TACL
Therapeutic Advances in Childhood Leukemia and Lymphoma

T2012-002: A Pilot Study of Vincristine Sulfate Liposome Injection (Marqibo®) in Combination with Chemotherapy for Children, Adolescents, and Young Adults with Relapse of Acute Lymphoblastic Leukemia
IND 128316

Protocol Chairperson
Nirali N. Shah, MD

Protocol Biology Chair
Brigitte Widemann, MD

Protocol Vice-Chair
Alan S. Wayne, MD

TACL Member Institutions

All Children's Hospital	National Cancer Institute, Pediatric Oncology Branch
Children's Healthcare of Atlanta at Egleston	Oregon Health & Science University
Children's Hospital and Clinics of Minnesota	Primary Children's Hospital
Children's Hospital Los Angeles	Rainbow Babies & Children's Hospital
Children's Hospital New York-Presbyterian	Royal Children's Hospital, Melbourne
Children's Hospital Orange County	Seattle Children's Hospital
Children's Hospital of Philadelphia	Sidney Kimmel Cancer Center at Johns Hopkins
Children's National Medical Center	St. Jude Children's Research Hospital Memphis
Cincinnati Children's Hospital	Sydney Children's Hospital
Cook Children's Medical Center	Texas Children's Cancer Center, Baylor
CS Mott Children's Hospital, Ann Arbor	The Children's Hospital at Westmead
Dana-Farber Cancer Institute	The Children's Hospital, University of Colorado
Levine Children's Hospital	UCSF School of Medicine
Lurie Children's Hospital of Chicago	University of Miami
Medical College of Wisconsin	University of Texas Southwestern Medical Center
Nationwide Children's Hospital	

TACL OPERATIONS CENTER
CHLA, 4650 Sunset Blvd, MS-54, Los Angeles, CA 90027
Phone: (323) 361-3022 Fax: 323-261-4505 https://tacl.chla.usc.edu

TABLE OF CONTENTS

STUDY COMMITTEE

STUDY CHAIR Nirali N. Shah, MD National Cancer Institute – Pediatric Oncology Branch Phone: 301-451-0390 Email: shahnn@mail.nih.gov	**STUDY VICE CHAIR** Alan S. Wayne, MD Children's Hospital Los Angeles Phone: 323-361-3670 Email: awayne@chla.usc.edu
STUDY BIOLOGY CHAIR Brigitte Widemann, MD National Cancer Institute – Pediatric Oncology Branch Phone: 301-496-7387 Email: widemanb@mail.nih.gov	**STUDY STATISTICIAN** Yueh-Yun Chi, PhD Children's Hospital Los Angeles Phone: 323-361-8582 Email: ychi@chla.usc.edu Jemily Malvar, MS Children's Hospital Los Angeles Phone: 323-361-8720 Email: jmalvar@chla.usc.edu
STUDY PHARMACIST Teresa Rushing, Pharm D, BCPS, BCOP Children's Hospital Los Angeles Phone: 323-361-4791 Email: TRushing@chla.usc.edu	**PHYSICIAN STUDY COMMITTEE MEMBER** Eric Schafer, MD Texas Children's Hospital Phone: 832-824-4241 Email: esschafe@texaschildrens.org
PHYSICIAN STUDY COMMITTEE MEMBER Lewis Silverman, MD Dana-Farber Cancer Institute Phone: 617-632-5710 Email: lewis_silverman@dfci.harvard.edu	**PHYSICIAN STUDY COMMITTEE MEMBER** Paul Gaynon, MD Children's Hospital Los Angeles Phone: 323-361-5600 Email: pgaynon@chla.usc.edu

TACL OPERATIONS COORDINATOR	**PHYSICIAN STUDY COMMITTEE MEMBER**
Children's Hospital Los Angeles Phone: 323-361-5429 Email: TACL@chla.usc.edu	Kenneth Heym, MD Cook Children's Hospital Phone: 682-885-4020 Email: kenneth.heym@cookchildrens.org

EXPERIMENTAL DESIGN SCHEMAS

Cohort A: UK ALL R3/Marqibo (Days 1-28)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 29
Marqibo®	●					●	●					●	Response Evaluation
Dexamethasone	●	●	●	●	●		●	●	●	●	●		
Mitoxantrone	●	●											
Pegaspargase			●						●				
IT Methotrexate	●					●							

Cohort B: UK ALL R3/Marqibo without anthracycline (Days 1-28)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 29
Marqibo®	●					●	●					●	Response Evaluation
Dexamethasone	●	●	●	●	●		●	●	●	●	●		
Pegaspargase			●						●				
IT Methotrexate	●					●							

Cohort C: **Modified Maintenance with Marqibo® (Days 1-14)**

Cycle 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Daily through day 13	Day 14
Marqibo®	●							Response Evaluation
Dexamethasone	●	●	●	●	●			
Methotrexate (PO)	●					●		
Mercaptopurine (PO)	●	●	●	●	●	●	●	
IT Methotrexate as needed no more than once weekly								

Option to repeat Cycle 1 of Cohort C for a second cycle. Cycle 2 may start on Day 15 – 22 of Cycle 1.

Marqibo Dose Levels
Dose Level 1: 1.5 mg/m^2
Dose Level 2: 2.0 mg/m^2

As of Amendment 3, cohorts A and B will be treating at dose level 1; Cohort C will be treating at dose level 2. Dose level may be modified as per guidance in the statistical section and sites will be appropriately notified if a change will be made.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objectives

1.1.1 To assess the safety and feasibility of vincristine sulfate liposome injection (VSLI, Marqibo®) as replacement of standard vincristine in the UK ALL R3 induction regimen (Cohort A).

1.1.2 To assess the safety and feasibility of vincristine sulfate liposome injection (VSLI, Marqibo®) as replacement of standard vincristine in the UK ALL R3 induction regimen that omits Mitoxantrone (Cohort B).

1.1.3 To assess the safety and feasibility of vincristine sulfate liposome injection (VSLI, Marqibo®) as replacement of standard vincristine in a modified maintenance chemotherapy regimen (Cohort C).

1.2 Exploratory Objectives

1.2.1 To describe the constellation of toxicities experienced by patients treatment with each of these three regimens.

1.2.2 To describe the number of patients who achieve a complete remission (CR), including CR + CR with incomplete blood count recovery (CRi) rate for patients with acute lymphoblastic leukemia (ALL) and first to third relapse who are treated in cohorts A and B.

1.2.3 To describe the number of patients with CR at end of induction who become minimal residual disease (MRD) negative by flow cytometry (i.e., $< 10^{-4}$ blasts in a central lab) in cohorts A and B.

1.2.4 To assess the pharmacokinetics of Marqibo® when used in combination with the UK ALL R3 induction chemotherapy regimen, in UK ALL R3 induction chemotherapy without mitoxantrone, and in ALL maintenance therapy.

2.0 BACKGROUND

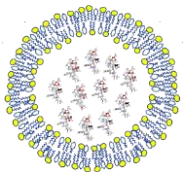
Although the majority of children diagnosed with acute lymphoblastic leukemia (ALL) can be cured with current standard treatment regimens, approximately 20% will relapse. Although remission can often be achieved using multi-agent re-induction regimens, long-term progression free survival (PFS) rates after relapse remain low and most of these patients will ultimately succumb to their leukemia. [1]

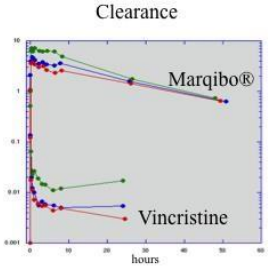
2.1 Vincristine in pediatric ALL

Vincristine is an important component of therapy for ALL, as well as many other malignancies. However, this agent has a narrow therapeutic index due to neurotoxicity, most commonly acute and chronic peripheral neuropathy. Notably, the risk of neurotoxicity is higher among adolescents and young adults. [2] The dose of vincristine is commonly limited to a maximum individual dose of 2 mg to avoid severe neurotoxicity. Despite this, however, vincristine-induced neurotoxicity is still observed and neuropathic symptoms may appear after only a few doses even with capping. However, some reports suggest that lower vincristine exposure in ALL may contribute to relapse and that capping the vincristine dose may contribute to the poorer outcome of adolescents and obese children. Thus, intensification of vincristine therapy might lead to superior outcomes in ALL provided that neurotoxicity is not treatment limiting. This hypothesis was the basis for Children's Oncology Group (COG) trial AALL0433, which was designed to assess the impact of vincristine intensification in pediatric patients with relapsed ALL. In this study, standard vincristine dosing at 1.5 mg/m^2 with a maximum dosage cap of 2 mg was compared to higher dose of 2 mg/m^2 with a cap at 2.5 mg. Interim analysis, demonstrated excessive peripheral neuropathy in patients older than 13 years of age and the study was closed early due to toxicity, preventing the ability to assess the efficacy of vincristine intensification in this setting.

2.2 Marqibo® (vincristine sulfate liposomes injection/VSLI)

Liposomal drug carriers are capable of increasing the therapeutic index of anticancer drugs by altering the drug's pharmacological behavior. Marqibo® was designed to deliver a larger dose of vincristine via encapsulation within an aqueous core of nanoparticles comprised of sphingomyelin and cholesterol liposomes. [3](Figure)





Mechanism of action: The active drug in Marqibo® is vincristine. Vincristine is a cell cycle-specific agent that binds tubulin, a protein component of microtubules, and arrests cell growth in metaphase by disrupting cell division. Marqibo® formulation optimizes vincristine pharmacokinetics, prolongs circulating half-life, and increases vincristine penetration and concentration in tissues with fenestrated vasculature (i.e., bone marrow, lymph nodes, spleen, and tumors). A

pharmacokinetic (PK) study was conducted in a non-human primate model at the NCI using rhesus monkeys (*macaca mulatta*) which allowed for direct comparison of vincristine to Marqibo®. This study demonstrated that the clearance of vincristine sulfate exceeded that of Marqibo® by approximately 400-fold (Figure).[4] Additionally, no penetration was noted into the CSF for either preparation.

Preclinical studies: Marqibo® was more active than vincristine sulfate in 9 tumor models representing 7 cancer types. Improved activity of Marqibo® over vincristine sulfate was observed using a variety of dosing schedules and routes of tumor implantation. In murine and human tumor models (L1210 and P388 leukemia, B16/BL6 melanoma and human A431 solid tumor xenografts) unencapsulated vincristine had negligible antitumor activity. In contrast, liposomal vincristine evaluated in the same tumor models had significantly greater, dose-dependent, antitumor activity.[3] These results are consistent with complementary studies demonstrating significant increases in the amount of vincristine accumulating in these tumors as a result of liposomal encapsulation. This increase in antitumor activity compared to equivalent doses of vincristine has been demonstrated in a wide range of tumor models, including lymphoma and leukemia.

Clinical studies and FDA approval: Marqibo® has been evaluated in more than a dozen clinical trials in over 600 subjects (primarily adults) with ALL, non-Hodgkin lymphoma, and other cancers. Clinical experience indicates that Marqibo® can be administered safely at individual and cumulative doses exceeding those typically employed for standard vincristine and may provide anticancer activity without increased toxicities. It has been used both as a single agent as well as in conjunction with combination chemotherapy. Phase I studies established safe dosing for monotherapy.[5] In 2012 the US Food and Drug Administration (FDA) granted accelerated approval of Marqibo® for adults with relapsed and refractory Philadelphia chromosome-negative ALL.[6] This approval was based on a pivotal Phase II study (rALLy trial) in which Marqibo® was administered as a single agent weekly at a dose of 2.25 mg/m^2 without a dose cap. There was a 20% (13/65) CR/CRi rate and an overall response rate (ORR) of 35% (23/65; 13 CR/CRi, 4 morphologic remissions without blood count recovery, and 6 partial responses).[7] Eight of the 13 patients achieving CR/CRi achieved MRD negative status. Responses were seen in both T- and B-lineage ALL.

Pediatric studies: A small Phase II study was conducted in children (P99-401). Marqibo® was well tolerated and some activity was seen, although data were quite limited. Subjects were treated with Marqibo at 2.0 mg/m^2 IV over 1 hour every 14 days ± 2 days (1 cycle). Only 1 subgroup (sarcomas) fully accrued prior to termination of this study. Only one patient with ALL was treated on that trial. Of the 29 dosed and evaluable subjects, the responses to treatment were as follows: 2 subjects had a PR (7%), 8 subjects had stable disease (28%) and 19 subjects had disease progression (66%). Seven (24%) subjects were alive at the last protocol specified survival follow-up. The median time to progression was 52 days for all subjects. Only 1 subject experienced a possibly related Grade 3 or higher neurologic event (peripheral neuropathy). Results of this study were never published beyond abstract form.[8]

A single-agent pediatric Phase I dose-escalation trial to evaluate the safety, toxicity and pharmacokinetics of Marqibo® in children with relapsed refractory leukemia or solid tumors was recently completed at the NCI (http://clinicaltrials.gov/ct2/show/NCT01222780). Marqibo® was administered weekly with a cycle consisting of four doses. A rolling-six design was employed and 21 patients were treated on this trial: 6 at dose level #1 (1.75 mg/m^2/dose); 10 at dose level #2 (2.25 mg/m^2/dose), with an additional 6 subjects treated at dose level #2 in the expansion phase of the protocol for subjects with ALL only. (Table) The highest dose level tested was the adult maximum tolerated dose (MTD) of 2.25mg/m^2. Although the MTD had not been exceeded at dose level 2, the decision was made to forego further dose escalation and to open the expansion cohort for subjects with ALL at dose level 2 in accordance with protocol allowances. This was based on the observed toxicity profile and clinical activity at dose level 2 (2.25 mg/m^2/dose x 4 weekly doses), which also represented the FDA approved dose and schedule for adults, and the likelihood that the safety profile would be negatively impacted by further dose escalation. Notably, ongoing dosing of VSLI appeared to be associated with the development of peripheral neuropathy on this trial, consistent with results in adults with ALL where cumulative dose was correlated with earlier onset and higher-grade neurotoxicity. A total of 17 subjects with ALL were treated.

Pt #	Dose Level	Diagnosis	Age/Sex	Dose (mg)	# Doses Received	# Cycles Received	DLT (Y/N)	Best Response
1	1	ALL	18/F	3.7	2	1*	N	NE
2	1	ALL	15/M	2.5	4	1	N	SD
3	1	Solid	17/M	2.9	12	3	N	SD
4	1	ALL	11/M	2.5	2	1*	N	NE
5	1	Solid	13/M	2.3	4	1	N	PD
6	1	ALL	12/M	2	12	3	N	CR
7	2	Solid	2/F	1.3	8	2	N	SD
8	2	ALL	14/M	3.4	1	1*	Y**	NE
9	2	ALL	14/M	4.1	4	1	N	PD
10	2	ALL	5/M	1.9	4	1	N	SD
11	2	BL	15/M	3	2	1*	N	NE
12	2	ALL	19/M	---	0	0	N/A	Not treated
13	2	ALL	5/F	2.1	3	1*	N	NE
14	2	ALL	16/F	3.8	4	1	N	SD
15	2	ALL	16/M	4.3	2	1*	N	NE
16	2	ALL	17/M	4.5	4	1	N	SD
17	2	ALL	10/M	2.5	9	3*	N	HI
18	2	ALL	9/M	2.9	4	1	N	SD
19	2	ALL	15/F	3.3	4	1	N	PD
20	2	ALL	2/F	1.4	8	2	N	SD
21	2	ALL	6/F	1.9	2	1*	N	PD
22	2	ALL	11/F	3.4	5	2*	N	SD

Table: Summary of 21 subjects treated on the pediatric phase I trial of Marqibo® (VSLI). (Subject 12 enrolled but did not receive any protocol specific therapy)* cycle not complete; ^ dose de-escalation with Cycle 2 Dose #3 due to paresthesias, **Grade 4 LFT elevation, ALL: Acute lymphoblastic leukemia; BL: Burkitt's Lymphoma; CR:

complete remission; SD: stable disease; PD: progressive disease; NE: non-evaluable for response; HI=hematologic improvement; DLT=dose limiting toxicity (grade 4 hepatic transaminase elevation)

In general, Marqibo® has been well tolerated with the majority of treatment-related AEs consisting of reversible Grade 1/2 toxicities. Drug-related Grade 3/4 AEs included decreased neutrophil count, decreased lymphocyte count, decreased white blood cell count and elevated liver transaminases. No DLT was seen at dose level 1. One patient treated at dose level 2 developed dose-limiting toxicity (DLT) that consisted of Grade 4 hepatic transaminase elevation and this dose level was expanded. Notably, in this subject who had pre-existing transaminase elevation and a history of chemotherapy-associated hepatic dysfunction, the grade 4 transminase elevation was transient. After receiving the first dose of Marqibo® hepatomegaly improved and transaminase levels returned to levels improved from the baseline. Subjects enrolled on this protocol will have close monitoring for hepatotoxicity with laboratory assessments prior to each dose of Marqibo® and dosing delays for transaminase and bilirubin elevations as specified in section 4.3.1.

