Early pharmacokinetic data from a Phase I study of SQ3370 (NCT04106492) in patients with advanced solid tumors provides proof-of-concept for the click chemistry-based CAPAC platform

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Presentation Number 547P | Contact: science@shasqi.com

CAPAC™ and SQ3370 Overview

SQ3370, a novel therapy that activates doxorubicin (Dox) at the tumor site while minimizing systemic exposure, is based on an intratumoral injection of a protodrug-activating tetrazine-modified sodium hyaluronate biopolymer (SQL70) followed by five daily intravenous (IV) doses of an attenuated *trans*-cyclooctene (TCO)-modified protodrug of Dox (SQP33). SQ3370 utilizes Shasqi's proprietary **C**lick **A**ctivated **P**rotodrugs **A**gainst **C**ancer (**CAPAC**) platform, a click chemistry-based approach that activates cancer drugs at an injected tumor with minimal systemic toxicity (Figure 1). SQ3370 is the first click chemistry-based treatment to be used in humans.

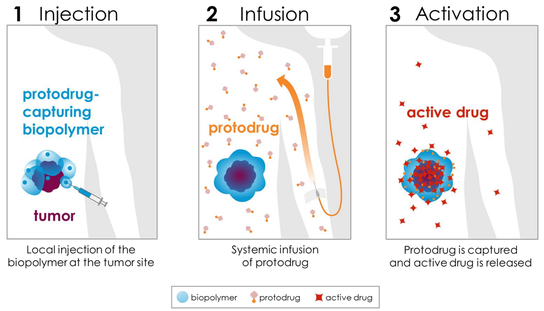


Figure 1: (**1**) SQL70 biopolymer is locally injected at the tumor site and (**2**) SQP33 protodrug is infused systemically. (**3**) SQP33 protodrug is activated by SQL70 biopolymer at the tumor site through a rapid covalent reaction between tetrazine and trans-cyclooctene moieties, followed by chemical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

Study Design

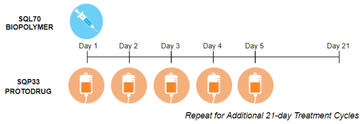
Phase 1, first-in-human, single-arm, open-label, dose-escalation study of SQ3370 in patients with locally advanced or metastatic solid tumors that are refractory/relapsed following, or otherwise ineligible for, standard of care therapy. The study has an accelerated titration design comprising initial single-patient cohorts and subsequent 3+3 cohorts.

Objective:

Safety, tolerability of SQ3370, and determination of the maximum tolerated dose and recommended Phase 2 dose.

Treatment:

- 10 mL of SQL70 biopolymer is injected on Day 1 of each 21-day cycle into a single lesion.
- SQP33 protodrug is infused after SQL70 biopolymer injection Day 1 through Day 5 (5 doses) each 21-day cycle.



Demographics and Dosing

- Enrolled patients received a mean of 2.33 prior systemic regimens.

Pt	Tumor Types	Prior Systemic Regimens	Prior Dox (mg/m^2)	SQ3370 Cycles Received	Total Dox Given as SQP33 (mg/m^2)#	Dox Equiv. Dose*
01	Chondrosarcoma	4	0	6	171	0.38x
02	Myxoinflammatory Fibroblastic Sarcoma	1	75	2	115	0.76x
03	Inflammatory Myofibroblastic Tumor	0	0	4	396	1.53x
04	Merkel Cell Carcinoma	1	0	1	208	2.8x
05	Unclassified Pleomorphic Sarcoma	3	140	2^	249	
06	Triple Negative Breast Cancer	3	233	2	413	
07	Leiomyosarcoma	4	225	5	1516	4x
09	Squamous Cell Carcinoma	2	0	4	1218	
11	Leiomyosarcoma	3	100	2	547	

All treated patients included; patient 08 and 10 failed screening.
milligram amount is shown as Dox molar equivalents. 1g of SQP33 contains an equimolar amount of Dox as 0.7153g of Dox HCl.
* Where 1x = 75 mg/m^2 of Dox (this applies to all other figures and tables where x is used to refer to dose/amount of SQ3370)
^ only received dose on Day 1 of cycle 2.

