CONTROL ID: 3465290

CURRENT CATEGORY: Soft Tissue sarcoma

TITLE: SQ3370-001: A MULTI-CENTER, OPEN-LABEL PHASE I DOSE-ESCALATION STUDY OF SQ3370, A NOVEL INTRATUMORAL AND SYSTEMIC APPROACH TO ADMINISTER ANTHRACYCLINES FOR TREATING SOFT TISSUE SARCOMAS AND OTHER ADVANCED SOLID TUMORS.

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ABSTRACT BODY:

Objective: Anthracyclines are regarded as the first-line treatment of choice for soft tissue sarcoma (STS) and other solid tumors. However, objective responses are uncommon and risks of cardiotoxicity limit treatment to a maximum of 4-5 months. In this first-in-human (FIH) Phase 1 study, we are evaluating the safety and tolerability of SQ3370, a novel treatment approach that involves local intratumoral injection of a prodrug-capturing biomaterial (SQL70) followed by 5 daily systemic infusions of an attenuated prodrug of doxorubicin (SQP33). Complementary chemical groups in the 2 components allow the local capture and release of active doxorubicin in situ. In pre-clinical models, this approach allowed an 8.95-fold increase in doxorubicin dosing with minimal systemic adverse events including cardiotoxicity in dogs. In addition, there was clear evidence of tumor regression in non-injected distal lesions, suggesting a systemic anti-tumor effect of the treatment. (Preclinical data is presented in a separate abstract.) The local capture and activation technology of SQ3370 is solely based on chemistry and is independent of tumor biomarkers or local factors such as enzymatic activity, pH or oxygen levels.

Methods: SQ3370-001 is a Phase I study that will enroll patients ≥ 18 years of age with an injectable local or metastatic lesion of STS or other solid tumors, for which published data indicates responsiveness to anthracyclines. Patients must be relapsed or refractory following standard of care therapy and have not received more than 225 mg/m^2 of doxorubicin (or equivalent anthracycline). Treatment cycles will be 21 days long with no limit on total cycles. Dose escalation will follow an accelerated titration design and then switch to a 3+3 design. The starting human dose of SQP33 prodrug with a fixed volume of SQL70 biomaterial was determined in accordance with ICH S9 guidelines, which propose using 1/6th of the human equivalent dose highest non-severely toxic dose (HNSTD) seen in a GLP toxicology study in dogs (the relevant species for doxorubicin).

Results: The primary objective will be to assess the safety and tolerability of SQ3370 and to determine the recommended Phase 2 dose (RP2D). Secondary objectives include characterizing the pharmacokinetic profile, assessing preliminary signals of anti-tumor activity per RECIST 1.1 and immune responses. This study is expected to enroll up to 40 patients.

Conclusion: 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. Further, SQ3370's systemic anti-tumor effect could greatly benefit patients with widely disseminated or undetectable micro-metastatic lesions. This FIH study will validate the local capture and activation technology, and in the future, could be applied to a variety of cytotoxic drugs that have been limited by their systemic toxicity. SQ3370-001 is open to enrollment in the United States and Australia.