Seventeen subjects with ALL were treated on this trial. One of these, a 12-year-old with chemotherapy refractory ALL after 2 prior allogeneic stem cell transplants achieved a CR with no evidence of minimal residual disease (MRD) by flow cytometry, following two cycles on therapy. In several patients with circulating peripheral blasts, dramatic reductions in absolute peripheral blast count were seen, including 1 patient who experienced a greater than 4-log10 reduction in circulating blasts after a single dose of Marqibo®. Another patient had a 3-log10 reduction in circulating blasts after a single dose of Marqibo®, however, this subject was taken off treatment due to DLT. Six patients were non-evaluable for response because they were taken off treatment prior to completion of a full cycle (one for alternative therapy and the others due to complications of ALL). Thus, we have observed anti-leukemia activity including a CR with single agent Marqibo® in children with multiply relapsed/refractory ALL treated on this trial.[9]

Combination studies: Prior studies of Marqibo® with combination chemotherapy have been conducted in adults. The largest trial (CA00004) enrolled 72 previously untreated subjects with non-Hodgkin lymphoma and was conducted to examine the efficacy and safety of substitute Marqibo® for conventional vincristine in standard CHOP chemotherapy with or without rituximab. Subjects were treated with 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 2 mg/m^2 Marqibo on Day 1, and prednisone 100 mg orally on Days 1 to 5 in 21-day cycles. Sixty-six subjects with B-cell histology received 375 mg/m^2 IV of rituximab prior to administration of CHOP (R-CHOP). An ORR of 96% was demonstrated (69/72), with 66 achieving a CR (92%), 2 a CRu (3%) and 1 a PR (1%). Favorable response rates, PFS, and overall survival were observed regardless of age group and IPI status. No subjects died within 30 days of last dose received. Common related Grade 3 and higher treatment emergent adverse events ($\geq$10% of subjects) included febrile neutropenia (19%), neutropenia (64%), and thrombocytopenia (14%). A total of 23 subjects (32%) experienced SAEs. 18(5%) of the SAEs were assessed as possibly related to study drug. The most common treatment-associated SAEs were febrile neutropenia (19%) and neutropenia (15%).

There are currently two ongoing Phase III trials in adults patients with newly diagnosed ALL and NHL utilizing combination chemotherapy with Marqibo®. Preliminary results from these trials

support safety with the use of Marqibo® with combination therapy. (Clinicaltrials.gov: NCT01439347 and NCT01478542)

Toxicity: In its standard formulation, vincristine neurotoxicity is dose-dependent and symmetrical, and is manifested as both peripheral sensory and motor neuropathy. Progressive neuropathy may occur, leading for example to weakness with foot and wrist drop. Vincristine induced peripheral neuropathies are generally reversible although recovery may take months and is often incomplete.

The major side effects of Marqibo® are due to the active vincristine component, Thus, the most common treatment-related adverse events of Marqibo® have been neurological. Adverse events occurring in greater than or equal to 30% of patients treated with single agent Marqibo® include neuropathy, constipation, nausea, neutropenic fever, pyrexia, decreased appetite, and diarrhea.

Patients with ALL who receive Marqibo® will generally have received vincristine previously and cumulative toxicity from prior vincristine exposure is possible. On the single-agent Phase II rALLy trial, all patients had prior vincristine exposure and patients received a median of four doses of Marqibo® at nearly twice the usual dose intensity of standard vincristine. Some received up to 70 mg total vincristine exposure. Notably, 77% had prior neuropathy at study entry. Despite that, the observed neurotoxicity was comparable to that seen with standard vincristine. 86% had some neuropathy, but Grade 3 neurotoxicity was observed in only 23% of patients. Thus, even in patients with prior vincristine exposure, Marqibo® was fairly well tolerated. Other significant adverse events observed on the rALLy trial were neutropenic fever and tumor lysis syndrome. [7] Such patients may also have experienced prior hepatotoxicity, which in the setting of Marqibo® administration, risk for hepatotoxicity may be increased in combination with other hepatotoxic chemotherapeutic agents and thus all subjects will be monitored daily.

There is the potential of toxicity to liposome carrier (sphingomyelin/cholesterol) as these are biological lipids that are important components of plasma membranes. However, no toxicity has been observed in pre-clinical toxicology studies conducted with empty liposomes in mice, rats and dogs.

2.3 Overview of UK ALL R3 Regimen:

The UK ALL R3 platform has been shown to be among the most successful regimens in the management of relapsed ALL, with superiority of the mitoxantrone (vs. idarubicin) arm. [10]This trial investigated the combination of vincristine, dexamethasone and pegaspargase with randomization to mitoxantrone versus idarubicin for the initial block of re-induction. Two hundred thirty-nine patients were enrolled on ALL R3 with 109 idarubicin and 103 mitoxantrone patients evaluable. Forty-four percent of idarubicin and 40% of mitoxantrone patients were MRD positive at a level of 10^{-4} at the end of Block 1 (p=0.90). Although there were no significant differences in MRD levels at week 5 between the mitoxantrone and idarubicin arms, the progression-free survival (PFS) at 3-years for those who received idarubicin was 36% vs. 65% for those who received mitoxantrone (p=0.0004). This difference continued to be significant when adjusted for differences in risk group, country, age, gender, and cytogenetic subtype. Among the standard risk

and intermediate-risk patients, the differences in outcome were most significant (5-yr PFS 74% in mitoxantrone arm vs. 37% in idarubicin arm, p=0.0001). Overall mitoxantrone was reported to be better tolerated and less toxic than idarubicin; however a competing effects model showed that the difference between the two drugs was primarily related to disease control rather than toxicity of treatment (p=0.09). In patients who proceeded to HSCT, 35% who received idarubicin (n=48) and 5% who received mitoxantrone (n=44) have relapsed posthaste. Based on an intention to treat analysis, intermediate-risk patients who received transplant did worse in the idarubicin arm but had comparable results in the mitoxantrone group to those who received chemotherapy alone (p=0.01). As a result of these results, further randomization between the mitoxantrone and idarubicin arms was discontinued. [10]

Following this trial, additional patients were treated on the mitoxantrone induction arm by the UK ALL R3 investigators (n=298). (Personal communication, V. Saha, April 2013). Complete data are available on 201 of 298 patients. There were 8 known deaths during induction (4% treatment related mortality [11]). 135 of 201 (67%) patients experienced a grade 3, 4, or 5 event. No patient was removed after induction due to toxicity and thus 193 of 201 (96%) proceeded to the consolidation phase.

Outcomes for patients treated with the UK ALL R3 induction regimen reported to date have been for patients in first relapse on ALL. On this protocol, patients with first to third relapse will be eligible and thus many are likely to be more heavily treated and at greater risk of toxicity than previously reported patients. Limited data reporting on the experience with the UK ALL R3 induction regimen in multiply relapsed patients who had received at least two prior treatment attempts demonstrated that there was no appreciable difference in the grade $\geq$ 3 toxicities between first and multiply relapsed patients. However, amongst this group of patients, grade $\geq$ 3 infection was reported in 53/59 (90%) patients and 55/59 (97%) of patients experienced at least one grade $\geq$ 3 non-hematologic adverse event.[12] Importantly, in this recent retrospective review, 7% (3/42) of patients treated with the UK ALL R3 induction regimen in first relapse had a delay in starting their next treatment course beyond day 49 (95% CI 1.5% - 19.5%), and 38% (6/16) of patients treated in second or greater relapse were similarly delayed (95% CI 15% - 65%).

Toxicity data were reported on a completed COG trial of 4-drug reinduction chemotherapy (COG AALL 01P2) in patients with first or greater relapse. [13, 14] This frequency of nonhematologic Grade 3 and 4 toxicities ranged up to 58%. The post-induction toxic death (TD) rate prior to modification of the regimen was 14% (n=3).[13] On a Phase II trial of single agent clofarabine in children with ALL who were in a second relapse or beyond, inclusive of those with post-transplant relapse, 8% (n=5) of subjects experienced a TD that was considered at least possibly related to study drug. [15] Similarly on a Phase II study that incorporated bortezomib with combination chemotherapy in patients who were in second relapse or beyond, including those with post-transplant relapse there was a 14% (n=3) TD rate, primarily due to infection associated complications. [16] Based on these data, we anticipate at least a 10% toxicity death rate on this trial. We also would consider it unacceptable should 45% of subjects not be able to proceed to further therapy by day 49 due to toxicity of any grade.

2.4 Study Rationale

Based on the encouraging results from the UK ALL R3 trial, the promising results observed in Marqibo® studies, and the potential benefit of vincristine intensification in childhood ALL, we are pursuing incorporating treatment with Marqibo® as replacement for standard vincristine in combination with UK ALL R3 induction for children with relapsed ALL. Our hypothesis is that the incorporation of Marqibo® with combination chemotherapy will be safe and feasible. In the context of this pilot study, overall outcomes and efficacy will be a secondary objective. We hypothesize that data from this combination may show improved efficacy including, complete remission (CR), minimal residual disease (MRD) negativity, and progression free survival (PFS) rates and safety (i.e., neurotoxicity) in comparison to outcomes in historical regimens, including the UK ALL R3 with standard vincristine.

Dose justification: This is a limited Pilot study. As this represents the first combination chemotherapy study utilizing Marqibo® in pediatrics, the starting dose of Marqibo® will be 1.5 mg/m^2/dose (dose level 1), with no dose cap, matching the standard vincristine dose utilized in the UK ALL R3 induction regimen. If an acceptable safety profile is demonstrated at this dose level, escalation to 2.0 mg/m^2/dose (dose level 2), with no dose cap, will be performed. This higher dose represents a dose that has previously been safely used in combination therapy trials with Marqibo® in adults (CA00004). Both doses are below the highest dose tested in the pediatric Phase I single agent trial and the FDA approved single-agent dose for adults (2.25 mg/m^2/dose, weekly, no dose cap). Patients will receive a total of 4 weekly doses of Marqibo®.

2.4.1 Rationale for addition of cohorts B and C

As of April 25, 2018, 4 subjects had been treated on study and all have tolerated the therapy well without DLT. All 4 were able to achieve a morphologic remission, with one patient attaining an MRD negative remission, enabling the patient to proceed to a first allogeneic bone marrow transplant. In another patient, who had 3% disease by flow cytometry and MRD testing at day 29 evaluations, subsequent bone marrow demonstrated disease progression and the patient proceeded to alternative therapy.

In recognition of a growing reluctance to utilize a full intensive re-induction regimen in the era of targeted therapies, and other competing studies, but to allow for the ability to continue to explore VSLI, Marqibo®, the primary purpose of Amendment # 2 is to add two additional regimens which will allow for the continued exploration of VSLI, Marqibo® in the combination chemotherapy setting. The first regimen (B) is the same regimen (A) as initially proposed, but without the anthracycline-like agent (the anthracenedione, mitoxantrone). The second regimen (C) is to utilize VSLI, Marqibo® in a modified ALL maintenance type regimen. As both of these regimens B and C are inherently less toxic than the UK ALL R3 regimen, it is anticipated that these regimens will be well tolerated and still allow to explore the additional role of VSLI, Marqibo® as a substitution for standard vincristine. With the addition of these two regimens, the trial has been divided into 3 separate treatment cohorts with modified statistical design and a more appropriate

enrollment target. Both these regimens are appropriate therapeutic options for patients requiring lower intensity re-induction, or as bridging therapy.

2.4.2 Rationale for Amendment #3

As of April 24, 2020, a total of 13 subjects have been treated on study.

In cohort A (4-drug induction), a total of 8 subjects were treated at 2 dose levels. All four subjects at dose level 1 (1.5 mg/m^2/dose) tolerated the therapy well without DLT and thus cohort A proceeded to enrollment at dose level 2 (VSLI, Marqibo®=2.0 mg/m^2/dose). At dose level 2, cohort A, 2 subjects experienced DLT and thus cohort A was de-escalated to dose level 1 (1.5 mg/m^2/dose). The consent has been modified to update the toxicity profile. DLTs at dose level 2, cohort A were as follows: One patient had grade 4 sepsis, grade 3 peripheral neuropathy and grade 3 cardiac failure (which occurred in the setting of sepsis). The second patient had grade 5 encephalitis along with respiratory failure, hydrocephalus and vascular disorder.

In cohort B (3-drug induction without mitoxantrone), a total of 4 subjects have been treated: 2 at dose level 2 and 2 at dose level 1. Amongst the two patients at dose level 2, one subject experienced DLT with grade 3 hepatic transaminase elevation (AST/ALT) and grade 3 hyperbilirubinemia. The second subject did not meet DLT criteria but also had elevated hepatic transaminase elevation that was near DLT criteria and thus based on this experience, and in discussion with the study team, the decision was made to electively dose de-escalation to dose level 1. The IRB and DSMC were notified about this change. The first patient at dose level 1 did not complete the regimen due to progressive disease and was taken off study.

In cohort C, one patient has been treated at Dose Level 2.

3.0 PATIENT ELIGIBILITY CRITERIA AND ENROLLMENT

3.1 Patient Reservation

Investigators should consult the TACL web site (https://tacl.chla.usc.edu) to determine if the study is currently open for accrual before approaching patients for participation. Before enrolling a patient on study, a reservation must be made with the TACL Operations Center. In order to make a reservation you may call (323) 361-3022 or send an email to TACL@chla.usc.edu with the following information (if sending an email, please put "Reservation Request" in the subject line):

- Study for which you want to make a reservation:
- Name of the institution requesting reservation with contact information
- Patient Initials (Last, First)
- Patient month and year of birth

If an enrollment slot is available, you will receive an email from the TACL Operations Center to confirm your reservation. All reservations are good for five full calendar days starting with the next full day after the day the reservation is made.

3.2 Enrollment

An enrollment guide is available on the web site (https://tacl.chla.usc.edu). Patients must be enrolled prior to beginning treatment on this study. Patients will be enrolled by contacting the TACL Operations Center at Children's Hospital Los Angeles, Monday through Friday, 8:30 am – 5:00 pm Pacific Time at (323) 361-3022,. (weekend and holiday enrollments can be accommodated with advance notice to the TACL Operations Center). You will be asked to complete the eligibility form on the TACL RDE System prior to making your call. In addition, the supporting documentation, which confirms eligibility, should be faxed or emailed to the TACL Operations Office representative.

The "Day 1" intrathecal chemotherapy dose may be given during eligibility screening evaluation within two weeks prior to Day 1 chemotherapy, and does not need to be repeated on Day 1.

Each patient will be assigned a unique TACL registration and study subject number. An email confirming eligibility and assigned dose level will be sent to the treating facility, Study Chair, and Study Vice-Chair. Patients should begin treatment within three calendar days of study enrollment. If a subject cannot start therapy in the time allotted, they must be re-screened to confirm eligibility at a later date.

Contact: TACL Operations Center
Children's Hospital Los Angeles
4650 Sunset Blvd, MS #54
Los Angeles, CA 90027
Phone: (323) 361-3022
FAX: (323) 361-4505
Email: TACL@chla.usc.edu

3.3 Inclusion Eligibility Criteria

The eligibility criteria listed below are interpreted literally and cannot be waived.

3.3.1 Age

Patients must be ≥ 1 and ≤ 21 years of age at the time of enrollment.

3.3.2 Diagnosis

Cohort A: Patients must have a diagnosis of acute lymphoblastic leukemia (ALL, T or B cell) or mixed phenotypic acute leukemia with ≥ 5% blasts in the bone

marrow (M2 or M3 by aspirate or flow cytometry), with or without extramedullary disease~~)~~ or a diagnosis of lymphoblastic lymphoma.