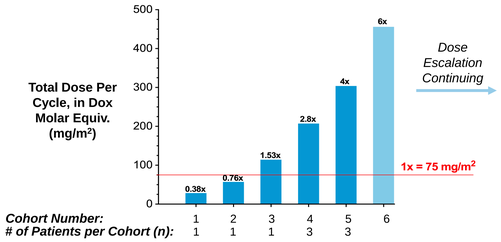


Figure 2: Dose escalation in Dox molar equivalents compared to clinical dose of Dox at 75 mg/m^2 (1x). Escalation is ongoing and dose level is 6x at the time of data cut-off.

Safety

- No dose-limiting toxicities have been observed to date.

Treatment Emergent AEs Occurring in ≥ 2 Subjects (n=9)

AE Term	Dose Levels (Dox Equiv. Dose)										Total N=9	
	.38x N=1		.76x N=1		1.53x N=1		2.8x N=3		4x N=3		All	Grade ≥ 3
	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3		
Fatigue	1	–	–	–	1	–	3	–	–	–	5	–
Nausea	–	–	1	–	1	–	2	1	1	–	5	1
Constipation	1	–	–	–	1	–	1	–	–	–	3	–
Pyrexia	–	–	–	–	–	–	2	–	1	–	3	–
Anaemia	–	–	–	–	–	–	1	–	1	–	2	–
Neutropenia	–	–	–	–	–	–	1	–	1	–	2	–
Oedema peripheral	–	–	–	–	1	–	1	–	–	–	2	–
Pain	–	–	1	–	–	–	1	1	–	–	2	1

– not observed
Treatment emergent AEs are regardless of attribution.

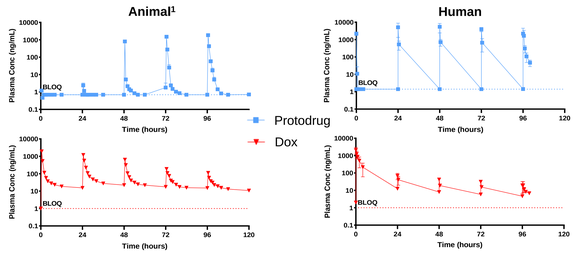
Treatment Emergent Grade ≥ 3 AEs (n=9)

Patient	Dox Equiv. Dose	AE Term	Relatedness#	Grade
01	.38x	Haemorrhagic transformation stroke	No	Grade 5^
01	.38x	Hypermagnesemia	No	Grade 3
03	1.53x	Flank Pain	No	Grade 3
06	2.8x	Nausea	Yes	Grade 3
06	2.8x	Pain	No	Grade 3

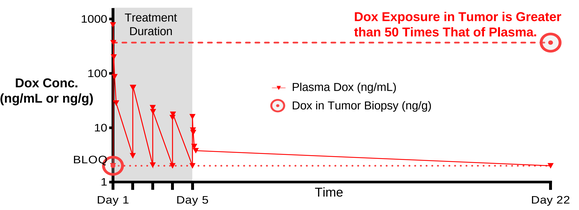
Investigator assessment
^ Occurred > than 4 weeks after last dose of SQ3370.

Pharmacokinetics

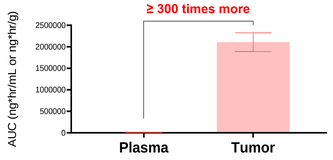
A **Pharmacokinetic Data is Consistent Between Animals and Humans**



B **Patient Plasma and Tumor Dox Concentrations Over 22 Days***



C **Rat PKPD Model Shows >300x Dox Exposure in Tumor Compared to Plasma**



D **Plasma Dox C_{max} and Exposure**

Dox Eq. Dose	.38x (n=1)	.76x (n=1)	1.53x (n=1)	2.8x (n=3)	4x (n=3)
C_{max} (ng/mL)	256	779	203	715.7 (±546.9)	2083 (±881)
AUC (0-inf) (ng*h/mL)	964*	1621*	1040*	2098 (±969)	6743 (±3114)

