0.001). The log-rank test showed that patients expressing a higher Top2b level (≥0.5 ng/µg) had a higher probability of LVEF decline over time (p=0.001) (Win 2018).
  - Myeloperoxidase, patients with elevated MPO levels (>350 µg/L) experienced a marked increased cardiac risk (adjusted hazard ratio [HR] 2.25 [1.32 to 3.82]; p=0.003) (Baldus 2003).
- Serum samples will be taken around the time of the ECHO/MUGA.

6.16.2. Phase 2a Expansion Groups

Blood (serum) will be collected at screening around the time of ECHO or MUGA scan, during treatment, and during safety follow-up (see Schedule of Assessments Appendices H-K).

- Screening: Blood (serum) will be drawn around the time of screening with an ECHO or MUGA scan
- Treatment: within 7 days from Cycle 3 Day 1, Cycle 5 Day 1, and Day 1 of every cycle thereafter.
- Safety Follow-Up: during the Safety Follow-Up visit if not performed in the previous 14 days.

6.17. TUMOR BIOPSIES

6.17.1. Dose Escalation

Unless the tumor is considered too small to be biopsied (based on the investigator's assessment) core needle tumor biopsies will be collected on Day 1* of Cycle 1, 2, and 3 (3-time points total) prior to the SQL70 biopolymer injection for 3 purposes:

- To assess immune response
- To measure minimal residual disease (MRD) and treatment responses
- To assess the concentration of active Dox and SQP33 following SQ3370 treatment at the local site

*or the biopsy can be collected:

- Cycle 1: during screening
- Cycle 2 & 3: up to 4 days prior to Day 1 (i.e., Day 18, 19, 20 or 21 of the previous cycle)

Per investigator assessment, additional optional biopsies may be collected of:

- non-injected tumors at the same timepoints as injected tumors
- injected and non-injected tumors on Day 1 after Cycle 3

6.17.2. Phase 2a Expansion Groups

See the Laboratory Manual for additional details on the collection process. Tumor biopsies should be taken from the same tumor as that being injected with SQL70 biopolymer. **Tumor biopsies are optional for Phase 2a Expansion Groups 2 and 3a**.

Group 1 – Extremity STS

Core needle tumor biopsies will be collected on Day 1* of Cycle 1, 2, and 3 (3-time points total) prior to the SQL70 biopolymer injection for 3 purposes:

- To assess immune response
- To measure minimal residual disease (MRD) and treatment responses.

- To assess the concentration of active Dox and SQP33 following SQ3370 treatment at the local site

*or the biopsy can be collected:

- Cycle 1: during screening
- Cycle 2 & 3: up to 4 days prior to Day 1 (i.e., Day 18, 19, 20 or 21 of the previous cycle)

Per investigator assessment, resected tumors will be divided into two and stored as fresh-frozen and FFPE.

- These tissues will be used to evaluate transcriptomic biomarkers (Chibon 2019).

Group 2 - Unresectable STS

Optional core needle tumor biopsies may be collected on Day 1* of Cycle 1, 2, and 3 (3-time points total) prior to the SQL70 biopolymer injection for 3 purposes:

- To assess immune response
- To measure minimal residual disease (MRD) and treatment responses.
- To assess the concentration of active Dox and SQP33 following SQ3370 treatment at the local site

*or the biopsy can be collected:

- Cycle 1: during screening
- Cycle 2 & 3: up to 4 days prior to Day 1 (i.e., Day 18, 19, 20 or 21 of the previous cycle)

Group 3a – Head and Neck

Optional core needle tumor biopsies may be collected on Day 1* of Cycle 1, 2, and 3 (3-time points total) prior to the SQL70 biopolymer injection for 3 purposes:

- To measure minimal residual disease (MRD) and treatment responses.
- To assess the concentration of active Dox and SQP33 following SQ3370 treatment at the local site

*or the biopsy can be collected:

- Cycle 1: during screening
- Cycle 2 & 3: up to 4 days prior to Day 1 (i.e., Day 18, 19, 20 or 21 of the previous cycle)

6.18. CT/MRI TUMOR IMAGING & MEASUREMENTS

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool.

The same method of assessment and the same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study

to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Assessment should be performed:

- During screening
- Every 6 weeks (-7-day window) from Cycle 1 Day 1 until end of treatment
- At the Safety Follow-Up Visit, if not performed in the previous 6 weeks
- If a patient comes off treatment due to non-RECIST progression, a scan should be obtained during Long Term Follow Up, until radiographic progression is noted.
- Additional scans may be conducted at other time points if deemed clinically appropriate

Scans will be read at the study site. Scans must include chest, abdomen, and pelvis, as well as any other areas of disease, whether or not measurable, present at screening and/or follow-up, including extremities.

Computed Tomography (CT) / Magnetic Resonance Imaging (MRI): Scans are required to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated). A brain scan is required to exclude brain metastasis if clinically indicated.

Clinical Examination: Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination. Tumors may also be assessed utilizing visual or palpable lesions on physical examination, including full assessment of all known metastases.

Copies of redacted radiology reports and interventional radiology procedure notes may be obtained for quality control.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, either a CT scan or documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is necessary.

6.18.1. Target and Non-Target Tumor Baseline Recording

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at screening and use it as a comparator for subsequent measurements.

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means that, in instances where patients have only 1 or 2 organ sites involved, a maximum of 2 and 4 lesions, respectively, will be recorded).

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum of the

diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

If a lesion "fragments" as it shrinks, the individual lesion diameters should be added together to calculate the target lesion size. If lesions coalesce and become inseparable, the longest diameter of the merged lesions should be used as the lesion size.

Note: Only target lesions can be selected for SQL70 biopolymer injection.

Non-Target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

See RECIST v1.1 (Eisenhauer 2009) for additional details.

6.18.2. Tumor Response Evaluation

Tumor response will be evaluated using RECIST v1.1 (Eisenhauer 2009) as outlined in Table 6 and Table 7 below. See RECIST v1.1 (Eisenhauer 2009) for additional details.

Table 6: Evaluation of Target Lesions

Response Type	Definition
Complete response	Disappearance of all target lesions; if a pathologic lymph node, reduction in the shortest axis to < 10 mm[a]
Partial response[b]	At least a 30% decrease in the sum of diameters of target lesions relative to the baseline sum of diameters[c]
Stable disease[b,d]	Neither a sufficient reduction to qualify as a partial response nor sufficient increase to qualify for progression[c]
Progressive disease[b]	At least a 20% increase in the sum of diameters relative to the smallest sum of diameters recorded (including the baseline sum of diameters) in conjunction with an increase of at least 5 mm in that smallest sum of diameters or the appearance of 1 or more new lesions[c,e]

Table 7: Evaluation of Non-Target Lesions

Response Type	Definition
Complete response	Disappearance of all nontarget lesions; all lymph nodes must be non-pathologic in size (i.e., < 10 mm on the short axis)
Non-complete response or non-progressive disease	Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive disease	Unequivocal progression[a] of any existing nontarget lesion or the appearance of 1 or more new lesions[b]

[a] For each pathologic lymph node considered a target lesion, the node must have a short axis measuring < 10 mm to be considered as a complete response. In such cases, the sum diameters may not be zero (as a normal lymph node can have a short axis of < 10 mm). If a non-nodal lesion has decreased in size to the point where it is difficult to distinguish residual tumor from normal tissue, a biopsy may be performed to help clarify whether a response is a CR or PR.

[b] For each pathologic lymph node considered a target lesion, the measurement of the short axis of the node is to be included in the sum diameters when determining partial response, stable disease, and progression.

[c] In this study, the "baseline sum diameter" is calculated based on the lesion measurements obtained at screening.

[d] Duration of stable disease is measured from the date of the first dose of Investigational Product until criteria for progressive disease are met based on the smallest sum diameters recorded (including the baseline sum diameters).

[e] The finding of a new lesion should be unequivocal and not possibly attributable to a difference in imaging modality or scanning technique. Post-baseline, fluorodeoxyglucose positron emission tomography (FDGPET) may be useful in assessing new lesions apparent on computed tomography (CT) scan.