Cohorts B & C: Patients must have a diagnosis of acute lymphoblastic leukemia (ALL, T or B cell), lymphoblastic lymphoma, or mixed phenotypic acute leukemia with any level of detectable disease (minimal residual disease level acceptable) with or without extramedullary disease

3.3.3 Performance Level Karnofsky > 50% for patients > 16 years of age and Lansky > 50% for patients ≤ 16 years of age. (Appendix 1)

3.3.4 Prior Therapy

a. Patients must have recovered from the acute toxic effects (≤ Grade 2 or baseline) of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study, unless otherwise specified. Subjects with disease related cytopenias will be eligible.

b. Patients must have relapsed or refractory disease.

c. Patients with Philadelphia chromosome t(9;22) positive disease must have received at least two prior tyrosine kinase inhibitors.

d. Patients who have experienced their relapse after a HSCT are eligible, provided they have no evidence of graft-versus-host disease (GVHD) and are at least 100 days post-transplant at the time of enrollment; and at least 30 days off any systemic immunosuppression.

e. Prior anthracycline lifetime cumulative exposure:

   1. Cohort A: Patients must have less than 320 mg/m^2 (or 400 mg/m^2 if prior cardioprotection) lifetime exposure of anthracycline chemotherapy (See Appendix 2 for anthracycline calculation worksheet).
   2. Cohorts B & C: There is no limit on prior anthracycline exposure.

f. Hematopoietic growth factors: It must have been at least seven days since the completion of therapy with GCSF or other growth factors at the time of enrollment. It must have been at least 14 days since the completion of therapy with pegfilgrastim (Neulasta®).

g. Biologic anti-neoplastic agents: At least seven days after the last dose of a biologic agent. For agents that have known adverse events occurring beyond seven days after administration, this period must be extended beyond the time during which

adverse events are known to occur. The duration of this interval must be discussed with the study chair or vice chair.

h. Monoclonal antibodies: At least three half-lives (or 30 days—whichever is longer) of the antibody must have elapsed after the last dose of monoclonal antibody. (e.g., Rituximab = 66 days, Epratuzumab = 69 days)

i. Immunotherapy: At least 30 days after the completion of any type of immunotherapy, e.g. tumor vaccines, chimeric antigen receptor T-cells.

j. Recent prior chemotherapy: At least 10 days after standard vincristine and the completion of any type of chemotherapy induction regimen. At least 3 weeks after radiation therapy. At least 30 days after the completion of any investigational neoplastic agent is also required. An investigational agent is defined as any drug that is not approved and licensed for sale by the FDA for institutions in the United States and by The Therapeutic Goods Administration for institutions in Australia.

k. Physiologic steroid replacement is allowed before enrollment and during protocol therapy.

Exceptions:

1. There is no time restriction in regard to prior intrathecal chemotherapy provided there is complete recovery from any acute toxic effects of such; it is allowable to enroll a patient that has received IT ARA-C, IT MTX or triple IT therapy within 14 days of enrollment as part of their evaluation to diagnose disease relapse. The IT therapy given within 14 days of initiation of protocol specified chemotherapy, may substitute for the day 1 IT in cohorts A and B.
2. Subjects with rapidly progressive disease may receive hydroxyurea until they begin study therapy;
3. Patients who relapse while on maintenance-type ALL therapy or are receiving maintenance therapy for disease stabilization will not require a wash-out period before entry into this study. However, there must be at least 10 days after any dose of standard vincristine.
4. For radiation therapy: Radiation therapy must have been completed at least 3 weeks prior to enrollment (including CNS radiation), with the exception that there is no time restriction if the volume of bone marrow treated is less than 10% and also the subject has measurable/evaluable disease outside the radiation port.

3.3.5 Renal and Hepatic Function

a. Renal function: Patient's serum creatinine must be ≤ 1.5 x institutional upper limit of normal (ULN) according to age. If the serum creatinine is greater than 1.5 times normal, the patient must have a calculated creatinine clearance or radioisotope

GFR ≥ 70mL/min/1.73m^2. Alternatively, a 24-hour creatinine clearance may also be used.

1. Pediatric Population (age <18): Calculated creatinine clearance ≥ 70 ml/min/1.73m^2 as calculated by the Schwartz formula for estimated glomerular filtration rate (GFR) where GFR (ml/min/1.73 m^2) = k*Height (cm)/serum creatinine (mg/dl). k is a proportionality constant which varies with age and is a function of urinary creatinine excretion per unit of body size; 0.45 up to 12 months of age; 0.55 children and adolescent girls; and 0.70 adolescent boys.
2. Adult Population (age ≥18): If serum creatinine >1.5 X ULN, then the estimated glomerular filtration rate (GFR) must be >70 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease equation where Predicted GFR (ml/min/1.73 m^2) = 186 x (Serum Creatinine)$^{-1.154}$ x (age in years)$^{-0.023}$ x (0.742 if patient is female) x (1.212 if patient is black.

b. Hepatic function: ALT and AST must be < 5 x institutional upper limit of norm ULN. Total bilirubin must be ≤ 1.5 x ULN (except in the case of subjects with documented Gilbert's disease ≤ 5 × ULN).

3.3.6 Cardiac Function

Patients must have a shortening fraction ≥ 27% or an ejection fraction ≥ 55% by echocardiogram, cardiac MRI or MUGA.

3.3.7 Reproductive Function

a. Female patients must not be pregnant and those of childbearing potential must have a negative urine or serum pregnancy test confirmed within one week prior to enrollment.
b. Female patients with infants must agree not to breastfeed their infants while on this study.
c. Male and female patients of childbearing potential must agree to use an effective method of contraception during the study.

3.4 Exclusion Eligibility Criteria

3.4.1 Active CNS disease (CNS 3) is exclusionary. Patients with CNS 1 or CNS 2 disease may be enrolled, which is inclusive of patients with a recent history of CNS3 disease which is now resolved to CNS1 or CNS2

3.4.2 Patients will be excluded if they have any isolated extramedullary disease, including isolated testicular or isolated CNS disease.

3.4.3 Patients will be excluded if they have previously received Marqibo®.

3.4.4 Patients will be excluded if they have a known allergy to any of the drugs used in the study, with the exception that patients with an allergy to pegaspargase who can receive Erwinia asparaginase are eligible. Patients unable to receive any formulation of asparaginase may only enroll on cohort C

3.4.5 Patients will be excluded if they have active, uncontrolled systemic fungal, bacterial, viral or other infection despite appropriate antibiotics or other treatment.

3.4.6 Patients who require azole antifungal agents will be excluded. Azoles must be discontinued at least one week prior to the start of Marqibo®.

3.4.7 Patients will be excluded if there is a plan to administer non-protocol chemotherapy, radiation therapy, another investigational agent or immunotherapy during the study period.

3.4.8 Patients with pre-existing, persistent grade 2 or greater sensory or motor neuropathy from any cause will be excluded**.** (Patients on chronic stable doses of gabapentin or similar agents for history of neuropathy may be included if there are no active neuropathic symptoms)

3.4.9 Patients will be excluded if they have significant concurrent disease, illness, psychiatric disorder or social issue that would compromise patient safety or adherence with the protocol treatment or procedures or interfere with consent, study participation, follow up, or interpretation of study results.

a. Patients with Down syndrome will not be eligible for enrollment on Cohort A

3.4.10 Patients with a known history human immunodeficiency virus (HIV) will be excluded due to the increased risk of complications such as severe infection and unknown interaction of Marqibo® with antiretroviral drugs.

3.4.11 Active hepatitis B or C infection as defined by seropositive for hepatitis B (hepatitis B surface antigen (HBsAg)) or hepatitis C and elevated liver transaminases (defined as above the ULN per the institution normal ranges).

3.5 Regulatory

3.5.1 Informed Consent

All patients and/or their parents or legal guardians must sign a written informed consent. Age appropriate assent will be obtained per institutional guidelines. To allow non-English speaking patients to participate in this study, bilingual health services will be provided in the appropriate language when feasible.

3.5.2 Protocol Approval

All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

The following sections detail the treatment plan for therapy. Please refer to the Drug Information section for additional administration guidelines. Treatment should begin within three calendar days of enrollment.

There are 3 treatment cohorts on this protocol. Please see protocol sections 2.4.1 and 2.4.2 for review of the experience to date on this protocol.

There will be no intrapatient dose escalation or de-escalation.

4.1 Treatment Course

Only 1 course of treatment will be permitted. Upon completion of treatment on this study, plans for additional therapy will be at the discretion of the treating team.

As of Amendment 3, cohorts A and B will be treating at dose level 1; Cohort C will be treating at dose level 2.

Marqibo Dose Levels
Dose Level 1: 1.5 mg/m^2
Dose Level 2: 2.0 mg/m^2

Cohort A:

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 29
Marqibo®	●					●	●					●	Response Evaluation
Dexamethasone	●	●	●	●	●		●	●	●	●	●		
Mitoxantrone	●	●											
Pegaspargase#			●						●				
IT Methotrexate	●					●							

asparaginase Erwinia chrysanthemi (Erwinaze®), crisantapase (Erwinase®) asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) may be substituted for allergy to Pegaspargase. See below.

Drug Administration Order

Marqibo will be administered first. Mitoxantrone will follow Marqibo administration on day 1 with dexrazoxane to be given immediately before mitoxantrone (when dexrazoxane is utilized [optional]). Timing of IT methotrexate is flexible in regards to the timing of Marqibo, but should not be given simultaneously in order to reduce the risk of administration route error.

Marqibo® (Dose level 1 only as of Amendment 3)

- Dose Level 1: 1.5 mg/m^2/dose (no dose cap) given IV over 60 minutes (±10 minutes) on days 1, 8, 15 and 22.
- ~~Dose Level 2: 2 mg/m^2/dose (no dose cap) given IV over 60 minutes (±10 minutes) on days 1, 8, 15 and 22.~~
- Review list of concomitant medications that are prohibited (CYP3A4 inhibitors) or to be used with caution (Appendix 3). See section 4.5 for drug interactions.
- Dose will be given over 60 minutes ± 10 minutes

Dexamethasone

- 20 mg/m^2/day divided BID given orally on days 1 through 5 and 15 through 19. The two doses should be separated by at least 8 hours
- Any oral formulation of dexamethasone is acceptable
- IV may be given if oral formulation is not tolerated (please document reason oral could not be given)

Mitoxantrone

- 10 mg/m^2/day given on days 1 and 2 as a short IV infusion over 5-15 minutes. Do not infuse over less than 3 minutes.
- Dose will be given over 5-15 minutes
- See section 5.6 for guidance on optional cardioprotection.

Pegaspargase

- 2,500 international units/m^2/day IM or IV on days 3 and 17. **(Cap individual dose at 3,750 IU, based on vial size)**
- If available and FDA approved, asparaginase Erwinia chrysanthemi (Erwinaze®), asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) or crisantapase (Erwinase®) may be substituted for pegaspargase in patients with systemic allergic reaction.
  - Asparaginase Erwinia chrysanthemi (Erwinaze®) or Cristantapase (Erwinase®): May be dosed per package insert guidelines as 25,000 IU/m^2/dose IM or IV over 1-2 hours. Give 6 doses of asparaginase Erwinia chrysanthemi (Erwinaze®) or Cristantapase (Erwinase®) over 2 weeks on a schedule of every other day (for example, q 48 hours, or M/W/F dosing) for each dose of planned pegaspargase.

- Erwinia chrysanthemi (recombinant)-rywn (Rylaze®): Refer to current FDA product information for dosing at the time of product administration.
- For any Erwinia formulation, **each individual dose not to exceed pegaspargase equivalent dosing of 3,750 IU (i.e., cap individual dose at 37,500 IU Erwinia).** Route of administration, dose schedule and total doses administered should be documented, as this could contribute to variability in PK data for Marqibo®.

- Dose may be administered by IM or IV per product information guidelines (Please document route of administration).
- Premedications may be given per institutional standard.

Intrathecal methotrexate

- Given intrathecally to all patients the dose defined by age below on days 1 and 8 (+ 2 days). *Note*: The "Day 1" intrathecal chemotherapy dose may be given during eligibility screening evaluation within two weeks prior to Day 1 chemotherapy, and does not need to be repeated on Day 1. Alternatively, per standard of care, ARA-C and hydrocorticosone may be substituted if methotrexate is contraindicated.
- IT methotrexate may also be given at day 29 (+/- 2 days) during disease assessment
- Timing of IT methotrexate is flexible in regards to timing of Marqibo®. However, these agents should not be given simultaneously in order to reduce the risk of administration route error.

Age (years)	Methotrexate (mg)
1-1.99	8 mg
2-2.99	10 mg
3-8.99	12 mg
≥ 9	15 mg

Cohort B: ALL R3/Marqibo without anthracycline

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 29
Marqibo®	●					●	●					●	Response Evaluation
Dexamethasone	●	●	●	●	●		●	●	●	●	●		
Pegaspargase#			●						●				
IT Methotrexate	●					●							

Asparaginase Erwinia chrysanthemi (Erwinaze®), crisantapase (Erwinase®) asparaginase Erwinia chrysanthemi (recombinant)-rywn (Rylaze®) may be substituted for allergy to Pegaspargase. See below.

Drug Administration Details:
As per Cohort A, without mitoxantrone

Marqibo®

- Dose Level 1: 1.5 mg/m^2/dose (no dose cap) given IV over 60 minutes (±10 minutes) on days 1, 8, 15 and 22.
- Dose Level 2: 2 mg/m^2/dose (no dose cap) given IV over 60 minutes (±10 minutes) on days 1, 8, 15 and 22.
- Review list of concomitant medications that are prohibited (CYP3A4 inhibitors) or to be used with caution (Appendix 3). See section 4.5 for drug interactions.
- Dose will be given over 60 minutes ± 10 minutes

Other agents and instructions as detailed above in Cohort A, without mitoxantrone.

Cohort C: **Modified Maintenance with Marqibo®**

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Daily through day 13	Day 14
Marqibo®	●							Response Evaluation
Dexamathasone	●	●	●	●	●			
Methotrexate (PO)	●					●		
Mercaptopurine (PO)	●	●	●	●	●	●	●	
IT Methotrexate as needed no more than once weekly								

Marqibo®

- Dose Level 1: 1.5 mg/m^2/dose (no dose cap) given IV over 60 minutes (±10 minutes) on day 1.
- Dose Level 2: 2 mg/m^2/dose (no dose cap) given IV over 60 minutes (±10 minutes) on day 1.
- Review list of concomitant medications that are prohibited (CYP3A4 inhibitors) or to be used with caution (Appendix 3). See section 4.5 for drug interactions.
- Dose will be given over 60 minutes ± 10 minutes

Dexamethasone

- 6 mg/m^2/day divided BID given orally on days 1 through 5. The two doses should be separated by at least 8 hours

- Any formulation of dexamethasone is acceptable

Methotrexate

- 20 mg/m^2/dose given orally on day 1 and day 8.

Mercaptopurine

- 75 mg/m^2/dose/day given orally, daily from days 1-13.

Intrathecal methotrexate

- Given intrathecally as needed, but no more than once weekly. Age-based dosing as below. Alternatively, per standard of care, ARA-C and hydrocorticosone may be substituted if methotrexate is contraindicated.
- Timing of IT methotrexate is flexible in regard to timing of Marqibo®. However, these agents should not be given simultaneously in order to reduce the risk of administration route error.

Age (years)	Methotrexate (mg)
1-1.99	8 mg
2-2.99	10 mg
3-8.99	12 mg
≥ 9	15 mg

See appendix 8 for starting dose guidelines.

Dose modifications: (for patients without pre-existing disease related cytopenia)
If neutrophil count falls below 500/mcL or if platelet count falls below 50,000/mcL during cohort C, mercaptopurine will be held until recovery of neutrophil count above 750/mcL and platelets > 75,000/mcL.

For the first drop in ANC or platelets, resume MP at the same dose the patient was taking prior to the episode of myelosuppression.

If neutrophil count falls below 500/mcL or if platelet count falls below 50,000/mcL for a second (or greater) time, discontinue doses of MP

In the setting of liver dysfunction, with 6MP and oral methotrexate:

For increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 5x ULN (Grade 3 toxicity), obtain total and direct bilirubin. Monitor SGPT/ALT, SGOT/AST and total and direct bilirubin as long as transaminases remain over 5x ULN.

Continue full dose therapy unless either of the following occurs:

- Direct bilirubin > 2 mg/dL

- SGPT/ALT or SGOT/AST > 20x ULN (Grade 4 toxicity) ~~on 2 determinations at least 1 week apart.~~
- If either of these occurs, hold mercaptopurine and monitor labs as above, weekly. Restart at full dose therapy when the transaminase elevation is < Grade 3 (less than 5x ULN), as long as direct bilirubin is < 2 mg/dl.

Exclude infectious hepatitis for persistent (> 1 month) Grade 3 elevations in SGPT/ALT or SGOT/AST above 5x ULN.

Consider discontinuing trimethoprim/sulfamethoxazole (TMP/SMX) in favor of an alternative approach to Pneumocystis prophylaxis and holding/modifying all other potentially hepatotoxic medications.

Cycle 2:
Patients who tolerate cycle 1 without DLT may have the option to repeat this cycle once. Cycle 2 may start on Day 15 – 22 of cycle 1.

4.2 Dose Limiting Toxicity

Toxicity will be graded using the CTCAE criteria, version 4.03. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Any dose-limiting toxicity (DLT) should be reported immediately through the TACL Operations Center to the Study Chair or Vice Chair. In addition to CTCAE, grading of sensory and motor neuropathies will be augmented by definitions listed in Appendix 5.

4.2.1 Definition of DLT: Dose limiting toxicity (DLT) will be defined as the occurrence of non-hematologic DLT and/or hematologic DLT as defined below.

