A Phase 1a/1b Trial of ST-001, a Fenretinide Phospholipid Suspension for 4-hour Intravenous Infusion, in Relapsed/Refractory T-Cell Non-Hodgkin's Lymphoma

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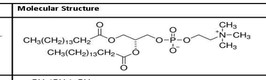
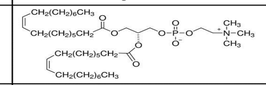
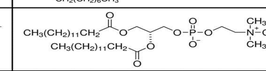
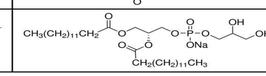
INTRODUCTION

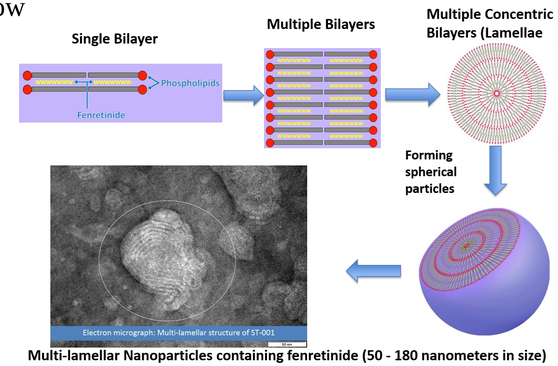
A phase 1a/1b trial is planned for specific types of T-cell non-Hodgkin's lymphoma (T-NHL) using a new formulation of fenretinide for intravenous (IV) administration (ST-001, IND# 135475). Despite documented anticancer properties, clinical development of fenretinide has been hampered by poor bioavailability of the oral preparations and poor water solubility for IV infusion although some progress has been made. A phase 1 clinical trial of a 20% soy oil-in-water emulsion containing 2mg/mL of fenretinide, administered via 24-hour daily infusions x5 q3wks, demonstrated activity in mycosis fungoides /Sézary syndrome (MF/SS) and in angioimmunoblastic T-cell lymphoma (AITL) (Mohrbacher et al 2017). However, all doses exhibiting disease activity were associated with grade 4 hypertriglyceridemia. ST-001 from SciTech Development, LLC is a second generation, triglyceride-free, phospholipid-based nano-dispersion formulation of higher potency fenretinide (12.5mg/mL) suitable for IV infusion.

METHODS

The SciTech Delivery Vehicle (SDV): Composed of 4 clinically acceptable phospholipids (DPPC, DOPC, DMPC, and DMPG). Table below

Name (Abbreviation)	Molecular Structure	CAS Number
1,2-Dipalmitoyl-sn-Glycero-3-Phosphocholine (DPPC)		63-89-8
1,2-Dioleoyl-sn-Glycero-3-Phosphocholine (DOPC)		4235-95-4
1,2-Dimyristoyl-sn-Glycero-3-Phosphocholine (DMPC)		18194-24-6
1,2-Dimyristoyl-sn-Glycero-3-[Phospho-rac-(1-glycerol)] (sodium salt) (DMPG)		200880-40-6

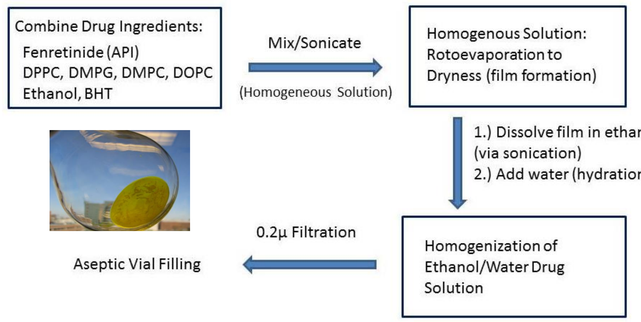
ST-001 Formulation: In the presence of fenretinide, the SDV forms lamellar bilayer structures <200nm in diameter. Figure below



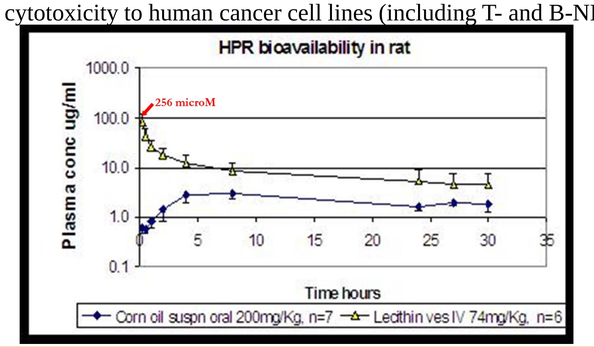
Multi-lamellar Nanoparticles containing fenretinide (50 - 180 nanometers in size)