6.19. ADMINISTRATION OF INVESTIGATIONAL PRODUCT

Figure 5 and Figure 6 below illustrates one cycle of IP administration. See section 5.3 Investigational Product Dosage and Administration and the study-specific Pharmacy Manual for additional details. Group 2: Unresectable STS will have a cohort that receives their dose of SQP33 protodrug in 3 days, instead of 5 days.

Figure 5: SQ3370 5-Day Administration Schedule

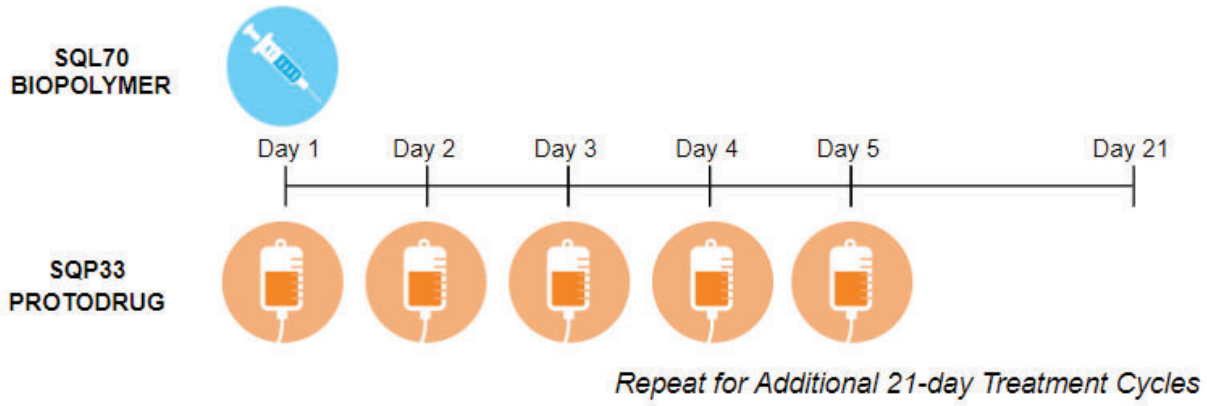
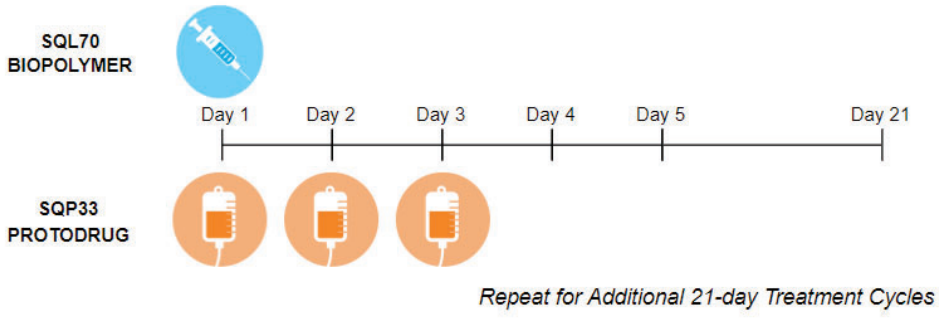


Figure 6: SQ3370 3-Day Administration Schedule



6.20. UNSCHEDULED VISITS

The Investigator will be responsible for monitoring AEs and other toxicities. Any additional visit(s) to monitor patient safety that is performed outside of scheduled visits will be recorded as an Unscheduled Visit. Unscheduled Visits can occur at any time, based on clinical need. The assessments and procedures conducted during the visit will be at the discretion of the Investigator. Data from unscheduled visits should be recorded in the eCRF and source documentation maintained by the Investigator in the same manner that data and source documentation are available for routine study visits.

6.21. PATIENT END OF STUDY

Patients end the study when either:

- Patients do not enter Long Term Follow-Up
- Patients end Long Term Follow-Up

6.22. WITHDRAWAL OF CONSENT

Patients have the right to voluntarily withdraw consent from the study at any time for any reason.

- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- The patient may withdraw consent for treatment and allow the sponsor to collect Long Term Follow-up information.
- If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study site study records and notify the Sponsor or designee.

6.23. LOST TO FOLLOW-UP

If a patient misses a visit and is not responding to telephone calls from the study center (**all attempts to contact the patient should be documented**), the center will need to take additional actions to locate the patient.

1. The center will make at least 2 attempts to contact the patient by telephone.
2. When possible, 2 additional attempts should be made to contact the patient's emergency contact by telephone.
3. If these attempts are not successful, when possible, a registered letter will be sent to the last known address of the patient.
4. If this is unsuccessful, the patient will be considered lost to follow-up.

6.24. STUDY SITE OR STUDY TERMINATION

The Sponsor has the right to terminate the participation of either an individual study site or the study at any time.

7. ADVERSE AND SERIOUS ADVERESE EVENTS

7.1. DEFINITIONS

7.1.1. Definition of Adverse Events

Per FDA 21CFR 312.32, an AE is an untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In this study, AEs will be captured from the time a subject signs the ICF to the last study visit and include the following:

- Any new sign, symptom, or disease
- Any new clinically significant or symptomatic laboratory/diagnostic test abnormality
- Any clinically significant worsening of laboratory/diagnostic test abnormality
- Any worsening (e.g., clinically significant change in frequency, nature and/or intensity) of a pre-existing condition

A pre-existing condition is a condition that is present prior to signing the ICF for the study. Pre-existing conditions such as illnesses, reactions, symptoms, progression of disease state, and other comorbidities, as well as pre-existing laboratory/diagnostic test abnormalities, will be documented in the subject's record as medical history. The disease/disorder being studied or expected progression, signs, or symptoms from the disease/disorder, which is more severe than expected for the participant's condition. Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event. If there is any uncertainty about a finding being due solely to progression of disease, the finding should be reported as an AE or SAE as appropriate.

Signs and symptoms will be reported individually as non-serious AEs, unless a medical diagnosis was provided. Medical diagnosis, whenever provided, will be reported rather than individual signs and symptoms.

Any AE that meets seriousness criteria (section 7.1.3 Definition of Serious Adverse Event (SAE)) must be reported as outlined in section 7.2 Reporting to Sponsor after consent is obtained, but prior to the administration of the IP, only AEs/SAEs caused by a protocol mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported as AEs/SAEs. Any other untoward medical occurrences should be reported as medical history.

7.1.1.1. Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild:** Usually transient and may require minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- **Moderate:** Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- **Severe**: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

7.1.1.2. Relationship to Study Treatment

The investigator will make a determination of the relationship of the AE to study drug using a binary system according to the following guidelines:

Not Related: A relationship between the AE and study drug can reasonably be ruled out based on lack of any temporal relationship of the event to study drug administration, or when the subject's underlying condition, medical history, or other therapy provide sufficient explanation for the observed AE.

Related: There is a reasonable possibility that the AE is associated with the use of the study drug, such as temporal relationship of the AE to study drug administration, or when other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed AE. Additionally, the AE abates upon discontinuation of the study drug, or follows a hypothesized cause and effect relationship and (if appropriate) re-appears when the study drug is reintroduced.

7.1.1.3. Action Taken for Adverse Events

The investigator or designee will record the action(s) taken with respect to study drug for the AE in the eCRF. Actions taken but not limited to:

- None/Dosed Not Changed: The study drug schedule was not changed.
- Drug Interrupted: The study drug schedule was modified by temporarily terminating the prescribed regimen of medication.
- Drug Withdrawn: the study drug schedule was modified through termination of the prescribed regimen of medication.
- Drug Reduced: The study drug schedule was modified by subtraction, either by changing the frequency, strength, or amount.
- Not Applicable: If the AE started after the End of Treatment date.

7.1.2. Definition of Adverse Events of Special Interest (AESI)

An AESI is one of scientific and medical concern specific to the study drug, which requires ongoing safety monitoring and prompt communication by the investigator to the sponsor. Depending on the nature of the event, Regulatory Authorities should be notified. Per ICH E2F such an event might require further investigation in order to characterize and understand it.

AESIs in this study include Dose-limiting Toxicities (DLTs), potential myocardial toxicity, COVID-19 infections, and AEs due to overdose.

7.1.2.1. Dose-limiting Toxicity

See section 3.2.6 Dose-Limiting Toxicity for definition.