4.2.1.1 Non-hematological DLT:

(Cohorts A and B) Any Grade 3 or greater non-hematological toxicity that is possibly, probably or definitely attributable to the protocol regimen and prevents a patient from receiving the required number of doses of therapy (as specified in Section 9.0) or from proceeding with further therapy by day 49 of the treatment cycle.

(Cohort C) Any Grade 3 or greater non-hematological toxicity that is possibly, probably or definitely attributable to the protocol regimen and prevents a patient from receiving the required number of doses of therapy (as specified in Section 9.0) or from proceeding with further therapy by day 21 of the treatment cycle for Stratum C.

4.2.1.2 Hematological DLT:

(Cohorts A and B) The absence of peripheral blood count recovery (ANC >500/µL and platelet count > 20,000/µL) 7 weeks (49 days) after the start of chemotherapy in the absence of persistent leukemia or documented myelosuppressive infection. Subjects with abnormal blood counts (Grade 1 through 4) at baseline due to disease will not be evaluable for hematologic DLT and will be considered not having had hematologic DLT for the purposes of the definition in 4.2.1.

(Cohort C) The absence of peripheral blood count recovery (ANC > 500/µL and platelet count > 20,000/µL) 3 weeks (21 days) after the start of chemotherapy in the absence of persistent leukemia or documented myelosuppressive infection. Subjects with abnormal blood counts (Grade 1 through 4) at baseline due to disease will not be evaluable for hematologic DLT and will be considered not having had hematologic DLT for the purposes of the definition in 4.2.1.

Adverse events (AEs) that are considered disease-related (not suspected of relationship to protocol specified therapy) will not be considered dose-limiting toxicities.

4.3 Dose Delays and Modifications

The intent of this study design is for all patients to receive and complete one course of therapy. Patients who exhibit signs of disease progression or experience an unacceptable toxicity will be discontinued from treatment. For Marqibo® dosing delays due to hepatotoxicity (see sections 4.3.1.3 and 4.3.1.4), a maximum delay of 7 days is allowed per dose and no dosing is permitted beyond day 35. There will be no dose delays or dose reductions of study drugs for hematologic toxicity during therapy. At the time that interim analysis is performed to evaluate toxicity (see sections 9.2 - 9.5), if it is determined that the regimen has excessive toxicity, protocol amendment may be considered to modify the dose of Marqibo®.

4.3.1 Marqibo®

4.3.1.1 Weekly assessment of neurologic function should be performed prior to administration of Marqibo®. (Appendix 4).

- Subjects who develop grade 3 or greater sensory or motor neuropathy will discontinue Marqibo® treatment.
- Subjects with < grade 3 neuropathy will be closely monitored without any adjustment to Marqibo® dose

4.3.1.2 Dosing will NOT be held for cytopenias.

4.3.1.3 Transaminase elevation: Marqibo® dosing will be delayed for grade 3 or higher AST (aspartate aminotransferase) or ALT (alanine aminotransferase) elevation

until resolution to grade 2 or baseline, then resume full dose. Maximum allowable delays are specified in section 4.3.

4.3.1.4 Hyperbilirubinemia**:**

Bilirubin Level	Dose Delay
Total bilirubin < 1.5 x upper limit of normal and direct bilirubin < 1.4 mg/dL	None, administer full dose
Total bilirubin > 1.5 x upper limit of normal, and/or direct bilirubin ≥ 1.4 mg/dL	Withhold dose until resolution to grade 1 bilirubin or baseline and direct bilirubin < 1.4, then resume full dose. Maximum allowable delays are specified in section 4.3.

For subjects with documented Gilbert's disease, no modification is necessary unless the total bilirubin exceeds 5 x ULN or the direct bilirubin is ≥ 1.4 mg/dL.

4.3.1.5 Jaw Pain: Treat with analgesics; do not modify Marqibo® dose.

4.3.1.6 Extravasation: In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures according to institutional guidelines.

4.3.1.7 Drug Interactions: See Section 4.4

4.3.2 Pegaspargase

4.3.2.1 Allergic Reactions

Local Reactions (inflammation at injection site, swelling): Continue pegaspargase administration in the presence of Grade 1 allergy (transient flushing or rash; drug fever < 38°C).

Anaphylaxis/Systemic Allergic reactions: Systemic allergy is associated with the presence of pegaspargase neutralizing antibodies, which render asparaginase therapy ineffective. Discontinue if the patient develops a systemic allergic reaction (urticaria, wheezing, laryngospasm, hypotension, etc).

4.3.2.2 Coagulopathy: If symptomatic, hold pegaspargase until symptoms resolve, allowing for up to a one-week delay in scheduled dosing or resume with the next scheduled dose. Consider factor replacement (FFP, cryoprecipitate, factor

VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.

4.3.2.3 Hyperbilirubinemia: Pegaspargase should be held in patients with an elevated direct bilirubin ≥ 1.4 mg/dL. Resume when direct bilirubin < 1.4 mg/dL, may give within one week of scheduled dosing.

Direct Bili	Dose modification
≤ 3 mg/dL	Full dose
3.1-5 mg/dL	Hold asparaginase and result when direct bilirubin ≤ 2 mg/dL
>5 mg/dL	HOLD asparaginase; do not substitute other asparaginase products; do not make up missed doses

4.3.2.4 Hyperglycemia: Do not modify dose. Treat hyperglycemia as medically indicated.

4.3.2.5 Hyperlipidemia: Do not modify dose.

4.3.2.6 Ketoacidosis: Hold pegaspargase until blood glucose can be regulated with insulin.

4.3.2.7 Pancreatitis

Grade 2 (Enzyme elevation or radiologic findings only) Hold until symptoms and signs subside, and enzyme levels return to normal and then resume at full dose, allowing for up to a one-week delay from scheduled dosing

Grade 3-4 Asparaginase should be permanently discontinued. elevation (> 2.0x ULN). Severe pancreatitis is a contraindication to additional asparaginase administration.

4.3.2.8 Thrombosis (excluding minor central venous catheter tip related): Withhold pegaspargase and treat with appropriate anticoagulant and/or antithrombotic therapy, as indicated. Upon resolution of symptoms consider resuming asparaginase, while continuing anticoagulant and/or antithrombotic therapy, may allow for up to a one-week delay from scheduled dosing. Do not withhold dose for abnormal laboratory findings without clinical sequelae. Consider evaluation for inherited predisposition to thrombosis.

4.3.2.9 CNS Events (bleed, thrombosis or infarction): Hold pegaspargase. Treat with FFP, factors or anticoagulation as appropriate. Resume at full dose when all

symptoms have resolved (and evidence of recanalization in case of thrombosis by CT/MRI). May allow for up to a one-week delay from scheduled dosing. Consider evaluation for inherited predisposition to thrombosis.

4.3.3 Intrathecal Methotrexate

4.3.3.1 Systemic toxicity: The dosage for IT methotrexate will not be reduced for systemic toxicity (myelosuppression, mucositis, etc.). Instead, leucovorin may be used at a dose of 5 mg/m^2/dose every 12 hours x 2 doses, beginning 48 hours after the IT therapy has been delivered. This may reduce the risk of worsening myelosuppression or mucositis. Leucovorin may also be used in subjects with hepatic transaminase elevation to reduce risk of worsening hepatotoxicity from IT methotrexate.

4.3.3.2 Dose modifications following an episode of acute neurotoxicity: The treating physician must evaluate the patient and, with the family, make the best possible decision with respect to the relative risk and benefit of continued therapy.

4.3.3.3 Hydrocephalus, microcephaly or known abnormality of CSF flow precluding intrathecal chemotherapy via lumbar puncture: Intraventricular chemotherapy via Ommaya catheter may be used in place of intrathecal therapy delivered by LP. Intraventricular chemotherapy should be given according to the same schedule, but at **50% of the corresponding age-based doses** that would be given by LP. NOTE: Obstruction to CSF flow may be a contraindication to intrathecal and/or intraventricular therapy.

4.3.3.4 Viral, bacterial, or fungal meningitis: Omit until resolved.

4.3.4 Dexamethasone

4.3.4.1 Hypertension: Dose should not be reduced. Sodium restriction and antihypertensives should be employed in an effort to control hypertension. Avoid calcium channel blockers due to their potential prohemorrhagic effect.

4.3.4.2 Hyperglycemia: Do not modify dose. Treat hyperglycemia as medically indicated.

4.3.4.3 Pancreatitis: Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis (abdominal pain > 72 hours and > Grade 3 amylase elevation (> 2.0x ULN). Steroids may resume with resolution of pancreatitis, as defined by amylase and lipase to baseline or $\leq$ grade 1 and resolution of pain.

4.3.4.4 Osteonecrosis: Do not modify corticosteroid therapy for osteonecrosis.

4.3.4.5 Severe infection: Do not hold or discontinue steroids without contacting the study chair or vice chair.

4.3.4.6 Severe psychosis: Steroid dose may be reduced by 50%.

4.3.5 Mitoxantrone

4.3.5.1 Hyperbilirubinemia

Total Bilirubin	Dose Reduction
< 5.0 mg/dL	Full dose
≥ 5.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

4.4 Concurrent Therapy and Drug Interactions

Anti-Cancer Therapy: Concurrent anti-cancer therapy not defined within this protocol, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.

Investigational Agents: No other investigational agents may be given while the patient is on protocol therapy.

Complementary/Alternative Therapies: Use of complementary/alternative therapies is not specifically prohibited, but is discouraged. All therapies should be reviewed with the study team for the potential of drug interactions with Marqibo® or any of the other chemotherapeutic agents.

Allopurinol: Tumor lysis syndrome prophylaxis should be employed for all patients. Allopurinol should ideally be started at a dose of approximately 100 mg/m^2/dose PO TID (maximum dose 600 mg/day/subject) at least 8 hours prior to the first dose of chemotherapy and continue until it is apparent that no tumor lysis has developed after 1 week of treatment. Alternatively, rasburicase may be employed as clinically indicated.

Drug Interactions: No formal drug interaction studies have been conducted with Marqibo®. Marqibo® is expected to interact with drugs known to interact with standard formulation vincristine sulfate. Simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included non-liposomal vincristine sulfate have been reported to reduce blood levels of phenytoin and to increase seizure activity. Close monitoring is recommended for subjects taking agents with narrow therapeutic indices and metabolized by the

liver, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine and digoxin.

Vincristine sulfate, the active agent in Marqibo®, is a substrate for cytochrome P450 3A isoenzymes (CYP3A); therefore the concomitant use of strong CYP3A inhibitors should be avoided (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin). Concurrent administration of itraconazole with vincristine has shown to increase onset and severity of neuromuscular adverse effects of vincristine. If anti-fungal therapies are required during study treatment, alternative anti-fungals should be evaluated prior to considering any azoles. ***In the event that it is determined that an azole antifungal is required to treat a documented or suspected fungal infection, the decision to initiate therapy should be made after discussion with the Study Chair or Vice Chair.*** If permission is granted for the use of azole therapy, all azole therapy must be held for 24 hours before AND after each dose of Marqibo®.

Similarly, the concomitant use of strong CYP 3A inducers should be avoided (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) as these may decrease Marqibo® levels.

Vincristine sulfate is also a substrate for p-glycoprotein (p-gp). The effects of concomitant use of potent p-gp inhibitors or inducers has not been investigated; it is likely that these agents will alter the pharmacokinetics or pharmacodynamics of Marqibo®. Therefore the concomitant use of potent p-gp inhibitors or inducers should be avoided.

5.0 SUPPORTIVE CARE

Best supportive care and treatment will be given as appropriate to each patient (antiemetics, antibiotics, transfusions, oxygen therapy, nutritional support, palliative treatment for pain or cough, etc.). Patients may experience profound myelosuppression and immune suppression during this time. Since steroids may mask fever as well as other components of the inflammatory response sepsis during induction may be associated with very mild and subtle symptoms. Caregivers must also be made aware that patients may experience very rapid clinical deterioration. This suggests the need for a supportive care network that can recognize and respond to sudden changes in a patient's condition. Aggressive supportive care improves outcome. The following guidelines are intended to give general heath direction for optimal patient care and to encourage uniformity in the treatment of this patient population. Notify the Study Chair or Vice Chair of any unexpected or unusually severe complications.

5.1 Blood Products:

Investigators should follow institutional guidelines regarding administration of blood products.

5.2 Infection Control and Prophylaxis

Pneumocystis prophylaxis: PJP prophylaxis is **required**, with agents and dosing provided according to institutional guidelines.

Antibacterial prophylaxis: It is recommended that consideration be given to anti-bacterial prophylaxis during periods of neutropenia (ANC $<0.75 \times 10^9$/L). Treating physicians may follow their institutional guidelines.

Herpes simplex virus (HSV) prophylaxis: Patients with history of HSV or positive antibodies should receive prophylaxis according to institutional guidelines.

Fever and Neutropenia: All patients with a fever ≥38.5°C on a single occasion, or >38°C on 2 occasions within 12 hours, and an ANC $<0.500 \times 10^9$/L are to be treated immediately with intravenous broad-spectrum antibiotics after obtaining appropriate cultures. It is recommended that such patients be hospitalized. The specific choice of antibiotics to be used in empiric treatment of febrile neutropenia is dependent on each institution's experience regarding the type of infecting organisms, and their antibiotic sensitivity patterns. Duration of therapy should be determined by site of infection, culture results, and response to treatment. Antifungal treatment is to be considered for the persistence of fever, or emergence of a new fever in neutropenic patients. Surveillance radiographic imaging surveillance for sites of infection should also be performed as clinically indicated. When severe mucositis or a sepsis syndrome is present in patients with febrile neutropenia, or a patient has a history of alpha hemolytic streptococcal infection, consider inclusion of vancomycin in the empiric antibiotic regimen.

Anti-fungal treatment and prophylaxis: Azole antifungal agents (i.e,. fluconazole, itraconazole, voriconazole, posaconazole) given concurrently with Marqibo® can increase risk of neurotoxicity and are prohibited. Anti-fungal prophylaxis is **mandated** in all subjects enrolled in Cohorts A and B from the start of therapy until day 29, and ideally until neutrophil count recovery. All subjects are encouraged to continue antifungal prophylaxis beyond the treatment period especially if neutrophil count recovery has not occurred. The echinocandin class (e.g., caspofungin, micafungin) or the amphotericin class should be employed following institutional guidelines. Any exceptions must be discussed with the Study Chair or Vice Chair.
In the event that it is determined that an azole antifungal is required to treat a documented or suspected fungal infection, the decision to initiate therapy should be made after discussion with the Study Chair or Vice Chair.

All azole therapy must be discontinued at least 1 week prior to the start of initiation of protocol therapy with Marqibo®.

Mucositis/Perirectal Cellulitis: Mucositis should be managed with IV hydration and hyperalimentation if indicated, effective analgesia, broad-spectrum gram-positive and gram-negative antibiotic therapy and empiric antiviral and antifungal therapy as indicated. Management of perirectal cellulitis should include broad-spectrum antibiotic therapy with dual gram-negative coverage as well as anaerobic coverage (i.e. ceftazidime + aminoglycoside + metronidazole; or piperacillin-tazobactam + aminoglycoside), Sitz baths, a strong barrier technique and effective analgesia.

5.3 Antiemetic Protection

Antiemetics should be given to all patients. Dexamethasone administration can be timed accordingly.

5.4 Filgrastim

The routine use of filgrastim is not recommended, but may be used at the discretion of the investigator in situations of serious infection with neutropenia.

5.5 Bowel Prophylaxis (Appendix 6)

All patients must receive prophylaxis against constipation starting with the first dose of Marqibo unless there is diarrhea.

5.6 Dexrazoxane

Dexrazoxane as a cardioprotectant may be used per treating physician discretion.

Since most of the patients entering this study will have been previously treated with anthracyclines, the use of dexrazoxane prior to mitoxantrone will be allowed in attempt to mitigate further cardiotoxicity that might occur from additional mitoxantrone exposure. While the use of dexrazoxane before mitoxantrone is not as well documented as its use with doxorubicin,[17] several papers have reported benefit with dexrazoxane given prior to mitoxantrone in doses 30-60 fold times the mitoxantrone dose.[18-20] The recommended dose of dexrazoxane for use with doxorubicin is ten-times the doxorubicin dose. Based on the Children's Oncology Group recommendations and a recent paper by Feijen et al,[21] the equipotent dose of mitoxantrone to doxorubicin is estimated to be about 1:4. Thus, the dose of dexrazoxane recommended prior to mitoxantrone is 40 times the mitoxantrone dose (400 mg/m^2 in this study). The dexrazoxane infusion should be given rapidly over 15 minutes just prior to starting the bolus dose of mitoxantrone.

6.0 DRUG INFORMATION

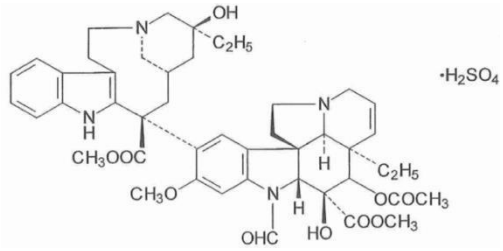
6.1 Marqibo®

Marqibo® (vincristine sulfate liposome injection) is vincristine encapsulated in sphingomyelin/cholesterol liposomes for intravenous administration.