FIGURES

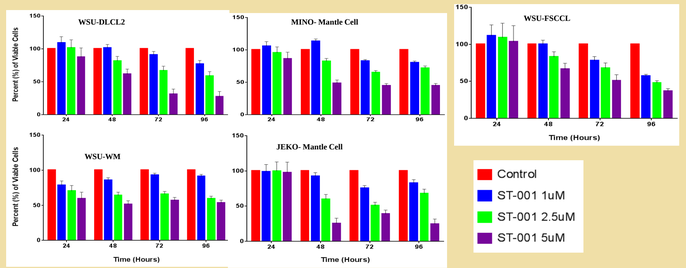
ST-001 Drug Product Formulation



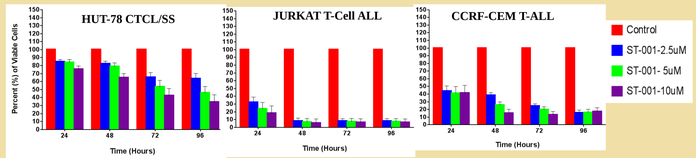
Pharmacokinetic (PK) studies: IV administration of ST-001 in the Sprague-Dawley rat model achieved fenretinide blood levels required for in vitro cytotoxicity to human cancer cell lines (including T- and B-NHL).



ST-001 In Vitro Activity Against B-Lymphoma Cell lines



ST-001 In Vitro Activity Against T-Cell Lines



Protocol Design

- US multicenter phase 1a/1b trial
- Primary objective
  - To determine the maximum tolerated dose (MTD) (one dose level below the maximally administered dose) and dose limiting toxicity (DLT) (grade 3 or higher toxicity) of ST-001 when administered as IV infusion over 4h daily x 5 days Q21 days in patients with relapsed/refractory T-cell non-Hodgkin's lymphoma (T-cell NHL)
- Secondary objectives:
  - To describe the toxicity profile of ST-001 in patients with T-cell NHL
  - To observe and record anti-tumor activity of ST-001 in T-cell NHL
  - To investigate clinical pharmacology of ST-001 in T-cell NHL (PK/PD)
- Simon 4B design (table below):

Dose Level	Dose of ST-001 (mg/m²/day X 5 days every 21 days)	Regimen	Expected D1 CpMAX
Accelerated Phase 1a			
Level 1	1.25 (1 patient)	4-hr CIVI	0.64 µM
Level 2	2.5 (1 patient)	4-hr CIVI	1.28 µM
Level 3	5.0 (1 patient)	4-hr CIVI	2.56 µM
Level 4	10 (1 patient)	4-hr CIVI	5.12 µM
Level 5	20 (1 patient)	4-hr CIVI	10 µM
Level 6	40 (1 patient)	4-hr CIVI	20 µM**
Level 7	80 (1 patient)	4-hr CIVI	41 µM
Level 8	160 (1 patient)	4-hr CIVI	82 µM
Standard Phase 1a			
Level 9	320 (3-6 patients)	4-hr CIVI	164 µM
Level 10	448 (3-6 patients)	4-hr CIVI	230 µM
Level 11	627 (3-6 patients)	4-hr CIVI	322 µM
Expanded Phase 1b	MTD (20 patients)	4-hr CIVI	TBD

MTD: Maximum tolerated dose, which will also be the recommended phase 2 dose
**highest Css of fenretinide that was not associated with SAEs in 5/5 adult patients, as reported from a Phase 1 clinical trial of the emulsion formulation administered by 120-hr continuous infusion[41]. This Css resulted from treatment at dose level was 640 mg/m²/d

- Patient eligibility
  - Age: 18 years or older, MF/SS (stages IB-IV, TNM system), non-CTCL T-cell NHL [PTCL,AITL, FTCL] stages II-IV (Ann Arbor staging).
  - 2+ prior systemic therapies, PS 0-1 and acceptable organ function
  - CD30 targeted therapy for CD30 +ve disease
- Drug administration: 4-hr CIVI qdx5 q3weeks to maximum of 8 cycles.
- Phase 1b: 20 patients at MTD in diseases with efficacy signal during 1a
- Statistical analysis: descriptive statistics for PK and PD

Summary

A multi-center US phase 1a/b trial is planned for relapsed/refractory cutaneous and non-cutaneous T-cell NHL patients who have failed 2 or more systemic regimens. The study will evaluate a second generation fenretinide phospholipid suspension for IV administration. Based on its higher potency (12.5mg of fenretinide/mL) and absence of triglycerides, ST-001 is expected to achieve plasma levels sufficient for anti-lymphoma activity without associated hypertriglyceridemia. Funded by SBIR grants R43/R44-CA093115 from NIH; fenretinide (NSC 374551) was provided by the National Cancer Institute, NIH.