7.1.2.2. Potential Myocardial Toxicity

Since Dox is known to cause myocardial toxicity, especially at high cumulative doses, events such as myocardial infarction, elevated serum troponin-T, significantly decreased ejection fraction on echocardiogram or MUGA, symptoms or signs of new congestive heart failure, new onset of arrhythmias or heart block, etc. should be reported to the Sponsor immediately and IP administration should be halted. The patient should be evaluated and if there appears to be significant evidence of myocardial injury, study treatment should be discontinued permanently.

7.1.2.3. COVID-19

Given information regarding COVID-19 infections and the global pandemic continue to evolve, the Sponsor will provide sites with separate guidance for how to report confirmed or suspected cases of COVID-19 infections and manage study treatment. Guidance will include definitions for confirmed and suspected infections as well as rules for stopping or interrupting study treatment as applicable.

7.1.2.4. Overdose

Study drug overdose is the accidental or intentional use of an Investigational Product in an amount higher than the dose indicated per protocol for a given subject. Any study product overdose during the study should be recorded on the source document and eCRF. In the event of overdose, the subject should be closely monitored for any potential AEs.

7.1.3. Definition of Serious Adverse Event (SAE)

A serious adverse event is an AE that in view of the Investigator or Sponsor, results in any of the following outcomes:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/Birth Defect
- Other Important Medical Events: based on appropriate medical judgement, they may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or seizures/convulsions that do not result in hospitalization

In this study, elective, or pre-planned surgery (prior to study entry) or routine clinical procedures, which are not the result of an AE, will not be considered as an SAE, but will be entered in the

subject's record and entered in the eCRF. If any serious untoward event is reported during the procedure, it will be reported as an SAE and assessed for causality and expectedness. SAEs that occurred after 30 days since the last dose of study drug should be reported only if they are deemed by the investigator to be "RELATED" to the investigational medicinal product. The investigator must review all AEs (serious and non-serious) and the outcome throughout the study.

7.2. REPORTING TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to the Investigational Product:

- SAEs
- AEs of Special Interest (see section 7.1.2 Definition of Adverse Events of Special Interest (AESI))
- Pregnancies

Investigators must also comply with local requirements for reporting SAEs to their local IRB/EC.

7.2.1. Follow-up of Adverse Events

Every reasonable effort will be made to follow-up with patients who have AEs. AEs will be collected from the time the subject signs the ICF until 30 days after last dose of study drug, whether or not judged by the Investigator to be related to study drug. Any subject who has an ongoing AE that is related to study drug or study procedures at subsequent visits, will be followed-up, where possible, until resolution.

Any subject who has an AE that is not related to study drug or study procedures at the Follow-up Visit can be closed out as ongoing at the Investigator's discretion.

7.2.2. Serious Adverse Event Notification, Documentation, and Reporting

The investigator must report an SAE within 24 hours of becoming aware of the event. The Investigator must report such events to the Sponsor immediately by sending an SAE Report Form via email to SAE@shasqi.com; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event.

The initial report must not be delayed in order to obtain additional information. Any additional information will be reported as a follow-up to the initial report within 24 hours of collection. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to the Investigational Product:

- SAEs
- AEs of Special Interest (see section 7.1.2 Definition of Adverse Events of Special Interest (AESI))

Investigators must also comply with local requirements for reporting SAEs to IRB/IEC.

In the event of any SAE (other than death) occurring after the last dose of study drug and prior to the Follow-up Visit, the subject will be instructed to contact the investigator immediately using the instructions provided on the ICF.

The Medical Monitor will review reported SAEs and may contact the Investigator directly for further information.

The Sponsor will comply with all applicable local regulatory requirements related to reporting of SAEs to the appropriate Regulatory Authorities in the countries and regions this study is conducted, while the investigator and designated study personnel with applicable local regulatory requirements related to reporting of SAEs to the Institutional Review Board (IRB), Ethics Committee (EC), and the sponsor.

If the SAE is not previously documented in the Investigator Brochure (IB), it's a new occurrence, and it's thought to be related to the investigational treatment, the sponsor or designee may urgently (e.g., a change in study risk, diagnostic test results, laboratory reports) require further information from the investigator for Regulatory Authority reporting.

It is the responsibility of the Sponsor to collect and report all AEs that meet criteria as Suspected Unexpected Serious Adverse Reactions (SUSARs) to Regulatory Authorities and relevant IRBs/ECs in accordance with national regulatory requirements, e.g., in the United States (US) such as FDA 21CFR 312.32 and Australia requirements as per Pharmacovigilance Responsibilities of Medicine Sponsors Australian Recommendations and Requirements Guidance.

The Sponsor will preserve the investigator's assessment and will give due consideration to it when making regulatory reporting decisions.

As applicable, the sponsor will also notify other participating investigators of all Safety Reports to ensure prompt notification of significant new AEs and safety risks with respect to study drug. This notification will occur as soon as possible and in compliance with country specific applicable regulations.

The Medical Monitor should be contacted by study sites requiring additional clarification on an SAE.

7.3. PREGNANCY REPORTING

If a female subject becomes pregnant during the study and up to 30 days after the end of study, the subject must inform the study site as soon as possible. If a female partner of a male subject becomes pregnant during the study and up to 7 days after the end of study, the subject must inform the site. Upon confirmation of the pregnancy, the female subject will be discontinued from the study. The investigator or designee must complete a study specific pregnancy form upon confirmation of a pregnancy and send it to the sponsor as directed on the pregnancy form within 24 hours of confirmation of the pregnancy. Pregnancy itself is NOT an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The investigator will follow the pregnancy until resolution, and in case of a live-born

offspring, up to 1 month of age of the infant. See APPENDIX E – Collection of Pregnancy Information for additional details.

The investigator will notify the sponsor, as directed on the pregnancy report form, of the outcome as a follow-up of the initial pregnancy form. All pregnancies must be reported to the sponsor and as applicable to IRBs/ECs.

The effects of SQ3370 on the developing human fetus are unknown. For this reason, **women of childbearing potential and men** must agree to use highly effective contraception for the duration of study participation and for **90 days following completion of treatment**.

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Additionally, men should not donate sperm for the duration of study participation and for 90 days following completion of treatment. Highly effective contraception for this study is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly.

Women of non-childbearing potential for this study are defined as a woman who:

- Has undergone surgical sterilization (total hysterectomy, bilateral tubal ligation, bilateral salpingectomy or bilateral oophorectomy), or
- Is < 60 years of age and has been naturally postmenopausal for at least 12 consecutive months (i.e., has not had menses at any time in the preceding 12 consecutive months) and confirmed by elevated follicle-stimulating hormone levels (using local reference ranges).
- Is ≥ 60 years of age

Men of non-childbearing potential for this study are defined as a man who has:

- Azoospermia either from a vasectomy or from an underlying medical condition.

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining whether they should be considered women or men of childbearing potential.

Note: Documentation can come from the study site personnel's review of the participant's medical records, medical examination, or medical history interview.

7.4. REGULATORY REPORTING

The Sponsor will promptly evaluate all SAEs and AEs of Special Interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

The Sponsor has a legal responsibility to notify investigators, the local regulatory authority, and other regulatory agencies about the safety of an Investigational Product under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and will be forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

7.5. MANAGEMENT OF STUDY-SPECIFIC ADVERSE EVENTS

7.5.1. Management of SQL70 Biopolymer Injection Reactions

Investigators should monitor the patient for injection site reactions, including vitals as outlined in section 6.6 Vital Signs.

Prevention:

- Consider administering a subcutaneous local anesthetic or topical anesthetic before SQL70 biopolymer injection.
- Some lesions may accept SQL70 biopolymer more easily than others, and leakage may occur if the lesion is resistant to SQL70 biopolymer injection. In such cases, the health care provider should apply slow, steady pressure, moving the needle slightly if necessary.

Management:

- If the patient reports pain after injection, apply an ice pack to the injection site for 5 to 10 minutes, apply compression to the site, and elevate at or above heart level if possible.
- In the event of any acute hypersensitivity reactions, the patient may be treated with histamine 1 blocking agents, histamine 2 blocking agents, and acetaminophen.
- In the unlikely event of a severe systemic reaction, corticosteroids and/or epinephrine may be appropriate followed by careful monitoring of vital signs and clinical status.

7.5.2. Management of SQP33 Protodrug Infusion Reactions

Investigators should monitor the patient for infusion reactions, including vitals as outlined in section 6.6 Vital Signs.