6.1.1 Nomenclature and Molecular Structure

22-oxo-vincaleukoblastine sulfate, which is the chemotherapeutic agent and active ingredient in Marqibo®.
Other names: Vincristine sulfate
Molecular Formula: $C_{46}H_{56}N_4O_{10}H_2SO_4$, M.W.: 923.04

IND number: #59056



6.1.2 Mode of Action and Pharmacology
Vincristine is a natural product belonging to the class of compounds commonly known as vinca alkaloids. It is isolated from the periwinkle (Vinca rosea Linn.) and prepared as a sulfate salt. It is supplied as Vincristine Sulfate Injection, USP which is a component of the Vincristine Sulfate Liposomes Injection (0.16 mg/mL) Marqibo® kit. Marqibo® is a sphingomyelin/cholesterol liposome-encapsulated formulation of vincristine sulfate. Non-liposomal vincristine sulfate binds to tubulin, altering the tubulin polymerization equilibrium, resulting in altered microtubule structure and functions. Non-liposomal vincristine sulfate stabilized the spindle apparatus, preventing chromosome segregation, triggering metaphase arrest and inhibition of mitosis.

6.1.3 Toxicity/Adverse Events
See investigator's brochure (IB) or package insert for a complete discussion of AEs.

a. Neurotoxicity is the DLT of Marqibo®
b. Constipation is common but rarely progresses to serious situations such as bowel obstruction or paralytic ileus.
c. The neuropathy events caused by Marqibo® are characterized by early sensory impairments (numbness, tingling, and paresthesias), followed by deep tendon reflex abnormalities and weakness. Cranial nerve involvement may be heralded by jaw pain, facial numbness, or facial muscle weakness.
d. Myelosuppression occurs frequently, but severe myelotoxicity occurs infrequently
e. Fatigue and non-severe gastrointestinal symptoms (nausea, vomiting, and constipation) occur frequently.
f. Severe infections, including pneumonia, sepsis, and bacteremia, and alopecia have been seen infrequently.
g. Insomnia is common. It may persist and resolve over time.
h. Headache is frequent.

In a Phase 1 open-label, single-center, single-arm dose escalation study to evaluate the safety, activity and pharmacokinetics of Marqibo in children and adolescents with refractory malignant disease, the most commonly reported adverse events were:

- Increases in liver enzyme tests
- Fatigue
- Anemia, white blood cell decreased, platelet count decreased, neutrophil count decreased
- Decreases in blood levels of potassium, calcium, magnesium, albumin, sodium, phosphorus
- Increases in blood levels of glucose, triglycerides, bilirubin, cholesterol, magnesium, uric acid
- Abdominal pain
- Fast heart rate
- Diarrhea
- Nausea, vomiting
- Febrile neutropenia
- Prolonged bleeding time
- Bruising, epistaxis
- Anorexia
- Constipation
- Low blood pressure
- Infections
- Back pain, headache, pain, myalgia
- Parasthesia
- Pruritus
- Rash maculo-papular

In general, nonclinical toxicology studies show that Marqibo and vincristine exhibit comparable toxicological profiles. In clinical studies, the safety profile of Marqibo has been similar to that of vincristine; however, infusion-related pyrexia, which is not typical with vincristine, has been observed at a low incidence rate with Marqibo.

Possible side effects of vincristine:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Insomnia	Jaw pain, headache	Extravasation (rare) but if occurs=local ulceration; shortness of breath and bronchospasm

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Prompt: Within 2-3 weeks, prior to the next course	Alopecia, constipation	Weakness, abdominal pain; mild brief myelosuppression (leukopenia, thrombocytopenia, anemia)	Paralytic ileus; ptosis, diplopia, night blindness; hoarseness; vocal cord paralysis; SIADH, seizure; defective sweating,
Delayed: Any time later during therapy, excluding the above conditions	Loss of deep tendon reflexes	Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop; abnormal gait	Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (including bladder atony, dysuria, polyuria, nocturia, urinary retention); autonomic
			neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss
Late: Any time after completion of treatment			
Unknown Frequency and Timing: Fetal and teratogenic toxicities. Fetal toxicities and teratogenic effect of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities have included: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk.			

Pregnancy and Breast Feeding

Risks to a fetus and newborn are unknown. Individuals who are pregnant or lactating will not be candidates for this protocol.

6.1.4 Formulation and Stability

Marqibo® is supplied as a single-use, 3-vial kit designed to enable entrapment of vincristine in sphingomyelin/cholesterol liposomes at the time of use. The active agent consists of vincristine sulfate as an aqueous solution and the vehicle consists of sphingomyelin/cholesterol liposomes with a sodium phosphate buffer as described in the 3-vial kit component table below.

Component (Abbreviation)	**No. of Vials/Kit**	**Description**
Active (VSI)	1	Vincristine Sulfate Injection, USP (1 mg/mL, 5 mL)
Liposomes (SCLI)	1	Sphingomyelin/Cholesterol Liposomes Injection (103 mg/mL, 1 mL)
Buffer (SPI)	1	Sodium Phosphate Injection (14.2 mg/mL, 25 mL)

6.1.5 Preparation and Administration

Marqibo® and its components are to be stored in a controlled refrigerator (2-8°C; 36-46°F) until the time of constitution; refrigeration temperature logs (or equivalent records) should be maintained. Retain vials in carton until time of use. **DO NOT FREEZE**

Constitution should take place under strict aseptic conditions following detailed instructions included in the kit. After constitution of Marqibo®, the constituted product should be stored in the constitution vial or in the infusion bag after being diluted according to instruction into an IV infusion bag containing 5% dextrose injection or 0.9% sodium chloride injection to a final total volume of 100 mL.

The constituted product, whether in the constitution vial or diluted in the infusion bag, should be stored at controlled room temperature (15-30°C; 59-86°F) and must be administrated within 12 hours of the constitution start time.

All unused Marqibo® kits will be destroyed at the site as per the institutional guidelines for pharmacy's cytotoxic agent destruction procedures and according to applicable regulations. Destruction on site should only occur with prior authorization from the TACL Operations Center. Documentation of local Marqibo® destruction must be provided. Marqibo® is an investigational drug. Drugs supplied for clinical investigation should be given by or under the supervision of the investigators throughout this study.

Marqibo® will be administered IV over 60 minutes (±10 minutes). Marqibo® may be infused through a free running peripheral or central venous catheter, without the use of an inline filter,

using an infusion pump. For peripheral venous access, a minimum 21-gauge catheter or butterfly should be used. It is extremely important that the intravenous needle or catheter be properly positioned before any Marqibo® is administered. Leakage into surround tissue during intravenous administration of Marqibo® may cause local irritation. If extravasation occurs, the injection should be discontinued immediately and managed per institutional procedures. Any remaining portion of the dose should be introduced into another vein. Marqibo® should be administered only by intravenous infusion and by individuals experienced with the administration of vincristine sulfate. In-line filters should not be used and closed transfer filtration devices should not be used in preparation without specific review and approval by TACL Operations. Marqibo® should be not mixed with or diluted with other drugs or solution other than 5% dextrose injection or 0.9% sodium chloride injection. It is not required that the Marqibo® dose be corrected for obese subjects.

The amount (in mg) of study drug to be administered will be determined based on body surface area (BSA). In calculating BSA, actual height obtained at screening and weights obtained at the onset of induction should be used. There will be no adjustment to "ideal" body weight.

6.1.6 Supplier

Acrotech Biopharma will supply Marqibo® on this study as well as the equipment necessary for preparation on an as needed basis, including a dry heat block, waterbath, thermometer and timer. Drug and equipment can be ordered directly from Acrotech Biopharma
using the forms and procedures provided in the member's only section of the TACL website.

6.1.7 Drug Accountability

All study drug supplies must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply study drug to other Investigators, subjects, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from the Sponsor.

The pharmacist will maintain complete drug accountability records. Periodically throughout the study, and again at the end of the study, TACL will require submission of the drug accountability record providing a complete accounting of the receipt and disposition of all study drug kits and the total number of kits dispense to each subject along with the Marqibo® kit lot number used for each individual patient administration. Information recorded during the drug preparation steps are to be retained per institutional requirements.

6.1.8 Drug Disposal

Avoid contact with skin by using gloves. All needles, syringes, vials, and other materials that have come in contact with vincristine sulfate should be segregated in plastic bags, sealed, and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.

If incineration is not available, sodium hypochlorite (household bleach) may be added to the vial(s) to detoxify the vincristine sulfate. Care must be taken to vent the vial(s) to avoid a pressure build-

up of chlorine gas generated. Decomposition occurs within 10 minutes. Dispose of detoxified vials in a safe manner.

Dispose all components of the Marqibo® Kit that did not come into contact with vincristine sulfate as per established pharmacy procedures for non-bio hazardous waste.

6.2 Dexamethasone (Decadron®, Hexadrol®, Dexone®, Dexameth®) NSC#34521

6.2.1 Source and Pharmacology:
Dexamethasone is a synthetic fluorinated glucocorticoid devoid of mineralocorticoid effects. Dexamethasone, 0.75 mg, has potent anti-inflammatory activity equivalent to approximately 5 mg of prednisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Elimination half-lives for the following age groups have been reported to be: infants and children under 2 years of age: 2.3 to 9.5 hours, 8 to 16 years: 2.82 to 7.5 hours, and adults (age not specified): 3 to 6 hours. The biologic half-life is 36-72 hours. It is primarily metabolized in the liver and excreted by the kidneys.

6.2.2 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Insomnia, hyperphagia	Gastritis	Hyperuricemia
Prompt: Within 2-3 weeks, prior to the next course	Immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitaryadrenalaxis suppression, acne (L)	Hyperglycemia, facial erythema, poor wound healing, infections (bacterial,fungal, parasitic, viral), edema	Pancreatitis (L), increased intraocular pressure (L), hypertension, psychosis, vertigo, headache
Delayed: Any time later	Cushing's syndrome (moon facies, truncal obesity)	Striae and thinning of the skin, easy bruising,	Spontaneous fractures (L),

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
during therapy, excluding the above conditions		Muscle weakness, osteopenia	growth suppression, peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L)
Late: Any time after completion of treatment		Cataracts (which may be reversible on discontinuation of dexamethasone in children)	
Unknown Frequency and Timing: dexamethasone crosses the placenta with 54% metabolized by enzymes in the placenta. In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. There are no reports of dexamethasone excretion into breast milk in humans; however, it is expected due to its low molecular weight that it would partition into breast milk.			

(L) Toxicity may also occur later.

6.2.3 Formulation and Stability:
Available in 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 mg tablets; liquid formulations are available in 0.5mg/5ml and 0.5mg/0.5ml concentration. Inactive ingredients vary depending on manufacturer but tablet formulations may include: calcium or magnesium stearate, corn starch, lactose, and various dyes. Liquid formulations may include: 5%-30% alcohol, Benzoic acid, sorbitol, sodium saccharin, glycerin, purified water, and various dyes.

Dexamethasone sodium phosphate solution for injection is available as 4 mg/ml, 10 mg/ml, 20 mg/ml and 24 mg/ml. 4 mg of dexamethasone sodium phosphate is equivalent to 3.33 mg of dexamethasone. Vial sizes include 1 ml, 5 ml, 10 ml, 25 ml, 30 ml and are available in multidose vials as well as unit of use vials and syringes. Inactive ingredients vary depending on manufacturer but include creatinine, sodium citrate, sodium hydroxide to adjust pH, Water for Injection, sodium sulfite, bisulfite and metabisulfite, methyl and propyl paraben, benzyl alcohol, and EDTA.

6.2.4 Guidelines for Administration:
See Treatment and Dose Modifications section of the protocol for dose and schedule.

Dexamethasone Sodium Phosphate for Injection may be given IV, or IM undiluted. For IV use, it may be further diluted in dextrose or saline containing solutions. Avoid benzyl alcohol containing dexamethasone solutions for use in neonates. Diluted solutions that contain no preservatives should be used within 24 hours, but maintain stability for at least 14 days in PVC bags at room temperature protected from light.

6.2.5 Supplier: Commercially available. See package insert for further information.

6.3 Mitoxantrone (Novantrone®, CL 232315, DAD, DHAD, Mitozantrone) NSC #301739

6.3.1 Source and Pharmacology:
Mitoxantrone is a substituted alkylaminoanthraquinone and is a potent inhibitor of DNA and RNA synthesis in vitro and binds strongly to DNA. Mitoxantrone most likely acts through intercalation between base pairs of the DNA double helix causing crosslinks and strand breaks. In addition, it is a topoisomerase II inhibitor, an enzyme responsible for uncoiling and repairing damaged DNA. It has a cytocidal effect on both proliferating and non-proliferating cultured human cells, suggesting lack of cell cycle phase specificity. The drug disappears rapidly from plasma (drug found only in the 3-minute sample) and < 1% appears in the urine in 24 hours. The mean alpha half-life of mitoxantrone is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours and the mean gamma (terminal or elimination) half-life is 23 to 215 hours (median approximately 75 hours). Primary excretion is biliary with 25% appearing in the feces; renal excretion accounting for only 11% of the total dose. Mitoxantrone clearance is reduced by hepatic impairment. Patients with severe hepatic dysfunction (bilirubin > 3.4 mg/dL) have an AUC more than three times greater than that of patients with normal hepatic function receiving the same dose. Mitoxantrone is approximately 95% protein bound.

6.3.2 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, diarrhea, fever, anorexia, green blue discoloration of the urine and/or sclera	Abdominal pain, back pain, headache, phlebitis, constipation	Anaphylaxis, angioedema, cardiac arrhythmias1 (bradycardia), seizures, extravasation reactions rare but if occur can lead to: (erythema, swelling, pain, burning and/or blue discoloration of the skin and rarely tissue necrosis), tumor lysis

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (L), mucositis /stomatitis, immunosuppression, alopecia, fatigue	Transient elevation of LFTs, pruritis with desquamation of the skin due to progressive dryness	Rash, conjunctivitis, (GI) hemorrhage, interstitial pneumonitis
Delayed: Any time later during therapy, excluding the above conditions	Amenorrhea, menstrual disorders, temporary reduction in sperm count	Cardiotoxicity (decreased LVEF)2 (L)	CHF, hepatotoxicity
Late: Any time after completion of treatment			Secondary malignancy
Unknown Frequency and Timing: Fetal toxicities and teratogenic effects of mitoxantrone have been noted in animals. Toxicities include: low birth weight and prematurity. Mitoxantrone is excreted in human milk and significant concentrations (18 ng/mL) have been reported for 28 days after the last administration.			

1 Rarely clinically significant.
2 Risk increases with chest radiation and prior anthracycline dosage (L) Toxicity may also occur later.

6.3.3 Formulation and Stability:
The concentrate is a sterile, non-pyrogenic, non-preserved, dark blue aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride (0.80% w/v), sodium acetate (0.005% w/v), and acetic acid (0.046 % w/v) as inactive ingredients with 0.14 mEq of sodium per mL. Mitoxantrone is provided as 20 mg (10 mL), 25 mg (12.5 mL) and 30 mg (15 mL) vials. Store intact vials at 15°-25°C (59°-77°F). Undiluted mitoxantrone injection should be stored not longer than 7 days between 15°-25°C (59°-77°F) or 14 days under refrigeration. Refrigeration of the concentrate may result in a precipitate, which redisolves on warming to room temperature. DO NOT FREEZE.

6.3.4 Guidelines for Administration:

See Treatment and Dose Modifications sections of the protocol.

Mitoxantrone must be diluted prior to injection. DO NOT GIVE IV PUSH. The dose of mitoxantrone should be diluted to ≤ 0.4 mg/mL with either 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP). The dilution is stable at room temperature for 48 hours with no loss of

potency. Admixture with heparin may result in precipitation. Mitoxantrone is an irritant: Care should be taken to avoid extravasation; the use of a central line is suggested. If it is known or suspected that subcutaneous extravasation has occurred, it is recommended that intermittent ice packs be placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and surgery consultation obtained early if there is any sign of a local reaction.