Figure 3: **A)** 5-day plasma concentration-time curves of SQP33 protodrug and active Dox in rats and humans (n=3, cumulative dose of 304 mg/m^2 Dox Eq [4x]) treated with SQ3370. Rats were given one SC SQL70 biopolymer injection 1 h before SQP33 protodrug dosing. 21.5 mg/kg/dose Dox Eq of SQP33 protodrug was administered IV at 0, 24, 48, 72, and 96 h. **B)** Plasma and tumor concentration-time curve for Patient 02. Dox was detected in tumor 3 weeks after start of treatment. **C)** Rat tumor and plasma Dox exposure was obtained using a a 5-compartment PBPK model. **D)** Table showing Dox C_{max} and AUC for all cohorts. Single patient cohort exposure was estimated with a two-compartment model fitted to data from each individual patient. Three patient cohort values show mean ± SD.
* Dox detected in 1 out of 6 patient tumor biopsies.

Swimmer's Plot

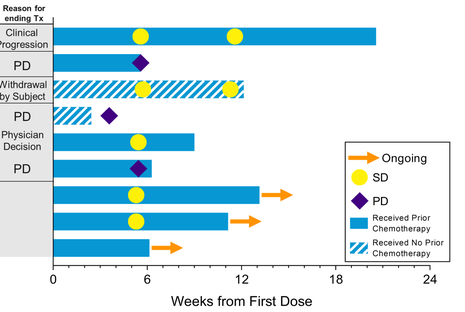


Figure 4: All treated patients are included. Patients 08 and 10 failed screening. Patient 07 showed progressive disease after 3 cycles of Dox / ifosfamide. Patient 09 showed progressive disease through prior carboplatin therapy.
Tx = treatment; SD = stable disease; PD = progressive disease per RECIST; N = no prior therapy. U = Unknown.

Percent Changes in Target Lesions

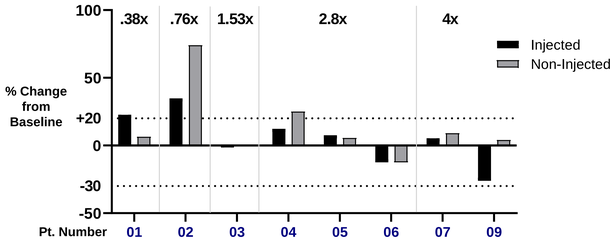


Figure 5: Percent change from baseline in injected and non-injected target lesions, based on most recent scan. Patient 03 had a single lesion. In Patient 06 new lesion observed after 2 cycles of SQ3370.

Summary

- Shasqi's CAPAC lead candidate, SQ3370, is the first investigational product in the clinic to utilize click chemistry – an innovative approach to target tumors with cytotoxics.
- Preclinical and clinical PK data are consistent, demonstrating more than 50 times higher exposure of Dox in tumor versus plasma.
- SQ3370 demonstrates proof-of-concept for the CAPAC platform.
- SQ3370 shows a promising safety profile, with no dose-limiting toxicities observed to date, in heavily pretreated patients receiving up to 4x the clinical dose of conventional Dox.
- Dose escalation is continuing.

Additional info

- We would like to thank all patients and their families for participating in SQ3370-001.
- For more information, please visit https://www.shasqi.com
- ClinicalTrials.gov Identifier: NCT04106492
- Presented at the European Society for Medical Oncology (ESMO), 2021.
- **Source**: SQ3370-001: data as of 2021-07-26 for Cohorts 1 through 5, data collection and cleaning is ongoing. [1]Wu K, Yee NA, Srinivasan S, Mahmoodi A, Zakharian M, Oneto JM, Royzen M. Chem Sci. 2021, 12 (4), 1259-71.

Dr. Subbiah relevant disclosure statement: clinical trial funding by Shasqi.

See Shasqi's ESMO Preclinical Presentation *(Number 9P)* for more on SQ3370