Investigator should monitor patients and precautions should be observed during the administration of SQP33 protodrug. Emergency agents including oxygen, oral and endotracheal airways, intubation equipment epinephrine, antihistamines, and corticosteroids should be available and used if required at the Investigator's discretion.

Patients should be instructed that symptoms associated with cytokine release syndrome / infusion reaction can occur within 48 hours following the administration of SQP33 protodrug, and if such symptoms develop while they are at home, they should contact the Investigator and/or seek emergency medical care if appropriate.

- Grade 2: stop infusion and treat symptoms following guidance in Table 8. If symptoms resolve within two hours, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr).
- Grade 3-4: stop infusion and treat symptoms following guidance in Table 8; no additional study treatment should be administered.

Table 8: Infusion-related Reaction Management Recommendations

Suspected Infusion Reaction	Recommended Treatment	
Mild toxicity requiring symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)	• Vigilant supportive care • Maintain adequate hydration • Antipyretics, nonsteroidal anti-inflammatory drugs, antihistamines, anti-emetics, analgesics as needed • In case of mild symptoms persisting for > 24 hours assess for infections; empiric treatment of concurrent bacterial infections	
Symptoms or clinical findings requiring and responding to moderate intervention, such as: • O^2 requirement < 40% • Hypotension responsive to fluids ± low dose of 1 vasopressor (e.g., < 50 mg/min of phenylephrine) • CTCAE Grade 2 organ toxicity	No extensive comorbidities or Age ≤ 70 years	• All of the above AND • Monitor cardiac and other organ functions closely
	Extensive comorbidities or Age ≥ 70 years	• All of the above AND • Corticosteroids
Symptoms or clinical findings requiring aggressive intervention, such as: • O^2 requirement ≥ 40% • Hypotension requiring high dose or multiple vasopressors • Ventilator support required • CTCAE ≥ Grade 3 organ toxicity	• All of the above AND • Corticosteroids	

7.5.3. Management of SQP33 Protodrug Extravasation

Upon IV administration of SQP33 protodrug, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. Preclinical data from animals who received SQP33 did not suggest that SQP33 acted as a vesicant. The preclinical findings at the injection site consisted of minimal to slight inflammation and changes typically associated with indwelling catheters (see SQ3370 Investigators Brochure for details). **If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated** and treated according to local study site procedures or per institutional practice for conventional Dox.

The infusion should then be restarted in another vein.

Although local tissue injury has not been observed in animal studies, if extravasation is suspected, the Sponsor recommends considering the precautions used for conventional Dox infusions:

- Intermittent application of ice to the site for 15 minutes, 4 times daily for 3 days may be useful.
- Because of the progressive nature of conventional Dox extravasation reactions, close observation and plastic surgery consultation should be considered.

7.5.4. Management of Potential Myocardial Toxicity and ECHO / MUGA Changes

SQ3370 should be stopped at the first sign of impaired cardiac function. ECG changes such as dysrhythmias or conduction delays may be indicative of anthracycline-induced cardiomyopathy. A 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of 45% or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function. In general, if test results indicate deterioration in cardiac function associated with SQ3370, the benefit of continued treatment should be carefully evaluated against the risk of producing irreversible cardiac damage. Acute life-threatening arrhythmias have been reported to occur during or within a few hours after conventional Dox administration.

Other events such as myocardial infarction, anginal symptoms, elevated serum troponin-T, or symptoms or signs of new congestive heart failure should be reported to the Sponsor immediately and Investigational Product administration should be halted. The patient should be evaluated and if there appears to be significant evidence of myocardial injury, study treatment should be discontinued permanently.

7.5.5. Management of Myelosuppression

Myelosuppression is a well-known toxicity of Dox and may be dose-limiting for SQ3370. Standard oncologic management of cytopenias, including neutropenia, febrile neutropenia and sepsis or bleeding due to thrombocytopenia should be instituted if indicated.

7.5.6. Management of Hepatotoxic Risk

Investigators should monitor the patient for elevated levels of AST and/or ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury and investigational treatment should be stopped as they are considered potential cases of drug-induced liver injury (DILI).

The following laboratory values should be evaluated for Hy's Law cases taking into consideration specific clinical symptoms of the patient and evaluation of other causes of hepatic impairment:

- Aminotransferases (AT), ALT or AST elevation > 3 times the upper limit of normal (ULN); AND
- Total bilirubin (TBL) > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase); AND

- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including but not limited to viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Patients with labs that are suspicious of DILI should return to the clinic as soon as possible, or at least within 48 hours, to be evaluated with laboratory tests, a detailed history and physical assessment.

The possibility of other causes for elevated liver function tests should be evaluated. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) at a minimum may be warranted.

If on the repeat laboratory testing for drug induce liver injury (DILI), results continue to meet the threshold listed above, and after a thorough evaluation for alternative explanations fail to provide a clear clinical explanation, the ongoing hepatic injury, per protocol, the diagnosis should be DILI. ALL investigational treatment should be stopped as they are considered potential cases of drug-induced liver injury.

7.6. DOSE MODIFICATIONS

7.6.1. Missed Doses

SQL70 Biopolymer Missed Doses: The injection of SQL70 biopolymer cannot be missed; it must be injected prior to SQP33 protodrug infusion. If the SQL70 biopolymer injection is missed on Day 1 of any cycle, alert the Medical Monitor immediately and do not inject SQP33 protodrug.

SQP33 Protodrug Missed Doses: Missed infusions of SQP33 protodrug may be made up, but only on Day 6. The Medical Monitor should be alerted immediately in the case of any missed infusions.

> Example: SQP33 protodrug infusions occur as scheduled on Day 1 and Day 2, but, due to extenuating circumstances (snowstorm, family emergency, etc.), the patient cannot attend their Day 3 visit. The Day 3 SQP33 protodrug infusion and other study procedures are therefore skipped and dosing resumes on Day 4 and Day 5. The missed dose may be made up on Day 6. If the dose cannot be made up on Day 6, then the patient only receives 4 infusions (Day 1, 2, 4, and 5) during that cycle.

7.6.2. Dose Reductions

SQL70 Biopolymer Volume: The volumes of SQL70 biopolymer under study are 10 mL or 20 mL. Please consult the medical monitor if there are questions regarding the volume of SQL70 to be injected.

- **Dose reductions**:
  - **Phase 1:** The SQL70 biopolymer volume in the 20 mL group may be reduced from 20 mL to 10 mL if 20 mL is not tolerated. If a dose reduction occurred and two lesions are being treated the investigator will need to choose a single lesion to inject with 10 mL of SQL70 biopolymer.

- **Phase 2a:** The SQL70 biopolymer volume in the 20 mL group may be reduced from 20 mL to 10 mL if 20 mL is not tolerated.

SQP33 Protodrug Dose:

- **Dose reductions**:
  - **Phase 1 and Phase 2a:** If a patient does not tolerate their initial or subsequent dose level of SQP33 protodrug the patient may be treated with a 25% reduction in SQP33 protodrug dose.

7.6.3. SQ3370 Treatment Interruptions

The Medical Monitor should be notified if the Investigator intends to interrupt SQ3370 treatment either during or in between cycles for any reason.

8. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

8.1. ANALYSIS PLAN

The statistical analysis plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses and procedures for accounting for missing, unused, and spurious data described in this section.

8.2. ANALYSIS POPULATION

The following populations are defined for statistical purposes:

Population	Description
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	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	All patients who received at least 1 dose of SQL70 biopolymer and/or SQP33 protodrug
PK	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	All patients with available biomarker data

8.3. DETERMINATION OF SAMPLE SIZE

Phase 1 Dose Escalation: Sample size for the dose escalation portion of the study is not predefined; total enrollment will depend on the DLTs observed and number of escalation cohorts.

Phase 2a Expansion Groups:

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 Table 9.

Table 9: Simon 2-Stage Design

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

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 subjects 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 subjects 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 cohort.

Table 10: 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 cohort, 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 cohort.

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.

8.4. STATISTICAL ANALYSES

8.4.1. Safety Analyses

Safety and tolerability will be summarized using AEs, SAEs, DLTs, deaths, events of special interest, events leading to discontinuation, and laboratory parameters for all participants who have received at least 1 dose of study treatment. 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.