6.3.5 Supplier: Commercially available. See package insert for more detailed information.

6.4 Methotrexate (MTX, AMETHOPTERIN) NSC #740 (112004)

6.4.1 Source and Pharmacology:
A folate analogue which inhibits the enzyme dihydrofolate reductase, halting DNA, RNA, and protein synthesis. Initial IV half-life is about 1.2 hours, with a second phase of 10.4 hours. About 50% is bound to protein. Transport into the cell is carrier-mediated. Once in the cell, MTX (Glu)n are formed, the number of which are related to the cytocidal effect. Once MTX (Glu)n are formed, they do not pass back out of the cell unless converted back to MTX. After oral administration, about 60% of a 30 mg/m2 dose is rapidly absorbed from the GI tract, with peak blood levels at 1 hour. Above this dose, absorption decreases significantly. Absorption can be very erratic, varying between 23% and 95%. A 20-fold difference between peak levels of drug has been reported (0.1 to 2mM). There is significant enterohepatic circulation of MTX: 9% of MTX is excreted in feces. MTX is excreted unchanged in the urine, except at high doses when it is partially metabolized to hydroxy-MTX and excreted.

6.4.2 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, headache	Arachnoditis: (headache, fever, vomiting, meningismus, nuchal rigidity, and pleocytosis)	Anaphylaxis, vomiting, seizures(L), confusion, back pain, rash, bleeding into subarachnoid or subdural space (risk > with platelet counts < 20,000),

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia, somnolence, cranial nerve palsy, subacute myelopathy (paraparesis/paraplegia), speech disorders, pain in the legs, bladder dysfunction
Delayed: Any time later during therapy, excluding the above conditions		Learning disability (L), Cognitive disturbance	Leukoencephalopathy[1] (L)
Late: Any time after completion of treatment			Progressive CNS deterioration[1]
Unknown Frequency and Timing: Fetal and teratogenic toxicities:			

[1] May be enhanced by HDMTX and/or cranial irradiation. (L)
Toxicity may also occur later.

6.4.3 Formulation and Stability:
Intact vials may be stored at room temperature (22°-25°C) and are stable for at least 2 years or until date of expiration. IT MTX: Available in various dosages in **preservative-free liquid**, 25 mg/mL in a 2 mL vial, or as a lyophilized powder. Reconstitute the powder with buffered saline solution. The methotrexate solutions may be further diluted with buffered saline or the patient's own CSF. After mixing it should be used within 24 hours, since MTX contains no antibacterial preservative.

6.4.4 Guidelines for Administration:
See Treatment and Dose Modification sections of the protocol.

6.4.5 Supplier:
All forms of methotrexate are commercially available. See package insert for further information.

6.5 Pegaspargase

(Pegaspargase, PEGLA, PEG-L-asparaginase, polyethylene glycol-L-asparaginase, Oncaspar®,) NSC #624239.

6.5.1 Source and Pharmacology:

Pegaspargase is a modified version of the enzyme L-asparaginase. L- asparaginase is modified by covalently conjugating units of monomethoxypolyethylene glycol (PEG), molecular weight of 5000, to the enzyme, forming the active ingredient PEG-L-asparaginase. The L-asparaginase (L-asparagine amidohydrolase, type EC-2, EC 3.5.1.1) used in the manufacture of Pegaspargase is derived from *Escherichia coli* which is purchased in bulk from Merck, Sharp and Dohme. L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. The ability to synthesize asparagine is notably lacking in malignancies of lymphoid origin. Asparaginase depletes L- asparagine from leukemic cells (especially lymphoblasts) by catalyzing the conversion of L-asparagine to aspartic acid and ammonia. In predominately L- asparaginase naïve adult patients with leukemia and lymphoma, initial plasma levels of L-asparaginase following intravenous administration of pegaspargase were determined. Apparent volume of distribution was equal to estimated plasma volume. L-asparaginase was measurable for at least 15 days following the initial treatment with Pegaspargase. The approximate t½ in adult patients is 5.73 days. The enzyme could not be detected in the urine. The half-life is independent of the dose administered, disease status, renal or hepatic function, age, or gender. In a study of newly diagnosed pediatric patients with ALL who received either a single intramuscular injection of pegaspargase (2500 IU/m2), *E. coli* L-asparaginase (25000 IU/m2), or *Erwinia* (25000 IU/m2), the plasma half-lives for the three forms of L-asparaginase were: 5.73 ± 3.24 days, 1.24 ± 0.17 days, and 0.65 ± 0.13 days respectively. The plasma half-life of pegaspargase is shortened in patients who are previously hypersensitive to native L-asparaginase as compared to nonhypersensitive patients. L-asparaginase is cleared by the reticuloendothelial system and very little is excreted in the urine or bile. Cerebrospinal fluid levels are < 1% of plasma levels.

6.5.2 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Allergic reactions (total likelihood of local, and or systemic reaction especially if previous hypersensitivity reaction to native asparaginase), pain at injection site, weakness, fatigue, diarrhea	Allergic reactions (total likelihood of local, and or systemic reaction if **no** previous hypersensitivity reaction to native asparaginase), rash	Anaphylaxis, hyper/hypotension, tachycardia, periorbital edema, chills, fever, dizziness, dyspnea, bronchospasm, lip edema, arthralgia, myalgia, urticaria, mild nausea/vomiting, abdominal pain, flatulence, somnolence, lethargy, headache, seizures (L), hyperuricemia

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Prompt: Within 2-3 weeks, prior to the next course	Hyperammonemia (L), coagulation abnormalities with prolonged PTT, PT and bleeding times (secondary to decreased synthesis of fibrinogen, AT-III & other clotting factors) (L)	Hyperglycemia, abnormal liver function tests, pancreatitis (L), increased serum lipase/amylase	Hemorrhage (L), DIC, thrombosis, anorexia, weight loss, CNS ischemic attacks, edema, azotemia and decreased renal function, mild leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, hemolytic anemia, infections (sepsis with/without septic shock, subacute bacterial endocarditis (SBE), URI), CNS changes including irritability, depression, confusion, EEG changes, hallucinations, coma and stupor, paresthesias, hypertriglyceridemia, hyperlipidemia, Parkinson- like syndrome with tremor and increase in muscular tone, hyperbilirubinemia, chest pain
Delayed: Any time later during therapy, excluding the above conditions			Renal failure, urinary frequency, hemorrhagic cystitis, elevated creatinine and BUN, fatty liver deposits, hepatomegaly, liver failure

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Unknown Frequency and Timing: Animal reproduction studies have not been conducted with pegaspargase. It is not known whether pegaspargase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, fetal toxicities and teratogenic effects of asparaginase have been noted in animals. It is unknown whether the drug is excreted in breast milk.			

(L) Toxicity may also occur later.

6.5.3 Formulation and Stability
Each milliliter of pegaspargase contains: PEG-L-asparaginase 750 IU ± 20%, monobasic sodium phosphate, *USP* 1.20 mg ± 5% dibasic sodium phosphate, *USP* 5.58 mg ± 5%, sodium chloride, *USP* 8.50 mg ± 5% , Water for Injection, *USP* qs to 1 mL. The specific activity of pegaspargase is at least 85 IU per milligram protein. Available in 5 mL vials as Sterile Solution for Injection in ready to use single-use vials, preservative free. Keep refrigerated at 2°-8°C (36°- 46°F). Do not use if stored at room temperature for more than 48 hours. **DO NOT FREEZE.** Do not use product if it is known to have been frozen. Freezing destroys activity, which cannot be detected visually.

6.5.4 Guidelines for Administration
For IM administration: the volume at a single injection site should be limited to 2 mL. If the volume to be administered is greater than 2 mL, multiple injection sites should be used. For IV administration: dilute pegaspargase in 100 mL of 0.9% sodium chloride injection (0.9% NaCl) or 5% dextrose injection (D5W) and infuse over 1 to 2 hours through a NS or D5W running infusion line. Pegaspargase admixed in 100 mL of NS or D5W is stable for 48 hours at room temperature. Pegaspargase diluted in 100 mL of 0.9% NaCl is stable for up to 72 hours refrigerated (4ºC [39°F]) (refrigerated stability data on file with Sigma-Tau). Avoid excessive agitation. DO NOT SHAKE. Do not use if cloudy of if precipitate is present. Have available during and after the infusion: antihistamine, epinephrine, oxygen, and IV corticosteroids. Observe patient for at least ONE hour after administration for signs of hypersensitivity reactions or per institutional standards.

6.5.5 Supplier:
Commercially available. See package insert for further information.

6.6 ASPARAGINASE Erwinia chrysanthemi (Erwinaze®) or cristantapase (Erwinase®) or Erwinia chrysanthemi (recombinant)-rywn (Rylaze®)

6.6.1 Source and Pharmacology:
L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. Neoplastic cells associated with acute lymphoblastic leukemia, acute myeloid leukemia and lymphoblastic lymphosarcoma are asparagine-dependent but lack asparagine synthetase activity. The administration of Lasparaginase produces an anti-neoplastic effect by catalyzing asparagine into aspartic acid and ammonia. As a result, these cells lack the ability to produce the asparagine necessary for protein

metabolism and survival. Deamination of glutamine may also play a role in the antineoplastic activity of asparaginase.

*Erwinia chrysanthemi [*Erwinaze® or Cristantapase (Erwinase®)] is asparaginase derived from cultures of *Erwinia chrysanthemi*. L-asparaginase is a tetrameric enzyme; each of the four identical subunits has a molecular weight of approximately 35 kDa. Asparaginase *Erwinia chrysanthemi* is immunologically distinct from *E. coli* L-asparaginase and may allow continued asparaginase therapy when a hypersensitivity reaction occurs to *Escherichia coli*-derived asparaginase. The package labeling states that there is insufficient information to characterize the incidence of antibodies to asparaginase *Erwinia chrysanthemi*. Several factors are involved in immunogenicity assay results and the assessment of antibodies, including assay methodology, assay sensitivity and specificity, sample handling, timing of sample collection, concomitant medications, and the underlying disease state. The following data have been reported on each of the three preparations of asparaginase:

Clinical Pharmacology of Asparaginase Formulation	Fetal toxicities and teratogenic effects of mitoxantrone have been noted in animals. Toxicities include: low birth weight and prematurity. Mitoxantrone is excreted in human milk and significant concentrations (18 ng/mL) have been reported for 28 days after the last administration.	**% Anti-Asparaginase Antibody positive patients**
Native *Escherichia Coli*	26-30 hours	45-75
Pegylated-asparaginase	5.5-7 days	5-18
Erwinia Asparaginase	16 hours (7-13 hrs)	30-50

From: Avramis, V; Panosyan, E; Pharmacokinetic/Pharmacodynamic Relationships of Asparaginase Formulations: The Past, the Present and Recommendations for the Future. Clin Pharmacokinet 2005; 44 (4): 367-393.

Effective asparaginase levels have been defined as activity of ≥ 0.1 International Units per mL. Clinical trials with asparaginase *Erwinia chrysanthemi (Ewinaze)* demonstrated that 100% of patients achieved effective asparaginase levels at 48 and 72 hours (n=35 and n=13, respectively) following the third total dose when given on a Monday, Wednesday, Friday schedule. No formal drug interaction studies have been performed with asparaginase *Erwinia chrysanthemi*.

Asparaginase erwinia chrysanthemi (recombinant)-rywn contains an asparagine specific bacterial enzyme (L-asparaginase). L-asparaginase is a tetrameric enzyme that consists of four identical 35 kDa subunits with a combined molecular weight of 140 kDa. The amino acid sequence is identical to native asparaginase *Erwinia chrystanthemi* (also known as crisantapase). The activity of

asparaginase erwinia chrysanthemi (recombinant)-rywn is expressed in units, defined as the amount of enzyme that catalyzes the conversion of 1µmol of L-asparagine per reaction minute, per mg of protein. Asparaginase erwinia chrysanthemi (recombinant)-rywn is produced by fermentation of a genetically engineered *Pseudomonas fluorescens* bacterium containing the DNA which encodes for asparaginase *Erwinia chrysanthemi*.

6.6.2 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Allergic reactions Anaphylaxis, urticaria	Local injection site reactions, fever
Prompt: Within 2-3 weeks, prior to the next course			Pancreatitis, glucose intolerance, thrombosis, hemorrhage, transient ischemic attack, disseminated intravascular coagulation, hyperbilirubinemia, alanine aminotransferase increased, aspartate aminotransferase increased, hyperglycemia, hyperammonemia, vomiting, nausea, abdominal pain, headache, diarrhea, seizure
Unknown Frequency and Timing: Fetal toxicities and teratogenic effects of L-asparaginase have been noted in animals. It is unknown whether the drug is excreted in breast milk. Adequate, well-controlled studies of asparaginase *Erwinia chrysanthemi* have NOT been conducted. It is not known whether asparaginase *Erwinia chrysanthemi* will cause fetal harm or affect the ability to reproduce. It is not known if asparaginase *Erwinia chrysanthemi* is excreted into breast milk. The use of asparaginase *Erwinia chrysanthemi* should be avoided in pregnant or lactating patients.			

6.6.3 Formulation and Stability

Asparaginase *Erwinia chrysanthemi* is supplied as a sterile, white lyophilized powder for reconstitution in a clear glass vial with a 3 mL capacity. Each vial contains 10,000 International Units of asparaginase *Erwinia chrysanthemi* and the following inactive ingredients: glucose monohydrate (5.0 mg), sodium chloride (0.5 mg). Store between 2°C and 8°C (36° to 46ºF). Store intact vials between 2°C and 8°C (36° - 46ºF). Protect from light.

Asparaginase erwinia chrysanthemi (recombinant)-rywn) Rylaze®) injection is supplied as a sterile, clear to opalescent, colorless to slightly yellow, preservative-free solution for intramuscular injection.

Each 0.5 mL contains 10 mg asparaginase erwinia chrysanthemi (recombinant)-rywn and the inactive ingredients: polysorbate 80 (0.1 mg), sodium chloride (1.5 mg), sodium phosphate dibasic anhydrous (0.8 mg), sodium phosphate monobasic monohydrate (0.6 mg), and trehalose (32.1 mg). Sodium hydroxide may be added to adjust the pH. The pH is approximately 7.

6.6.4 Guidelines for Administration
Follow manufacturer guidelines for preparation and administration. No more than 2 mL should be given at any one injection site. Doses larger than 2 mL should be divided and given in separate administration sites.

6.6.5 Supplier:

Commercially available. See package insert for further information.

6.7 Mercaptopurine

6.7.1 Source and Pharmacology (MP, purinethol®, 6-mercaptopurine) NSC#000755

Mercaptopurine is an analogue of the purine bases adenine and hypoxanthine. The main intracellular pathway for MP activation is catalyzed by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) which catalyzes the conversion of MP to several active nucleotide metabolites including thioinosinic acid, a ribonucleotide which can interfere with various metabolic reactions necessary for nucleic acid (RNA and DNA) biosynthesis. It can also cause pseudofeedback inhibition of the first step in de novo purine biosynthesis or convert to another ribonucleotide which can cause feedback inhibition. Mercaptopurine can be incorporated into DNA in the form of 6-TG nucleotides as well and thus produce toxicity. The absorption of an oral dose of MP is incomplete and variable, with only about 16%-50% of an administered dose reaching the systemic circulation secondary to a first pass metabolism in the liver. Food intake and co-administration with cotrimoxazole (TMP/SMX) significantly reduces absorption of MP. After IV administration, MP has a plasma half-life of 21 minutes in children and 47 minutes in adults. Approximately 19% is bound to protein. Mercaptopurine is well distributed into most body compartments except the CSF. (With high dose IV MP the CSF to plasma ratio is 0.15) MP is metabolized by xanthine oxidase in the liver to 6-Thiouric acid an inactive metabolite. In patients receiving both MP and allopurinol (a xanthine oxidase inhibitor) the dose of MP must be reduced by 50-75%. Since TPMT, 6-thiopurine methyltransferase, is also one of the enzymes involved in the metabolism of MP, those individuals who have an inherited deficiency of the enzyme may be unusually sensitive to the myelosuppressive effects of MP and prone to develop rapid bone marrow suppression following the initiation of treatment. Mercaptopurine is excreted in urine as metabolites and some unchanged drug; about half an oral dose has been recovered in 24 hours. A small proportion is excreted over several weeks.

6.7.2. Toxicology

Incidence	Toxicities

Common (>20% of patients)	Neutrophil count decreased, white blood cell decreased, anorexia, fatigue
Occasional (4 - 20% of patients)	diarrhea, nausea, vomiting, malaise, oligospermia, infection, fever, platelet count decreased, anemia, mucositis, stomach pain, ulcerative bowel lesion, skin rash, alanine aminotransferase increased, aspartate aminotransferase increased
Rare (≤3% of patients)	Urticaria, skin hyperpigmentation, alopecia, hyperuricemia, hepatic failure, hepatic necrosis, blood bilirubin increased, pulmonary fibrosis, secondary malignant neoplasm, renal toxicity, uricosuria, pancreatitis

Pregnancy Category D

Mercaptopurine can cause fetal harm, including an increased incidence of abortion and stillbirth. Advise women to avoid becoming pregnant while receiving mercaptopurine. Mercaptopurine was embryo-lethal and teratogenic in several animal species (rat, mouse, rabbit, and hamster). It is not known whether mercaptopurine is excreted in human milk; breastfeeding should be avoided.

