First-in-human Phase I Study of SQ3370, a Click Activated Protodrug Therapy, in Patients with Soft Tissue Sarcomas and Other Advanced Solid Tumors

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CAPAC™ and SQ3370 Overview

Anthracyclines, such as doxorubicin, are regarded as the first-line treatment of choice for soft tissue sarcoma (STS) and other solid tumors. Unfortunately, objective responses are uncommon and risks of serious adverse events such as cardiotoxicity limit treatment to a maximum of 4-5 months.

Shasqi's lead candidate, SQ3370, represents a new therapeutic modality to treat STS and other solid tumors by using a drug with known efficacy, doxorubicin, and expanding its pharmacological capabilities while minimizing its systemic toxicity. SQ3370 utilizes Shasqi's proprietary Click Activated Protodrugs Against Cancer (CAPAC™) platform, a click chemistry-based approach that activates cancer drugs at a specific tumor with minimal systemic toxicity. Unlike targeted therapies, the CAPAC™ platform is agnostic to tumor characteristics that can vary across patients and hence applicable to several types of tumors. SQ3370 consists of 2 components, SQL70 biopolymer and SQP33 protodrug. SQL70 is a tetrazine-modified sodium hyaluronate biopolymer which functions by activating the protodrug inside the body and does not contain a therapeutically active ingredient. SQP33 is a trans-cyclooctene (TCO)-modified protodrug of Doxorubicin (Dox) with attenuated cytotoxic activity.

In preclinical mouse fibrosarcoma models, this approach demonstrated a clear therapeutic benefit and decreased adverse effects compared to conventional systemic therapy[1]. In dogs, this approach allowed an 8.95-fold increase in doxorubicin dosing with minimal systemic adverse events including cardiotoxicity. SQ3370 is the first click chemistry-based treatment to be used in humans.

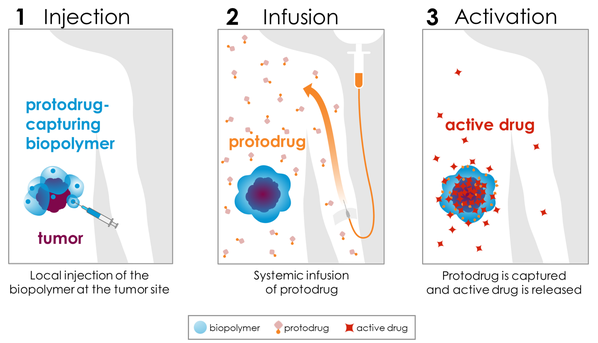


Figure 1: (**1**) SQL70 biopolymer is locally injected at the tumor site and (**2**) SQP33 protodrug is infused systemically. (**3**) SQP33 protodrug is activated by SQL70 biopolymer at the tumor site through a rapid covalent reaction between tetrazine and trans-cyclooctene moieties, followed by chemical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

[1]**JM Mejia Oneto**, et al. ACS Central Science, 2016.

Treatment

- A fixed amount of SQL70 biopolymer is injected on Day 1 of each 21-day cycle into a single lesion.
- SQP33 protodrug is infused after the SQL70 biopolymer injection on Day 1 QD until Day 5 (5 doses) for each 21-day cycle.

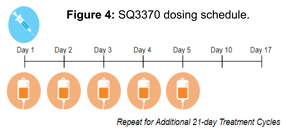
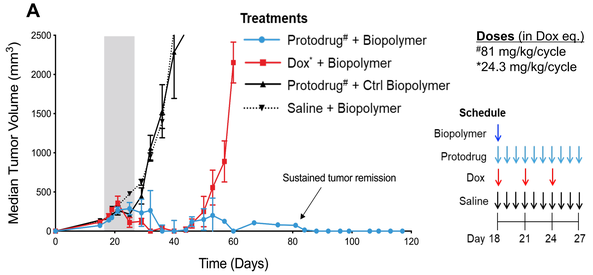


Figure 4: SQ3370 dosing schedule.

- 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.
- Patients may continue to receive treatment until they have either no injectable (as determined by the investigator) lesions, radiographic progression of disease per RECIST v1.1, unacceptable toxicity, or other treatment discontinuation criteria are met.

CAPAC™ Platform Improves Efficacy with Less Toxicity in Preclinical Sarcoma Model

CAPAC Protodrug Treatment Shows Greater Efficacy Over Conventional Dox



CAPAC Platform Enables Improved Safety Profile Over Conventional Therapy

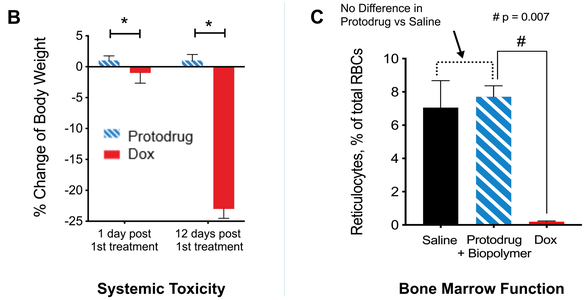


Figure 2: HT1080 fibrosarcoma xenograft in athymic nude mice. N = 5 mice in Doxorubicin (Dox) group, 4-7 mice in no therapy group, 10 mice in Dox Protodrug group. Plots show averages ± SEM.

*Reproduced from: [1]**JM Mejia Oneto**, et al. ACS Central Science, 2016.*

Study Objectives

Primary

- Assess the safety and tolerability of SQ3370, including determination of the maximum tolerated dose (MTD) and/or recommended Phase 2 dose.