8.4.2. Efficacy Analyses

8.4.2.1. Primary Endpoint

There are no efficacy analyses planned as part of the primary endpoint.

8.4.2.2. Secondary Endpoints

The endpoints below will be assessed by the Investigators. Time to event variables will be estimated using K-M methodology. Medians using the log-log transformation will be computed. Binary variables will be summarized by binomial response rates and their corresponding two-sided 95% exact CI. Quantitative variables will be summarized using the mean, median, minimum, and maximum values, and standard deviation. Categorical variables will be summarized using tables presenting counts and percentages for each category. Further explanation, description, and landmark analyses (e.g., at 12, 24 months) will be provided in the statistical analysis plan finalized before the first database lock.

- ORR is defined as the number and percentage of participants with a 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.
- DCR is defined as the proportion of participants whose BOR is CR or PR or SD among all randomized participants.

- DoR 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.
- Histopathologic Response
- Surgical outcome amputation/limb salvage vs. planned
- 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.
- 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.
- 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.
- Disease-free survival is defined as the time between the date of enrollment and the date of recurrence/relapse or death from any cause, whichever occurs first.
- PFS is defined as the time between the date of enrollment and the date of the initial objectively documented tumor progression per RECIST v1.1 or date of death from any cause, whichever occurs first.
- Time from enrollment to first subsequent therapy (TFST) is defined as the time between the date of enrollment to the date of first new anti-cancer therapy.
- OS is defined as the time between the date of enrollment to the date of death from any cause.

8.4.2.3. Exploratory Endpoints

Will be described in the statistical analysis plan finalized prior to first database lock.

- 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.
- Change in size of target lesion(s) (including both injected, if available, and non-injected tumors) is defined as the best percent change from baseline in the sum of diameters.

8.4.3. Biomarker Analyses

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. Further description will be provided in the statistical analysis plan.

PK in tumor and plasma and binary variable exploratory analyses will be described in the statistical analysis plan finalized before the first database lock.

8.5. INTERIM ANALYSES

There will be no formal interim analyses performed for this study. Data will be reviewed by the SRC for each dose escalation cohort (Phase 1) and for the safety run-ins in the Expansion Groups (Phase 2a). See section 3.2.7 Safety Review Committee.

9. DATA COLLECTION AND MANAGEMENT

9.1. DATA QUALITY ASSURANCE

The Sponsor or designee maintains a study-specific Data Management Plan, which includes specific procedures to ensure data quality. Study sites are responsible for data entry into the study-specific EDC system. In the event of discrepant data, the Sponsor or designee will request data clarification from the study sites, which the study sites will resolve electronically within the EDC system. CRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor or designee and records retention for the study data will be consistent with the Sponsor or designee's standard procedures.

9.2. SOURCE DATA DOCUMENTATION

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Study Monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered onto the CRFs are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

To facilitate source data verification, the Investigators and study sites must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/IEC review. The study site must also allow inspection by applicable health authorities.

9.3. CASE REPORT FORMS

CRFs are to be completed through use of a study-specific EDC system. Study sites will receive training and have access to guidelines for appropriate CRF completion. CRFs will be submitted electronically to the Sponsor or its designee and should be handled in accordance with instructions from the Sponsor or its designee.

All CRFs should be completed by designated, trained study site staff.

In accordance with Federal Regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The Principal Investigator will

approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

At the end of the study, the Investigator will receive patient data for his or her study site in a readable format that must be kept with the study records.

9.4. USE OF COMPUTERIZED SYSTEMS / ELECTRONIC HEALTH RECORDS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

10. QUALITY ASSURANCE & ETHICAL CONSIDERATIONS

10.1. COMPLIANCE WITH LAWS AND REGULATIONS

The study will be initiated and conducted under the sponsorship of Shasqi, Inc.

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the US or under a US Investigational New Drug (IND) application will comply with US FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU), or European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC). Studies conducted in Australia will comply with the National Statement (2007).

10.2. RESEARCH OUTSIDE THE TERMS OF THIS PROTOCOL

The Sponsor has a legal responsibility to report fully to the regulatory authorities all the results of administration of its Investigational Products. No investigative procedures other than those described in this protocol shall be undertaken on patients enrolled in this study (unless required for the care of the patient), without the agreement of the IRB/IEC and the Sponsor. The nature and results of any such procedures must be recorded and reported to the Sponsor or designee. The consent of the patients must be obtained before any such procedures are undertaken.

The investigational product provided to the Investigator for use under this protocol may not be used for any other purpose, including another study, compassionate use, or personal use.

10.3. INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/IEC by the Principal Investigator and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments.

In addition to the requirements for reporting all AEs to the Sponsor, Investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site’s study file.

10.4. INFORMED CONSENT

See section 6.1 Informed Consent.

10.5. PROTOCOL ADHERENCE & DEVIATIONS

Each Investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by the Sponsor or designee prior to seeking approval from the IRB/IEC. Each Investigator will be responsible for enrolling only those patients who have met protocol eligibility criteria.

The Investigator should document and explain any protocol deviations. The Investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor or designee and to the IRB/IEC in accordance with established IRB/IEC policies and procedures.

It is acknowledged that some protocol deviations may be inevitable due to COVID-19. These should be documented as such and reported as per the above. Consult with the Medical Monitor ahead of time, if possible, to discuss any necessary deviations to the protocol.

10.5.1. Important Protocol Deviations

Important protocol deviations are defined as those that potentially impact patient safety and/or data integrity and may include but are not limited to the following:

- Dosing errors
- Procedural errors
- Major violations of inclusion or exclusion criteria as determined by the Medical Monitor
- Delayed or non-reporting of SAEs
- Delays of greater than 14 days in scheduled CT scans

Important protocol deviations will be summarized and listed for the study using the Safety Population.

10.6. MONITORING AND STUDY SITE INSPECTIONS

This study will be monitored by an authorized Sponsor representative in accordance with current ICH GCP guidelines and other applicable regulations and guidelines. Study site visits will be performed for the purpose of inspection of all study-related materials and data, patients' medical records, and eCRFs. At any time, each study site may be audited either by Sponsor personnel, or by a contractor acting on behalf of the Sponsor, or by a regulatory agency such as the FDA.

10.7. RECORDS AND RECORD RETENTION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approval. In addition, at the end of the

study, the Investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

In accordance with US FDA regulations, the Investigator shall retain records for a period of:

- At least 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or,
- If no application is to be filed or if the application is not approved for such indication, until at least 2 years after the investigation is discontinued and FDA is notified.

In accordance with Australian TGA requirements, the sponsor shall retain records for a period of at least 15 years following the completion of a clinical trial.

No records may be disposed of without the written approval of the Sponsor or designee. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Records and documents pertaining to the conduct of this study and the distribution of Investigational Product include but are not limited to CRFs, ICFs, laboratory test results and shipping records, Investigational Product inventory records, the Investigator's Brochure, signed Financial Disclosures, Delegation of Responsibilities log, training records, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB/IEC correspondence and approval, signed patient ICFs).

10.8. CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. Information obtained during the conduct of this study will be collected, processed, and transmitted to or for the benefit of the Sponsor in accordance with applicable law, as discussed below.

Information contained therein will be maintained in accordance with applicable law protecting patient privacy and may be inspected by the clinical researcher, the researcher's staff, and the Sponsor and its representatives to check, process, evaluate, and use the information collected during the study. Processing, evaluation, or use of the information will be performed by a health professional for medical purposes and/or by those operating under a duty of confidentiality that is equivalent to that of a health professional. Information will be transmitted and processed as the Sponsor may direct, including to the Sponsor and its representatives in the US or elsewhere.

Information obtained from the study will likely be used by the Sponsor in connection with the development of the study drug, including possible filing of applications with governmental authorities for marketing approval, and for other pharmaceutical and medical research purposes. The study Investigator is obliged to provide the Sponsor with complete test results and all data developed in this study. This information may be disclosed to other physicians who are conducting similar studies and to the FDA/applicable regulatory agencies as deemed necessary by the Sponsor. Patient-specific information may be provided to other appropriate medical personnel only with the patient's permission.

All Investigators and other research study personnel who process information from the study and are employed by or otherwise affiliated with the study site are bound by the confidentiality terms of the Clinical Study Agreement between the Sponsor or designee and the study site covering the conduct of this clinical study. Investigators and other personnel should refer to the Clinical Trial Agreement for the specific measures that must be taken to prevent unauthorized or unlawful processing or disclosure of data.