6.7.3 Formulation and Stability:

Mercaptopurine is available as a 50 mg tablet containing mercaptopurine and the inactive ingredients corn and potato starch, lactose, magnesium stearate, and stearic acid. Store at 15°-25°C (59°-77°F) in a dry place. In the United States, mercaptopurine is also available as an oral suspension in a concentration of 20 mg/mL (2000 mg/100 mL per bottle). The oral suspension is a pink to brown viscous liquid supplied in amber glass multiple-dose bottles with a child resistant closure. It should be stored at 15°-25°C (59°-77°F) in a dry place.

NOTE: the concentration of the commercially available suspension (20 mg/mL) and the compounded suspension (50 mg/mL) are NOT the same; doses should be prescribed in the milligrams required, not mL.

6.7.4 Guidelines for Administration

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

Mercaptopurine should be taken consistently at the same time every day. If allopurinol is also given, the oral dose of mercaptopurine should be reduced by 67-75%. Patients with severe myelosuppression should have their thiopurine S-methyltransferase (TPMT) status and/or their thiopurine metabolite concentrations evaluated, so that the dose of mercaptopurine be reduced in patients with a TPMT defect. Patients with the rare homozygous deficient TPMT phenotype may tolerate only 1/10th to 1/20th the

average mercaptopurine dose. TPMT testing and thiopurine metabolite measurements are commercially available.

6.7.5 Supplier:

Commercially available. See package insert for further information.

Suspension:
For children unable to swallow the tablets whole, a 50 mg/mL oral suspension can be compounded. The suspension is prepared by crushing 50 mercaptopurine 50 mg tablets in a mortar and adding 8.5 mL sterile water for irrigation. The mixture is triturated to form a smooth paste. Next, 16.5 mL simple syrup (pH=7) are added with continuous mixing and finally cherry syrup (pH=7.1) is added to a total volume of 50 mL. The suspension is stable in amber glass bottles at room temperature (19oC -23oC) for up to 5 weeks. The suspension should be shaken well before each use. Procedures for proper handling and disposal of cytotoxic drugs should be used when preparing the suspension. (Aliabadi HM, Romanick M, Desai S et al. Effect of buffer and antioxidant on stability of mercaptopurine suspension. *Am J Heath-Syst Pharm.* 65:441-7, 2008).

Supplier: The tablets are commercially available from various manufacturers. In the United States, the commercially available oral suspension is available through AnovoRx Distribution, LLC (1-888-470-0904). See package insert for further information. **PLEASE NOTE there is a difference in the concentration of the commercially available (20 mg/mL) and extemporaneously compounded (50 mg/mL) oral suspensions.**

7.0 REQUIRED OBSERVATIONS/MATERIAL AND DATA TO BE ACCESSIONED

7.1 Clinical and Laboratory Studies

All entry/eligibility studies must be performed within **one week** prior to study enrollment ("PreEnrollment") unless specified otherwise (e.g., Disease evaluation is required within two weeks prior to study enrollment. Obtain other studies as needed for good patient care.) Some evaluations will need to be performed within 3 days prior to starting therapy ("Pre-Treatment").

STUDIES TO BE OBTAINED	**Pre-Enrollment***	**Pre-Treatment** (within 3 days prior to starting protocol therapy)	**During Course 1 (Cohort A and B)**	**During Course 1 (Cohort C)**	**Final Visit/ Follow-up**
History	X	X			X
Physical Exam	X	X	Weekly	Weekly	X
Vital Signs	X	X	Weekly	Weekly	X
Height, Weight, BSA	X	X			X

STUDIES TO BE OBTAINED	**Pre-Enrollment***	**Pre-Treatment** (within 3 days prior to starting protocol therapy)	**During Course 1 (Cohort A and B)**	**During Course 1 (Cohort C)**	**Final Visit/ Follow-up**
CBC, differential, platelets	X	X	Twice weekly including at least within 1 day prior to Marqibo® doses #2, 3 and 4	Twice weekly	X
Chemistries[1]	X	X	Twice Weekly, including at least within 1 day prior to Marqibo® doses #2, 3 and 4	Twice weekly	X
Electrolytes[2]	X	X	Twice Weekly, including at least within 1 day prior to Marqibo® doses #2, 3 and 4	Twice weekly	X
HIV	X^				
HBsAg, HCV	X^				
Urine pregnancy or Serum β-HCG (for females of childbearing potential)	X		If pregnancy is suspected	If pregnancy is suspected	
Echocardiogram/ MUGA/Cardiac MRI	X^				

STUDIES TO BE OBTAINED	**Pre-Enrollment***	**Pre-Treatment** (within 3 days prior to starting protocol therapy)	**During Course 1 (Cohort A and B)**	**During Course 1 (Cohort C)**	**Final Visit/ Follow-up**
Neurological Examination/ Completion of Neurological Exam Form (Appendix 4).	X	X	Weekly including at least within 1 day prior to Marqibo® doses #2, 3 and 4	Weekly	X
EKG	X		Day 8 (+/- 2 days) [cohort A only]		
CSF Cell count and Differential (with IT Therapy if needed as per Section 4.1)	X^		At the time of LP for IT therapy and at restaging on day 29† (+/- 2 days)	At the time of LP for IT therapy if given and at restaging on day 14 (+2) or day 29 (+/-2) if 2 cycles are given§	
Bone marrow aspirate and/or biopsy for response assessment (Section 7.3)	X^		Day 29 (+/- 2 days)	Day 14 (+2) or day 29 (+/-2 days) §	
Bone marrow sample for MRD	X^# Bone marrow need not be repeated for this purpose.		Day 29 (+/- 2 days)		
Pharmacokinetic Studies (required) May be collected through the line used for Marqibo® infusion.			Immediately prior to Marqibo administration for Marqibo doses #1, 2, and 3 for arm A and B.	Arm C will be obtained prior to Dose 1 and a trough level on day 8, during each cycle.	

STUDIES TO BE OBTAINED	**Pre-Enrollment***	**Pre-Treatment** (within 3 days prior to starting protocol therapy)	**During Course 1 (Cohort A and B)**	**During Course 1 (Cohort C)**	**Final Visit/ Follow-up**
Peripheral Blood for Pharmacokinetic Studies (optional)			Day 1 (3 blood samples)	Day 1 (3 blood samples)	
Follow-up visit					Q 6months

*Required for verification of eligibility. FAX or email all results to the TACL Operations Center with study registration eligibility. If a patient has labs done prior to study entry that establish eligibility, then abnormal Day 1 labs do not deem them ineligible.
#Optional
^Within 2 weeks prior to enrollment is acceptable
†IT chemotherapy is not required at the time of day 29 LP, but can be given per investigator discretion.
§Cohort C disease restaging will be done after cycle 1, if only one cycle is administered. If a second cycle is planned, restaging may be done after cycle 2. Please see section 7.3 for additional guidance. A lumbar puncture will only be required after 2 cycles; and is optional after cycle 1.
1: BUN, creatinine, ALT, AST, LDH, alkaline phosphatase, glucose, total and direct bilirubin, albumin, total protein, uric acid
2: Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus

7.2 Required Supportive Care Therapies During Protocol Treatment

The following supportive care measures are required by protocol:

- Antifungal prophylaxis (mandatory only for Cohorts A and B):
    - Non-azole based anti-fungal prophylaxis is **mandated** in all subjects enrolled in Cohorts A and B from the start of therapy until day 29, and ideally until neutrophil count recovery. All subjects are encouraged to continue antifungal prophylaxis beyond the treatment period especially if neutrophil count recovery has not occurred. Any exceptions must be discussed with the Study Chair or Vice Chair. (See protocol section 5.2).

- All azole therapy must be discontinued at least 1 week prior to the start of initiation of protocol therapy with Marqibo®.

- *Pneumocystis prophylaxis:*
  - PJP prophylaxis is **required**, with agents and dosing provided according to institutional guidelines. (See protocol section 5.2)
- Bowel prophylaxis
  - All patients must receive prophylaxis against constipation starting with the first dose of Marqibo unless there is diarrhea. (See protocol section 5.5 and Appendix 6)

7.3 Disease Evaluations During Therapy

All patients should have a bone marrow aspirate/biopsy and lumbar puncture and CBC to assess response on day 29 (+/- 2 days)**.

**For cohort C: Restaging studies should be performed on day 14 (+ 2 days) of cycle 1, with the exception of those patients who proceed to a second cycle. Cohort C, cycle 2 may start on Day 15 – 22 of cycle 1. If a second cycle is administered, a single restaging on day 14 (+2 days) of cycle 2 is required. In summary, a day 14 (+2 days) evaluation is required in all subjects at the completion of treatment on cohort C, either after cycle 1 (if a second cycle is not administered), or after cycle 2. A day 14 evaluation will not be required in either scenario in the presence of circulating peripheral blasts.

A bone marrow procedure need not be performed if the patient has an absolute peripheral blast count (APBC) greater than or equal to 2,500/µL in the peripheral blood.

If the marrow is hypoplastic, and counts have not recovered to ANC $\geq$ 500/µL and platelets $\geq$ 50,000/µL repeat CBC weekly until recovery or progression.

If the patient has a M1 marrow but has not achieved an ANC > 500/µL and platelets > 50,000/µL, repeat CBC weekly and bone marrow every 1-4 weeks until count recovery or relapse.

7.4 Research Studies

Participation in pharmacokinetic (PK) studies is mandatory for a limited sample set, for which samples can be drawn from the same line used to administer Marqibo®. Institutional guidelines should be followed in regard to maximum blood draw limits for pediatric patients.

Participation in the collection of the Dose 1 PK specimens is encouraged but is voluntary and patients may still participate in the therapeutic part of the study if they decline participation in

the research samples. Institutions are encouraged to talk to their patients about participation. The more detailed PK studies, require samples to be drawn from a line separate from the one used to administer Marqibo®.

7.4.1 Bone Marrow MRD

Samples requested:	**<u>Bone Marrow Sample for MRD</u>** • Pre-treatment: optional* • Day 29 (+/- 2 days) Sample should also be submitted if the bone marrow procedure is repeated after day 29 to document marrow and count recovery.* Repeat bone marrow for this purpose is not required. For patients with circulating blasts, 10 mL of peripheral blood in a heparinized tube may be submitted. For all patients, prior flow cytometry report should be submitted. *Bone Marrow MRDs are performed as part of standard of care, however, the information from them will be used for research purposes. Not required for cohort C.
Bone marrow Collection procedure:	• Collect minimum of 2 mL of marrow into a syringe and place marrow into a large purple EDTA tube that are commonly used in all hospitals. Mix well. • Use multiple syringes and tubes as needed. Reposition marrow aspirate needle as least once during procedure to ensure the maximum quality of marrow
Specimen Labeling:	Please refer to the TACL MRD Lab Manual for instructions regarding specimen labeling.
Specimen Packaging and Shipping:	Please refer to the TACL MRD Lab Manual for instructions regarding specimen packaging and shipping.

*Results from MRD assessments must be forwarded to TACL Operations at tacl@chla.usc.edu

7.4.2 Marqibo® Pharmacokinetic Studies (Mandatory and Optional Studies)

Participation in PK studies is mandatory for a limited set, for which samples can be drawn from the same line used to administer Marqibo®. These studies include a baseline level drawn prior to the first dose and trough levels prior to the second and third dose of

Marqibo®. Participation in more detailed PK studies, which require samples to be drawn from a separate line than the one used to administer Marqibo® are voluntary. (Appendix 7).

The mandatory PK samples will be collected at the following time points for arm A and B.

- Generally performed 30-60 minutes before start of dose 1 infusion (SOI) ±10 minutes, but may be performed with routine morning labs as long as it is before start of infusion.
- Pre-dose #2 (trough level), up to 1 hour pre-dose is acceptable
- Pre-dose #3 (trough level), up to 1 hour pre-dose is acceptable

For cohort C, the mandatory PK samples will be drawn 30-60 minutes before start of dose 1 infusion (SOI) ±10 minutes, but may be performed with routine morning labs as long as it is before start of infusion; and a trough level will be drawn anytime on day 8.

The voluntary PK samples will be collected at the following time points (all cohorts):

- End of Infusion (EOI) of dose 1 ±5 minutes
- 3 hours (EOI + 2 hours) ±15 minutes
- 25 hours (EOI + 24 hours) ±30 minutes

Analysis will be conducted in the laboratory of the NCI POB Pharmacology and Experimental Therapeutics program. Quantification of total plasma vincristine will be performed by a qualified LC/MS/MS.

Samples requested:	Mandatory (Arm A & B) • Pre-dose 1 • Pre-dose #2 (trough level) • Pre-dose #3 (trough level) May be collected through the line used for Marqibo® infusion Mandatory (Arm C) • Pre-dose 1 • Day 8 will have a trough level	Voluntary (all cohorts) • End of infusion (EOI) of dose 1 • 3 hours (EOI + 2 hours) • 25 hours (EOI + 24 hours) Must be collected from a separate line from that used for Marqibo® infusion.

Sample Collection procedure:	• Peripheral blood samples of 3 mL will be collected in lavender-top (EDTA) vacutainers at each of the time points indicated above. • Invert the lavender-top vacutainer 10 times to mix completely • If blood samples are taken via an indwelling central venous cannula, an appropriate amount of fluid should be removed from the cannula to clear the line before each blood sample is taken. Place the samples on ice until centrifugation
Specimen Processing	• Plasma: should be separated by centrifugation at 10C (10 min at 1000 g or 2500 rpm) within four hours after collection. Separated plasma should be transferred to screw-capped polyproplyene tubes (i.e. Nunc 3.6 ml #379189, 366524 or equivalent). Plasma samples should be stored in the dark at less than -70° C.
Specimen labeling:	• Specimens should be labeled with the TACL registration number, date and time of sampling and the sample number (see appendix 7).

Specimen Packaging and Shipping:	• Participating sites should ship samples on dry ice using priority Federal Express. • Samples should be shipped Mon, Tues or Wed only and should not be sent on the day preceding a holiday. Lab receives samples Tuesday through mid-Friday. • All samples should be batched per patient • Send a notification email to marqibo@mail.nih.gov when sending samples. • Include the completed pharmacokinetic • worksheet (Appendix7) • Ship samples to: Figg Lab Clinical Pharmacology Program National Cancer Institute 9000 Rockville Pike Building 10, Room 5A08 Bethesda, MD 20892 (O) 240-760-6180 (F) 301-402-8606 For specimen shipping, please request a label from TACL Operations at least 24 hours in advance of shipment. Please call the TACL Operations Center for any questions at 323-361-3022.

7.5 Required Observations Following Completion of Protocol Therapy

When a patient discontinues the study, a Final Visit will be conducted. Following discontinuation of the study drug, the patient will be treated in accordance with the investigator's best clinical judgment. If a patient discontinues from the study due to an adverse event considered possibly or probably related to study drug, a Follow-up Visit must be conducted no later than 30 days after the last dose of anti-cancer therapy administered as part of this protocol. Safety assessments will be conducted at least every 30 days, until all toxicities resolve, return to baseline or become clinically satisfactory, stable, or are considered irreversible.

Upon completing protocol therapy or exiting the study, all patients will be followed for life or until otherwise notified by the study committee that the study is closed. Sites should submit follow-up a minimum of every 6 months. Events such as patient death, relapse or development of toxicity related to this therapy should be reported right away. The purpose is to assess safety, remission status, administration of alternative therapies, and survival.

The following data will be collected:

1) Disease status information
2) Anti-cancer therapy received after exiting the protocol
3) All adverse events thought to be related to this study's treatment
4) Date and cause of death

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY, OFF STUDY CRITERIA AND STUDY TERMINATION

8.1 Criteria for Removal from Protocol Therapy

a. Completion of protocol therapy
b. Progressive disease
c. Patient/parent withdrawal or refusal after beginning protocol therapy
d. Patient/parent withdrawal or refusal before beginning protocol therapy
e. Patient off treatment for other complicating disease
f. Non-compliance with protocol regimen and procedures
g. Unacceptable toxicity
h. Investigator determination
i. Female patient becomes pregnant or begins breast-feeding

8.2 Off Study Criteria

a. Death
b. Patient Lost to follow-up
c. Patient withdraws consent, refuses follow-up

8.3 Termination of the Study by TACL

The TACL Consortium may terminate this study prematurely, either in its entirety or at an investigative site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns.

9.0 STATISTICAL CONSIDERATIONS

The Phase I sample size for each dose level and each of the three cohorts is 6 evaluable patients for the primary endpoint, consistent with the sample size typically sufficient to demonstrate regimen tolerability in Phase I trials. The maximum sample size in any cohort at a particular dose level is 12 evaluable patients, including 6 evaluable patients for expansion.

As of Protocol Amendment #3, Cohort A will enroll at DL1 only. Cohort B will utilize DL1 and Cohort C will continue treatment at DL2. Dose escalation for Cohort B and de-escalation for Cohort C may still occur per study design.