Secondary

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

Exploratory

- Assess the concentration of active Dox and SQP33 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.

Study Design

- This multicenter, Phase 1, 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 that are refractory/relapsed following, or otherwise ineligible for, standard of care therapy.
  - ClinicalTrials.gov identifier: **NCT04106492.**

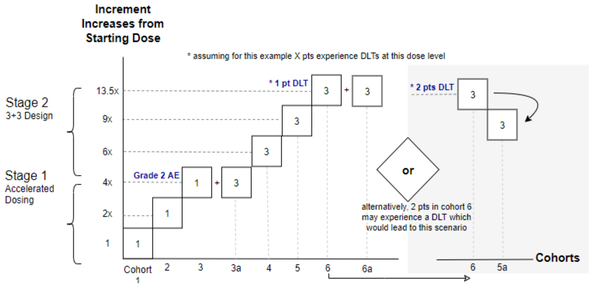


Figure 3: Dose-escalation trial design.

- The dose-escalation portion of the study will initially consist of a single-patient accelerated titration design (Stage 1) and then switch to a 3+3 design (Stage 2).

Assessments

- Tumor response will be assessed by the investigators using RECIST guidelines version 1.1.
- Blood (plasma) samples for determination of PK levels of SQP33 protodrug and active Dox following SQ3370 treatment to be collected from all patients.
  - PK bioanalysis will be conducted using validated LC/MS methods. Blood SQP33 protodrug and active Dox, following SQ3370 treatment, parameters will be calculated (if possible) from plasma concentrations, including C_{max} , T_{max} , AUC_t , AUC_{inf} , and CL/F.
- AEs and SAEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.
- Tumor biopsies and PBMCs will be collected to assess immune response and the concentration of active Dox and SQP33 at the local site following SQ3370 treatment.

Key Inclusion Criteria

- ≥ 18 years old
- local or advanced/metastatic solid tumor that is
  - responsive to anthracyclines
  - either refractory/relapsed or is ineligible for standard of care therapy
  - injectable defined as able to be injected with ultrasound guidance or palpable
  - not near vital structures or within a visceral organ
  - accessible for repeated intratumoral or peritumoral injection
- ECOG status score of 0-1
- Adequate
  - **Hematologic Function**:
    - ANC ≥ 1500 µL
    - Hemoglobin ≥ 9 g/dL
    - Platelet Count ≥ 100,000/µL
  - **Hepatic Function**:
    - Bilirubin ≤ 1.2 mg/dL
    - AST and ALT ≤ 3-times ULN
  - **Renal Function**:
    - Creatine Clearance ≥ 45 mL/min (Cockcroft-Gault)
  - **Coagulation Function**:
    - INR ≤ 1.5
    - PTT ≤ 5 seconds above ULN
- Resolution to Grade ≤ 1 of clinically significant toxicity of prior anti-cancer treatments

Key Exclusion Criteria

- Lifetime exposure to
  - >225 mg/m^2 Dox HCl, Doxil/Caelyx
  - 450 mg/m^2 of Epirubicin
  - 135 mg/m^2 of Daunorubicin
- Anticoagulants at therapeutic doses/known to cause abnormal coagulation/increase bleeding (incl. low dose ASA prophylaxis, oral Xa inhibitors, LMWH)
- CHF, severe myocardial insufficiency, cardiac arrythmia, or:
  - LVEF < 45%, QTc > 470 msec, history of QT prolongation, history/signs of active CAD, clinically significant cardiac arrhythmias, LBBB, high grade AV block
- Recent:
  - Chemotherapy, radiotherapy, other investigational product administration
  - Major surgery
  - Transfusion
  - Serious or systemic infection
- Positive HBsAb, and either positive HBsAg and/or detectable HBV DNA
- Resolved or treated hepatitis C virus
- Immunodeficiency
- Symptomatic pleural effusion, ascites, or pericardial fluid requiring drainage
- CNS metastases and/or carcinomatous meningitis or symptomatic brain mets
- Treated malignancies (exc. Palliative radiation) within 2 years (excl. resected NMSC, cervical CIS, and non-metastatic breast or prostate cancer)
- History of allergic reactions to the Investigational Product

Statistical Methods

- **Sample Size:**
  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. Patients will be replaced if they are enrolled into the study but do not receive (for reasons other than AEs/SAEs) a minimum of 4 doses of SQP33 protodrug.
- **Safety/Tolerability:**
  Electrocardiogram, vital signs, 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). 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 and ORR status will be summarized. Additionally, sub-set analyses will be performed on both injected and non-injected individual lesions.

Progress to Date

- As of October 1, 2020, the trial has begun at sites in the US and Australia, and 2 patients have been enrolled.

Summary

- SQ3370 is a promising new approach for the treatment of heterogeneous solid tumors including sarcomas.
- CAPAC™ based SQ3370 is completely independent of biomarkers and tumor biology and should be able to activate substantially higher doses of drug at the tumor, while limiting systemic exposure.
- SQ3370 is supported by broad *in vivo* anti-tumor activity and a positive therapeutic window in preclinical model systems.

Additional Info

- For more information please visit https://www.shasqi.com/.
- Visit our CTOS Preclinical Poster #207 (Abstract # 3465109) for our latest findings.
- Presented at the Connective Tissue Oncology Society Virtual Annual Meeting, November 18–21, 2020.