To ensure compliance with current Federal Regulations and the ICH GCP guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, applicable health authorities, the Sponsor, and the IRB/IEC for each study site.

10.9. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor or designee with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor or designee to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11. STUDY PUBLICATION AND AMENDMENTS

11.1. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The Sponsor will comply with all requirements for publication of study results.

The Sponsor intends to pursue publication of the results of the study both at scientific congresses and in peer-reviewed journals.

Sponsor approval is required for publication of any data subsets. Patient names and other personal data relating to an identified or identifiable patient (such as photographs, audio, videotapes, or other factors specific to physical, physiological, mental, economic, cultural, or social identity) may not be disclosed in any publication without prior written authorization from the Sponsor and the patient.

Authorship criteria for all publications of Shasqi-sponsored clinical trials are based on the International Committee of Medical Journal Editors (ICMJE) guideline “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” (ICMJE 2010). Authorship credit can be granted only to those who make substantial contributions to the publication.

11.2. PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor or designee. Protocol amendments will be submitted to the IRB/IEC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/IEC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

12. REFERENCES

ADRIAMYCIN (doxorubicin hydrochloride) injection [Australian Product Information], revised on 2019-06-11, and accessed on 2019-08-15. Source: http://secure.healthlinks.net.au/content/pf/retriever.cfm?product=pfpadrii10612

ADRIAMYCIN (doxorubicin hydrochloride) injection [United States Package Insert]. Bedford, United States (OH): Bedford Laboratories; April 2012.

Advisory Committee on Immunization Practices (ACIP). Altered Immunocompetence. General Best Practice Guidelines for Immunization. 2012. Accessed November 6, 2020. https://www.cdc.gov/vaccines/hcp/acip-recs/index.html

Albright CF, Graciani N, Han W, Yue E, Stein R, Lai Z, et al. Matrix metalloproteinase–activated doxorubicin prodrugs inhibit HT1080 xenograft growth better than doxorubicin with less toxicity. Mol Cancer Ther. 2005;4:751-60.

Arcamone F, Cassinelli G, Fantini G, Grein A, Orezzi P, Pol C, et al. Adriamycin, 14-hydroxydaunomycin: a new antitumor antibiotic from S. peucetius var. caesius. Biotechnol Bioeng. 1969;11:1101–10.

Baldus S, Heeschen C, Meinertz T, Zeiher AM, Eiserich JP, Munzel T, Simoons ML, Hamm CW, CAPTURE Investigators. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. Circulation. 2003;108:1440-1445, DOI: 10.1161/01.CIR.0000090690.67322.51

Bezu L, Gomes-de-Silva LC, Dewitte H, Breckpot K, Fucikova J, Spisek R, Galluzzi L, Kepp O, Kroemer G. Combinatorial strategies for the induction of immunogenic cell death. Front Immunol. 2015;6:187.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.

Cancer Genome Atlas Research Network. Comprehensive and Integrated Genomic Characterization of Adult Soft Tissue Sarcomas. Cell. 2017;171:950–65.

Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. Science. 2011;331:1559-64.

Chawla SP, Papai Z, Mukhametshina G, Sankhala K, Vasylyev L, Fedenko A, Khamly K, Ganjoo K, Nagarkar R, Wieland S, Levitt DJ. First-Line Aldoxorubicin vs Doxorubicin in Metastatic or Locally Advanced Unresectable Soft-Tissue Sarcoma: A Phase 2b Randomized Clinical Trial. JAMA Oncol. 2015 Dec;1(9):1272-80. doi: 10.1001/jamaoncol.2015.3101. PMID: 26378637.

Chibon F, Lesluyes T, Valentin T, Le Guellec S. CINSARC signature as a prognostic marker for clinical outcome in sarcomas and beyond. *Genes Chromosomes Cancer*. 2019;58(2): 124-129, doi: 10.1002/gcc.22703.

Chiong M, Wang ZV, Pedrozo Z, Cao DJ, Troncoso R, Ibacache M, Criollo A, Nemchenko A, Hill JA, Lavandero S. Cardiomyocyte death: mechanisms and translational implications. Cell Death Dis. 2011;2:e244, doi: 10.1038/cddis.2011.130.

Colombo C, Baratti D, Kusamura S, Deraco M, Gronchi A. The role of hyperthermic intraperitoneal chemotherapy (HIPEC) and isolated perfusion (ILP) interventions in sarcoma. J Surg Oncol. 2015;111:570-9.

Cooley T, Henry D, Tonda M, Sun S, O'Connell M, Rackoff W. A randomized, double-blind study of pegylated liposomal doxorubicin for the treatment of AIDS-related Kaposi's sarcoma. Oncologist. 2007;12:114-23.

DeFeo-Jones D, Brady SF, Feng DM, Wong BK, Bolyar T, Haskell K, et al. A Prostate-specific Antigen (PSA)-activated Vinblastine Prodrug Selectively Kills PSA-secreting Cells in Vivo. Mol Cancer Ther. 2002;1:451-9.

DeFeo-Jones D, Garsky VM, Wong BK, Feng DM, Bolyar T, Haskell K, et al. A peptideaivre -doxorubicin 'prodrug' activated by prostate-specific antigen selectively kills prostate tumor cells positive for prostate-specific antigen in vivo. Nat Med. 2000;6:1248-52.

DiPaola RS, Rinehart J, Nemunaitis J, Ebbinghaus S, Rubin E, Capanna T, Ciardella M, Doyle-Lindrud S, Goodwin S, Fontaine M, Adams N, Williams A, Schwartz M, Winchell G, Wickersham K, Deutsch P, Yao SL. Characterization of a novel prostate-specific antigen–activated peptide-doxorubicin conjugate in patients with prostate cancer. J Clin Oncol. 2002;20:1874-9.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guidelines (version 1.1). Eur J Cancer. 2009;45:228-47.

Faivre S, Alsabe H, Djafari L, Janot F, Julieron M, Domenge C, Djazouli K, Armand JP, Luboinski B, Raymond E. Locoregional effects of pegylated liposomal doxorubicin (Caelyx) in irradiated area: a phase I-II study in patients with recurrent squamous cell carcinoma of the head and neck. Eur J Cancer. 2004 Jul;40(10):1517-21.

Frustaci S, Gherlinzoni F, De Paoli A, Bonetti M, Azzarelli A, Comandone A, Olmi P, Buonadonna A, Pignatti G, Barbieri E, Apice G, Zmerly H, Serraino D, Picci Pet al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol. 2001;19:1238-47.

Ghigo A, Li M, Hirsch E. New signal transduction paradigms in anthracycline-induced cardiotoxicity. Biochim Biophys Acta. 2016;1863:1916-25.

Harrington KJ, Lewanski C, Northcote AD, Whittaker J, Peters AM, Vile RG, Stewart JSW, Phase II study of pegylated liposomal doxorubicin (Caelyx™) as induction chemotherapy for patients with squamous cell cancer of the head and neck, European Journal of Cancer, Volume 37, Issue 16, 2001, Pages 2015-2022.

International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals: Writing and editing for biomedical publication. J Pharmacol Pharmacother. 2010;1(1):42-58.

Jain D. Cardiotoxicity of doxorubicin and other anthracycline derivatives. J Nucl Cardiol, 2000;7:53-62.

Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, Kerst JM, Sufliarsky J, Whelan J, Hohenberger P, Krarup-Hansen A, Alcindor T, Marreaud S, Litière S, Hermans C, Fisher C, Hogendoorn PC, dei Tos AP, van der Graaf WT; European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014 Apr;15(4):415-23. doi: 10.1016/S1470-2045(14)70063-4. Epub 2014 Mar 5. PMID: 24618336.

Kratz F, Ehling G, Kauffmann HM, Unger C. Acute and repeat-dose toxicity studies of the (6-maleimidocaproyl)hydrazone derivative of doxorubicin (DOXO-EMCH), an albumin-binding prodrug of the anticancer agent doxorubicin. Hum Exp Toxicol. 2007;26:19-35.

Lefrak EA, Pitha J, Rosenheim S, Gottlieb JAet al. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer. 1973;32:302-14.