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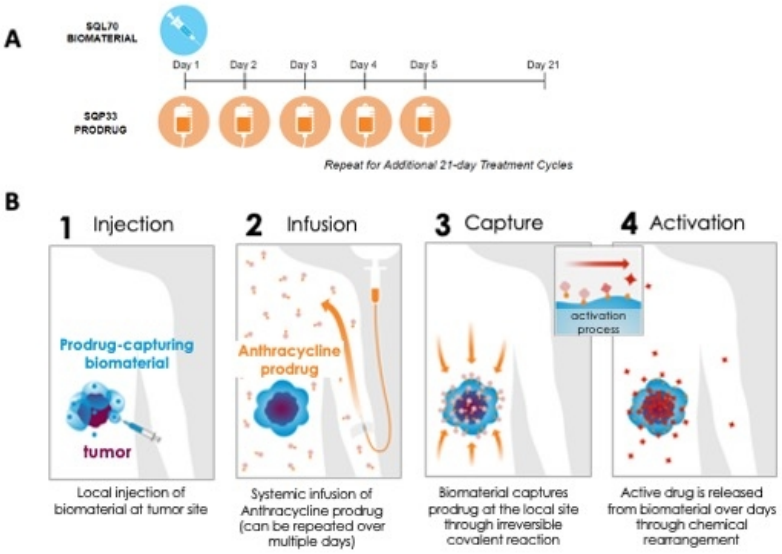
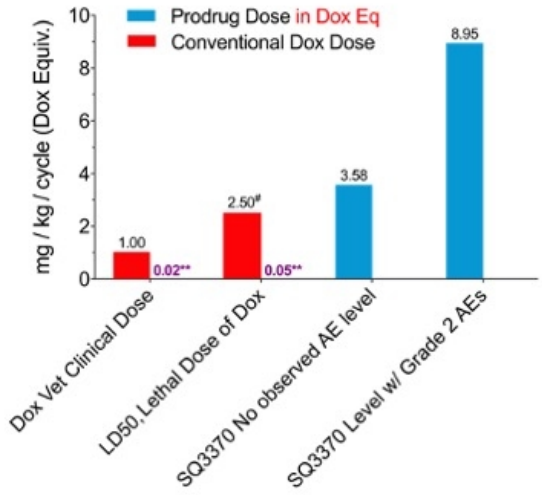
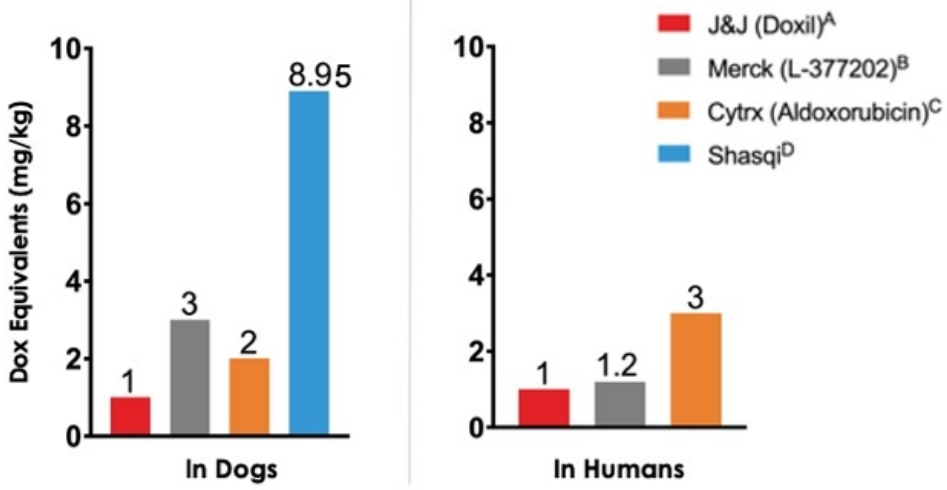


Figure 1. SQ3370 Investigational Product. (A) Treatment cycle and (B) Mechanism of Local Capture and Activation.



* Doxorubicin exposure to tumor,
# C. Bertazzoli et. al. Toxicol. Appl. Pharmacol, 1985; 79:412-422.
** C. Li et. al. J. Nuc. Med. 1997, 38, 1042 - 1047
ζ Grade 2 AE level corresponds to highest non-severely toxic dose (HNSTD)
Dox Eq = Doxorubicin equivalents

Figure 2. Dose Comparison of SQ3370 with Conventional Doxorubicin in Dogs (GLP Toxicology)



Dose per Cycle Resulting in ≥ Grade 2 Side Effects

Sources -
A: Working *et. al.* Hum Exp Toxicol, **1996**, 15, 751-85. **B:** DeFeo-Jones *et. al.* Mol Cancer Therap. **2002**, 1, 451-459; DiPaola *et. al.* J Clin Onc. **2002**, 20, 1874-1879.
C: Kratz *et. al.* Human & Exper Toxicol, **2007**, 26, 19-35; Unger *et. al.* Clin Cancer Res, **2007**, 13, 4858-4866. **D:** Unpublished results.

Figure 3. Dose Comparison of SQ3370 with other Doxorubicin approaches.