Liebner DA. The indications and efficacy of conventional chemotherapy in primary and recurrent sarcoma. J Surg Oncol. 2015;111:622-31.

Lipshultz SE, Lipsitz SR, Mone SM, Goorin AM, Sallan SE, Sanders SP,Orav EJ, Gelber RD, Colan SD. Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med. 1995;332:1738-43.

Mattarollo SR, Loi S, Duret H, Ma Y, Zitvogel L, Smyth MJ. Pivotal role of innate and adaptive immunity in anthracycline chemotherapy of established tumors. Cancer Res. 2011;71:4809-20.

McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM, Yellon DM. Anthracycline Chemotherapy and Cardiotoxicity. Cardiovasc Drugs Ther. 2017;31:63–75.

Mejia Oneto JM, Khan I, Seebald L, Royzen M. In vivo bioorthogonal chemistry enables local hydrogel and systemic pro-drug to treat soft tissue sarcoma. ACS Cent Sci. 2016;2:476-82.

Mita MM, Natale RB, Wolin EM, Laabs B, Dinh H, Wieland S, Levitt DJ, Mita AC. Pharmacokinetic study of aldoxorubicin in patients with solid tumors. Invest New Drugs. 2015;33:341-8.

Okuno SH, Mailliard JA, Suman VJ, et al. Phase II study of methotrexate, vinblastine, doxorubicin, and cisplatin in patients with squamous cell carcinoma of the upper respiratory or alimentary passages of the head and neck. Cancer. 2002 Apr;94(8):2224-2231. DOI: 10.1002/cncr.10442. PMID: 12001121.

Pfirschke C, Engblom C, Rickelt S, Cortez-Retamozo V, Garris C, Pucci F, Yamazaki T, Poirier-Colame V, Newton A, Redouane Y, Lin YJ, Wojtkiewicz G, Iwamoto Y, Mino-Kenudson M, Pisani, P., Airoldi, M., Allais, A., Aluffi Valletti, P., Battista, M., Benazzo, M., Briatore, R., Cacciola, S., Cocuzza, S., Colombo, A., Conti, B., Costanzo, A., Della Vecchia, L., Denaro, N., Fantozzi, C., Galizia, D., Garzaro, M., Genta, I., Iasi, G. A., Krengli, M., … Zigliani, A. (2020). Metastatic disease in head & neck oncology. *Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale*, *40*(SUPPL. 1), S1–S86. https://doi.org/10.14639/0392-100X-suppl.1-40-2020

Prescriber's Digital Reference. Doxorubicin Hydrochloride – Drug Summary. Accessed November 16, 2022. https://www.pdr.net/drug-summary/Doxorubicin-Hydrochloride-doxorubicin-hydrochloride-1876.2972

Price KA, Cohen EE. Current treatment options for metastatic head and neck cancer. Curr Treat Options Oncol. 2012 Mar;13(1):35-46. doi: 10.1007/s11864-011-0176-y. PMID: 22252884.

Rios Doria J, Durham N, Wetzel L, Rothstein R, Chesebrough J, Holoweckyj N, Zhao W, Leow CC, Hollingsworth R. Doxil synergizes with cancer immunotherapies to enhance antitumor responses in syngeneic mouse models. Neoplasia. 2015;17:661-70.

Ryan CW, Merimsky O, Agulnik M, Blay JY, Schuetze SM, Van Tine BA, Jones RL, Elias AD, Choy E, Alcindor T, Keedy VL, Reed DR, Taub RN, Italiano A, Garcia Del Muro X, Judson IR, Buck JY, Lebel F, Lewis JJ, Maki RG, Schöffski P. PICASSO III: A Phase III, Placebo-Controlled Study of Doxorubicin With or Without Palifosfamide in Patients With Metastatic Soft Tissue Sarcoma. J Clin Oncol. 2016 Nov 10;34(32):3898-3905. doi: 10.1200/JCO.2016.67.6684. Epub 2016 Sep 30. PMID: 27621408.

Sandler S, Bonomi P, Taylor B, Showel J, Slayton R, Lerner H. Doxorubicin and cisplatin for recurrent or metastatic squamous cell carcinoma of the head and neck. *Cancer Treat Rep.* 1984 Sep;68(9):1163-5.

Sarcoma Statistics. Australian Government Cancer Australia Web site. https://sarcoma.canceraustralia.gov.au/statistics. Updated August 26, 2019. Accessed August 30, 2019.

Savina M, Le Cesne A, Blay JY, Ray-Coquard I, Mir O, Toulmonde M, Cousin S, Terrier P,Ranchere-Vince D, Meeus P, Stoeckle E, Honoré C, Sargos P, Sunyach MP, Le Péchoux C, Giraud A, Bellera C, Le Loarer F, Italiano A. Patterns of care and outcomes of patients with METAstatic soft tissue SARComa in a real-life setting: the METASARC observational study. BMC Med. 2017 Apr 10;15(1):78. doi: 10.1186/s12916-017-0831-7. PMID: 28391775; PMCID: PMC5385590.

Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, Cohen V, Banchs J, Carver JR, Wiegers SE, Martin RP, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Cir. Cardiovasc. Imaging*. 2012;5(5):596-603, DOI: 10.1161/CIRCIMAGING.112.973321.

Schöffski P, Delord JP, Brain E, Robert J, Dumez H, Gasmi J, Trouet A-. First-in-man phase I study assessing the safety and pharmacokinetics of a 1hour intravenous infusion of the doxorubicin prodrug DTS-201 every 3 weeks in patients with advanced or metastatic solid tumours. Eur J Cancer. 2017 Nov;86:240-247.

Seddon B, Strauss SJ, Whelan J, Leahy M, Woll PJ, Cowie F, Rothermundt C, Wood Z, Benson C, Ali N, Marples M, Veal GJ, Jamieson D, Küver K, Tirabosco R, Forsyth S, Nash S, Dehbi HM, Beare S. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. Lancet Oncol. 2017 Oct;18(10):1397-1410. doi: 10.1016/S1470-2045(17)30622-8. Epub 2017 Sep 4. PMID: 28882536; PMCID: PMC5622179.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7-34.

Simon R, Freidlin B, Rubinstein L, Arbuck SG, Collins J, Christian MC. Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst. 1997;89:1138-47.

Skovgaard D, Hasbak P, Kjaer A. BNP predicts chemotherapy-related cardiotoxicity and death: comparison with gated equilibrium radionuclide ventriculography. *PLoS One.* 2014;9(5), e96736, doi: 10.1371/journal.pone.0096736.

Smith HG, Thomas JM, Smith MJF, Hayes AJ, Strauss DC. Major Amputations for Extremity Soft-Tissue Sarcoma. Ann Surg Oncol. 2018 Feb;25(2):387-393. doi: 10.1245/s10434-017-5895-2. Epub 2017 May 25. PMID: 28547562.

Tap WD, Papai Z, Van Tine BA, Attia S, Ganjoo KN, Jones RL, Schuetze S, Reed D, Chawla SP, Riedel RF, Krarup-Hansen A, Toulmonde M, Ray-Coquard I, Hohenberger P, Grignani G, Cranmer LD, Okuno S, Agulnik M, Read W, Ryan CW, Alcindor T, Del Muro XFG, Budd GT, Tawbi H, Pearce T, Kroll S, Reinke DK, Schöffski P. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial. Lancet. 2017;18:1089-1103. doi: 10.1016/S1470-2045(17)30381-9. Epub 2017 Jun 23. Erratum in: Lancet Oncol. 2018 Feb;19(2):e78. PMID: 28651927; PMCID: PMC7771354.

Unger C, Häring B, Medinger M, Drevs J, Steinbild S, Kratz F, Mross K. Phase I and Pharmacokinetic Study of the (6-Maleimidocaproyl) Hydrazone Derivative of Doxorubicin. Clin Cancer Res. 2007;13:4858-66.

Verschoor AJ, Litière S, Marréaud S, Judson I, Toulmonde M, Wardelmann E, LeCesne A, Gelderblom H. Survival of soft tissue sarcoma patients after completing six cycles of first-line anthracycline containing treatment: an EORTC-STBSG database study. Clin Sarcoma Res. 2020 Sep 9;10:18. doi: 10.1186/s13569-020-00137-5. PMID: 32944214; PMCID: PMC7488114.

Wheeler, G.M., Mander, A.P., Bedding, A. *et al.* How to design a dose-finding study using the continual reassessment method. *BMC Med Res Methodol* **19,** 18 (2019). https://doi.org/10.1186/s12874-018-0638-z

Whelan RS, Kaplinskiy V, Kitsis RN. Cell death in the pathogenesis of heart disease: mechanisms and significance. Annu Rev Physiol. 2010;72:19-44.

Win T, Naing TT, Win TT, Aung KK, Htun YY. Implications of plasma deoxyribonucleic acid topoisomerase 2 beta (TOP2B) level in breast cancer patients receiving doxorubicin-based chemotherapy. Ann. Oncology, 2018; 29(Suppl-9).

Working PK, Dayan AD. Pharmacological-toxicological expert report. CAELYX. (Stealth liposomal doxorubicin HCl). Hum Exp Toxicol. 1996;15:751-85.

Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. Immunity. 2013;39:74-88.

APPENDIX A – SPONSOR APPROVAL

Clinical Development Approved By Name, Signature & Date	DocuSigned by: Scott Wieland Signer Name: Scott Wieland Signing Reason: I approve this document Signing Time: 18-Nov-2022 | 6:02 AM PST 8AD417DC5BF147FB89AE91D5C37F3097 Scott Wieland, Ph.D, Sr. VP Clinical Development, Shasqi Inc.
Chief Medical Officer Approved By Name, Signature & Date	DocuSigned by: Steven Abella Signer Name: Steven Abella Signing Reason: I approve this document Signing Time: 18-Nov-2022 | 4:17 AM PST 32F1E8DBAAA24618A248AE720DC30D7C Steve Abella, M.D., Chief Medical Officer, Shasqi Inc.

APPENDIX B – RECIST V1.1

The Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (2009) can be viewed on-line at the following Web site:

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

APPENDIX C – EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS ASSESSMENT

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
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 house work, 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 selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX D – NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

The Cancer Therapy Evaluation Program NCI-CTCAE version 5.0 (November 27, 2017) can be viewed on-line at the following NCI Web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

APPENDIX E – COLLECTION OF PREGNANCY INFORMATION

- The Investigator will attempt to collect pregnancy information on:
  - Any dosed female patient who becomes pregnant while participating in this study
  - Any dosed male patient's female partner who becomes pregnant while the male patient is participating in this study (after obtaining the necessary signed ICF from the pregnant female partner directly)
- The initial information will be recorded on the appropriate pregnancy form and submitted to the sponsor via email to SAE@shasqi.com, within 24 hours of learning of the pregnancy.
- The mother will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is an AESI and not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the Investigational Product by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

APPENDIX F – PK SCHEDULE

Phase 1 Dose Escalation

CYCLE 1		
DAY	**PK Draw**	**PK Time Point Relative to SQP33 Protodrug Infusion**
Day 1	1	Pre-infusion
	2	5 min post-infusion (**+** 5 min)
	3	30 min post-infusion (± 5 min)
	4	1 h post-infusion (± 5 min)
	5	2 h post-infusion (± 10 min)
	6	4 h post infusion (± 10 min)
Day 2	7	24 h post-infusion (± 2.5 h) and Day 2 pre-infusion
	8	5 min post-infusion (+ 5 min)
	9	30 min post-infusion (± 5 min)
Day 3	10	Pre-infusion
	11	5 min post-infusion (+ 5 min)
	12	30 min post-infusion (± 5 min)
Day 4	13	Pre-infusion
	14	5 min post-infusion (+ 5 min)
	15	30 min post-infusion (± 5 min)
Day 5	16	Pre-infusion
	17	5 min post-infusion (+ 5 min)
	18	30 min post-infusion (± 5 min)
	19	1 h post-infusion (± 5 min)
	20	2 h post-infusion (± 10 min)
	21	4 h post infusion (± 10 min)

CYCLES 2, 3, & 4		
DAY	**PK Draw**	**PK Time Point Relative to SQP33 Protodrug Infusion**
Day 1	1	Pre-infusion
	2	5 min post-infusion (**+** 5 min)
	3	30 min post-infusion (± 5 min)
Day 2	4	24 h post-infusion (± 2.5 h) and Day 2 pre-infusion
Day 3	5	Pre-infusion
Day 4	6	Pre-infusion
Day 5	7	Pre-infusion

Note: Post dose PK timings are based on the end time of the SQP33 protodrug infusion, not the start.

Phase 2a Expansion Groups

Group 1: Extremity STS

Group 2: Unresectable STS (5-Day Infusion cohort)

	CYCLE 1	
DAY	**PK DRAW**	**TIMEPOINT**
Day 1	1	Pre-infusion
	2	15 min post-infusion (± 10 min)
	3	2 h post-infusion (± 30 min)
	4	4 h post infusion (± 30 min)
Day 2	5	Pre-infusion
	6	15 min post-infusion (± 10 min)
Day 3	7	Pre-infusion
	8	15 min post-infusion (± 10 min)
Day 4	9	Pre-infusion
	10	15 min post-infusion (± 10 min)
Day 5	11	Pre-infusion
	12	15 min post-infusion (± 10 min)
	13	2 h post-infusion (± 30 min)
	14	4 h post infusion (± 30 min)

	CYCLE 2	
DAY	**PK DRAW**	**TIMEPOINT**
Day 1	1	Pre-infusion
	2	15 min post-infusion (± 10 min)
Day 2	-	No draws
Day 3	3	Pre-infusion
	4	15 min post-infusion (± 10 min)
Day 4	-	No draws
Day 5	5	Pre-infusion
	6	15 min post-infusion (± 10 min)

Phase 2a Expansion Groups

Group 2: Unresectable STS (3-Day Infusion cohort)

	CYCLE 1	
DAY	**PK DRAW**	**TIMEPOINT**
Day 1	1	Pre-infusion
	2	15 min post-infusion (± 10 min)
	3	2 h post-infusion (± 30 min)
	4	4 h post infusion (± 30 min)
Day 2	5	Pre-infusion
	6	15 min post-infusion (± 10 min)
Day 3	7	Pre-infusion
	8	15 min post-infusion (± 10 min)
	9	2 h post-infusion (± 30 min)
	10	4 h post infusion (± 30 min)

	CYCLE 2	
DAY	**PK DRAW**	**TIMEPOINT**
Day 1	1	Pre-infusion
	2	15 min post-infusion (± 10 min)
Day 2	-	No draws
Day 3	3	Pre-infusion
	4	15 min post-infusion (± 10 min)

Phase 2a Expansion Groups

Group 3a: Head and Neck

	CYCLE 1	
DAY	**PK DRAW**	**TIMEPOINT**
Day 1	1 2 3 4	Pre-infusion 15 min post-infusion (± 10 min) 2 h post-infusion (± 30 min) 4 h post infusion (± 30 min)
Day 2	-	No draws
Day 3	-	No draws
Day 4	-	No draws
Day 5	5 6 7 8	Pre-infusion 15 min post-infusion (± 10 min) 2 h post-infusion (± 30 min) 4 h post infusion (± 30 min)

APPENDIX G – SCHEDULE OF ASSESSMENTS – PHASE 1 DOSE ESCALATION

CYCLES 1 - 4 TREATMENT SCHEDULE

		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 [C]				
	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		

Reminder: 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 FU AND LONG-TERM FU SCHEDULE

		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]				
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

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.

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.

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

APPENDIX H – 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 APPENDIX H – Schedule of Assessments – 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.

APPENDIX I – SCHEDULE OF ASSESSMENTS – 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 APPENDIX I – Schedule of Assessments –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.

APPENDIX J – SCHEDULE OF ASSESSMENTS – EXPANSION GROUP 2: UNRESECTABLE STS (3 DAY)

Study Day		Screening	Treatment				SFTY FU	LTFU
			Week 1			Week 2		
		Day -28 to Day -1	Day 1 [A]	Day 2	Day 3	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 APPENDIX J – Schedule of Assessments –EXPANSION GROUP 2: UNRESECTABLE (3 DAY)

A - Day 1-3 can begin on any day that allows for the completion of the three consecutive treatments within 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.

APPENDIX K – SCHEDULE OF ASSESSMENTS – EXPANSION GROUP 3A: 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 APPENDIX K – Schedule of Assessments –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.