The focus of the study design and statistical analysis is to determine whether Marqibo® can be substituted for standard vincristine and successfully administered to patients with relapsed ALL in three different treatment cohorts: (A) treatment with the UK ALL R3 regimen; (B) treatment with UK ALL R3 regimen without mitoxantrone, and (C) treatment with ALL maintenance therapy. Secondary objectives include estimating rates of serious toxicities and therapy delays in each of these cohorts. Achievement of response and achievement of an MRD undetectable status will only be evaluated in Cohorts A and B, as Cohort C is not being used to eradicate disease, rather is only intended for the purposes of disease stabilization.

9.1 Endpoints

9.1.1 Primary Endpoint

Cohort A

The primary endpoint in Cohort A is whether a patient is successfully treated with UK ALL R3/Marqibo® at nearly full dose without inordinate delays in the resolution of hematologic and non-hematologic toxicity that preclude timely continuation with subsequent treatment.

Specifically, a patient will be considered successfully treated if:

a. The patient has received 16 of 20 prescribed doses of Dexamethasone, 2 of 2 prescribed doses of Mitoxantrone, 3 of 4 prescribed doses of Marqibo®, and 1 of 2 doses of pegaspargase.

b. The patient has not experienced a dose limiting toxicity (DLT) as defined in section 4.2.

A patient will be considered NOT successfully treated if (s)he has experienced a dose limiting toxicity (DLT) as defined in section 4.2, or has received fewer than the minimum numbers of prescribed doses as described in (a) above for reasons not unequivocally unrelated to treatment toxicity (see section 9.3.1)

Cohort B

The primary endpoint in Cohort B is whether a patient is successfully treated with UK ALL R3/Marqibo® *without mitoxantrone* at nearly full dose without inordinate delays in the resolution of hematologic and non-hematologic toxicity that preclude timely continuation with subsequent treatment.

Specifically, a patient will be considered successfully treated if:

a. The patient has received 16 of 20 prescribed doses of Dexamethasone, 3 of 4 prescribed doses of Marqibo® and 1 of 2 doses of pegaspargase.

b. The patient has not experienced a dose limiting toxicity (DLT) as defined in section 4.2

A patient will be considered NOT successfully treated if (s)he has experienced a dose limiting toxicity (DLT) as defined in section 4.2, or has received fewer than the minimum numbers of prescribed doses as described in (a) above for reasons not unequivocally unrelated to treatment toxicity (see section 9.3.1)

Cohort C

The primary endpoint in Cohort C is whether a patient is successfully treated with one cycle (14 days) of the modified maintenance treatment at nearly full dose without inordinate delays in the resolution of non-hematologic toxicity that preclude timely continuation with subsequent treatment.

Specifically, a patient will be considered successfully treated if during the first course of modified maintenance treatment:

a. The patient has received 8 of 10 prescribed doses of dexamethasone, and 1 of 1 prescribed doses of Marqibo®, 1 or 2 prescribed doses of Methotrexate, and at least 50% of doses of mercaptopurine

b. The patient has not experienced a dose limiting toxicity (DLT) as defined in section 4.2

A patient will be considered NOT successfully treated if (s)he has experienced a dose limiting toxicity (DLT) as defined in section 4.2, or has received fewer than the minimum numbers of prescribed doses as described in (a) above for reasons not unequivocally unrelated to treatment toxicity (see section 9.3.1)

9.1.2 Exploratory Endpoints

a. Occurrence of toxicity, as graded using the NCI's Common Terminology Criteria for Adverse Events (CTCAE 4.03).

b. (Cohorts A and B) Achievement of CR or CRi during the course of therapy.

c. (Cohorts A and B) In those who achieve CR or CRi, achievement of MRD negative status (i.e., $<10^{-4}$ blasts by flow cytometry in a central lab).

d. Pharmacokinetic assessment of Marqibo®

9.1.3 Safety Endpoints

Toxic Death (TD): Any death that is not clearly related to disease progression or to external causes (e.g. accident) that occurs during protocol therapy or during recovery following protocol therapy, or prior to commencing subsequent non-protocol course of therapy, will be considered a toxic death for the purposes of this study.

9.2 Study Design

An open label design over two Marqibo® dose levels will be used to evaluate its substitution for vincristine in three different treatment cohorts: (A) patients treated with UK ALL R3, (B) patients treated with UK ALL R3 that omits Mitoxantrone, and (C) patients treated with a modified ALL maintenance regimen. Prior data on relapse ALL patients treated with standard UK ALL R3 and with COG protocol therapies (section 2.3) suggest that approximately 10% of patients treated in first relapse will experience grade 3 or higher toxicity sufficient to prevent the start of subsequent therapy by day 49. Data from patients treated in second or greater relapse, which will represent

the majority of patients on this study, suggest higher delay rates, but are imprecise due to the small number of patients.

For Cohort A, the original design criteria for escalation to DL2 (≤ 2/6 not successfully treated at DL1) has been satisfied. Hence, following Amendment #2, a minimum of 6 and a maximum of 12 patients (including 6 for expansion) who are evaluable for the primary endpoint will be enrolled at DL2. Following Amendment #3, Cohort A was dose de-escalated to DL1 given the development of two DLTs at DL2.

Since treatments in Cohorts B and C were expected to be less toxic than Cohort A, as detailed below Cohorts B and C initially opened to accrual at DL2.

For Cohort B, dosing began at DL2. The cohort was subsequently de-escalated to DL1 after 2 patients were enrolled. The decision to dose de-escalate was an elective decision made by the study committee in the context of known hepatic toxicity associated with Marqibo®, the development of hepatic DLT in one subject on this cohort, and a second subject who was close to meeting criteria for DLT based on hepatic function tests. Cohort B will remain open to accrual at DL1 with 6-12 evaluable patients. Cohort B may be re-escalated to DL2 pending further experience at DL1 (≤ 2/6 not successfully treated in the first 6 evaluable patients).

For Cohort C, dosing began at DL2. Cohort C will remain open to accrual at DL2 with 6-12 evaluable patients, provided the primary endpoint conditions are met, ie, ≤ 2/6 not successfully treated in the first 6 evaluable patients at this dose level. If Cohort C is de-escalated, the cohort may continue to accrue at DL1 between 6 to 12 evaluable patients at that dose level.

The occurrence of unsuccessful treatment, following the definition in Section 9.1.1, will be monitored in real time during the Phase I and expansion accruals. The design will not be prescriptive. Rather, if at any time after the third patient is enrolled either within a single cohort or in all cohorts combined, if nominally more than 1/3 of evaluable patients within a single cohort or in all cohorts combined are not successfully treated the study will be suspended pending review by the study committee of the types and severity of toxicities in all three cohorts, with possible determinations to continue at the specified dose level in all three cohorts, to de-escalate the dose of Marqibo® to DL1 in one or more cohorts, or to halt the study in one or more or cohorts, with appropriate amendments as necessary. In addition, during Phase I, the decision to de-escalate will be considered separately for each cohort and dose level when more than 1 patient is treated unsuccessfully after the first 6 evaluable patients have been enrolled. And the decision to escalate during Phase I will be considered separately for each cohort and dose level when no more than 1 patient is treated unsuccessfully after the first 6 evaluable patients have been enrolled. Accrual to the study will be halted, before reopening for expansion, once at least 6 evaluable patients have been treated at the final tested dose level in each of the three cohorts.
Treatment success, as defined in in Section 9.1.1, during the first course of treatment will continue to be monitored during the expansion. Assuming a treatment failure rate that exceeds 10% (i.e., $p_0>0.10$) is unacceptable, a Bayesian monitoring rule based on a pessimistic Beta (1,4) prior distribution will be used to judge the empirical evidence from both the Phase I and expansion

cohorts. This prior has mean 0.20, median 0.16, and 90% of support under 0.48. A posterior probability of greater than 80% that p0>0.10 will be considered statistical evidence that the treatment failure rates may exceed 10%. Operationally, this criterion will be satisfied if 2 or more of the first 5 evaluable patients in the expansion cohort experience a treatment failure as defined by the protocol, and subsequently, if 3 or more of the first 6 evaluable patients have a treatment failure. If this criterion is satisfied, the study will be suspended to accrual pending review of toxicities by the study committee, in consultation with the Data and Safety Monitoring Committee, to determine whether the study should continue as planned, be amended, or be terminated.

9.3 Patient Evaluability

9.3.1 Definition of a patient evaluable for the primary endpoint

A patient will be considered evaluable for the treatment success endpoint (section 9.1.1) if (s)he receives any portion of treatment, except if treatment or follow-up is terminated for reasons unequivocally unrelated to treatment toxicity (e.g., if a drug is omitted from the regimen for reasons aside from toxicity, or treatment is terminated because of problems unequivocally related to disease progression). Patient who are not evaluable for the primary endpoint will be replaced.

9.3.2 Definition of a patient evaluable for toxicity:

Any patient who receives at least one dose of any drug on study will be considered evaluable for toxicity.

9.3.3. Definition of a patient evaluable for response:

A patient will be considered evaluable for response if the patient receives all or part of protocol therapy and the patient is under follow-up for a sufficient period to evaluate the disease at the end of protocol therapy or to meet the definition of progressive disease. A patient who dies as a result of toxicity after receiving all or part of protocol therapy, or who is removed from therapy for problems possibly related to disease progression, will be considered a non-responder.

9.4 Definition of toxic death (TD)

Any death that is not clearly related to disease progression that occurs during protocol therapy or during recovery following protocol therapy, or prior to commencing subsequent non-protocol course of therapy, will be considered a toxic death for the purposes of this study.

9.4 Statistical Analysis

9.4.1 Treatment success rate: Given the small sample size in each cohort, the treatment success rate will only be estimable imprecisely within each cohort and overall.

9.4.2 Toxicity: The analysis of toxicity will be primarily descriptive, comprising tabulation of the fraction of patients who experience grade 3 or grade 4 toxicities.

9.4.3 Efficacy: Given the small sample size in each cohort, the CR/CRi rates and the MRD-negative rates will only be estimable imprecisely within each cohort and overall..

9.4.4 Pharmacokinetics analysis: The precision with which a detailed pharmacokinetic analysis of vincristine levels after exposure to Marqibo® in the context of UK ALL R3 treatment or maintenance therapy in this population of patients can be performed will depend on the number of patients who participate in the optional Day 1 PK component of this study, which includes sampling at end of infusion, 3 hours and 24 hours in addition to the mandatory day 8 and day 15 samples (applicable to only the UK ALL R3 with or without mitoxantrone arms A & B). Patients enrolled to arm C will only have pre-dose #1 (30 minutes before start of infusion (SOI) and a trough level at day 8 during the first cycle**.** Assuming first order elimination, these pharmacokinetic analyses will include estimation of total vincristine concentration, area under the curve through 168 hours, and, the half-life of vincristine when Marqibo® is given with combination therapy. However, the two mandatory samples at day 8 and 15 taken prior to the second and third dose of Marqibo®, representing vincristine trough levels, will be obtained on all patients. There are no data currently available to estimate interpatient variability of vincristine levels from Marqibo® in children, but data from [23] in adults indicate that the coefficient of variation (CV) of vincristine at trough levels will be approximately 100%. Hence, assuming that the study proceeds to the second stage, and that 25/30 patients are evaluable for PK assessment, the precision of the estimate of mean trough levels of vincristine at each of these times point will be CV=17%, resulting in a 95% confidence interval with bounds within 40% of the population value. This provides sufficient precision for meaningful comparison of vincristine concentration in this study to published adult study as well as the ongoing Marqibo® Phase I study in children. These analyses will be based on the total vincristine exposure and will not include distinguishing between the free and liposomal bound components.

9.5 Interim Monitoring of Toxic Death

The occurrence of toxic death (TD) per 9.3.4 will be a primary endpoint for safety monitoring. Based on prior studies, a 10% TRM rate in patients with advanced ALL is expected (see section 2.3). Hence a population toxic death rate that exceeds 10% will be considered unacceptable. No formal statistical monitoring will be employed. Rather, an observed TD rate that exceeds 10% at any time in any cohort will result in immediate suspension of the study, at which time the cause and circumstances of the death and its attribution to the study regimen will be reviewed with the study committee and with the Data and Safety Monitoring Committee (DSMC) to determine

whether modifications to or termination of the study is warranted. Operationally, this criterion will be satisfied if within a cohort, a TD is observed, and the nominal rate exceeds 10%.

9.6 Inclusion of Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. The small number of patients entered into this trial will obviate any analysis of variation in response rate with gender or ethnicity.

10.0 RESPONSE CRITERIA

10.1 Bone Marrow Status Definitions

M1 Marrow

Less than 5% blasts in a bone marrow aspirate and at least 200 cells counted.

M2 Marrow

5-25% blasts in a bone marrow aspirate with at least 200 cells counted.

M3 Marrow

Greater than 25% blasts in a bone marrow aspirate with at least 200 cells counted.

10.2 Bone Marrow Response Criteria

10.2.1 Complete Remission (CR)

Attainment of M1 bone marrow with no evidence of circulating blasts or extramedullary disease and with recovery of peripheral counts (ANC ≥ 500/μL and PLT count ≥ 50,000 μL). Qualifying marrow and peripheral counts should be performed within 1 week of each other.

10.2.2 Complete Remission with Incomplete Blood Count Recovery (CRi)

Attainment of M1 bone marrow with no evidence of circulating blasts or extramedullary disease, but with insufficient recovery of absolute neutrophil count (ANC < 500/μL) or platelets (< 50,000/ μL).

10.2.3 Partial Remission (PR)

Complete disappearance of circulating blasts and achievement of M2 marrow status, without new sites of extramedullary disease, and with recovery of absolute neutrophil count (ANC ≥ 500/μL).

10.2.4 Stable Disease (SD)

Patient does not satisfy the criterion for PD, and fails to qualify for CR, CRi, or PR.

10.2.5 Progressive Disease (PD)

An increase of at least 25% in the absolute number of circulating leukemic cells, development of new sites of extramedullary disease, or other laboratory or clinical evidence of PD, with or without recovery of ANC or platelets.

10.2.6 Toxic Death (TD)

Any patient who dies after receiving therapy on this protocol prior to receiving subsequent therapy.

10.2.7 Not evaluable (NE)

Patient does not satisfy the criterion for PD or ID, and either did not have a marrow evaluation, had inadequate marrow cell count, or had insufficient recovery of ANC to be classified as CR, CRp, PR, or SD.

10.3 CNS Status Definitions

CNS 1: In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of white blood cells (WBCs).

CNS 2: In CSF, presence < 5/µL WBCs and cytospin positive for blasts, or ≥ 5 /µL WBCs but negative by Steinherz/Bleyer algorithm:

CNS 2a: < 10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts;
CNS 2b: ≥ 10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts; and CNS 2c: ≥ 10/µL RBCs; ≥ 5/µL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm (see below)

CNS 3: In CSF, presence of ≥ 5/µL WBCs and cytospin positive for blasts **and/or** clinical signs of CNS leukemia:

CNS 3a: < 10/µL RBCs; ≥ 5/µL WBCs and cytospin positive for blasts;
CNS 3b: ≥ 10/µL RBCs, ≥ 5/µL WBCs and positive by Steinherz/Bleyer algorithm
CNS 3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome)

METHOD OF EVALUATING INITIAL TRAUMATIC LUMBAR PUNCTURES:

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/µL and blasts, the following Steinherz/Bleyer algorithm should be used

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF WBC ≥ 5/µL blasts, whose CSF WBC/RBC is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis.

Example: CSF WBC = 60/µL; CSF RBC = 1500/µL; blood WBC =46000/µL; blood RBC = 3.0 X 10^6/µL:

CSF calculation	Blood calculation
60 / 1500 = 0.04	46000 / 3.0×10^6 = 0.015 x 2 = .03

Therefore this patient has CNS disease because 0.04 > 0.03

10.4 CNS Response Criteria

Only subjects with CNS 1 or 2 status will be enrolled. Those with active CNS disease (CNS 3) are excluded until they achieve CNS 1 or 2 status. CNS status will only be evaluated for progressive disease, defined as below.

10.4.1 Progressive Disease (PD): Any subject who develops CNS 3 disease will be considered to have progressive disease.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

Adverse Event: An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event.

Unexpected Adverse Event or Unexpected Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not available, is not consistent with the risk information described in the general investigational plan.

Serious Adverse Events or Serious Suspected Adverse Reactions: An adverse event or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

Death of Patient	An event that results in the death of a patient.

Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/ Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (*e.g.,* sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An <u>important medical event</u> that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (*i.e.,* death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, pregnancy, or the development of drug dependency or drug abuse.

Grade 3 fever and neutropenia is not an SAE unless a new hospitalization is required or is associated with another medical complication deemed medically important or life threatening.

11.2 Data Collection

Adverse events and suspected adverse reactions will be collected and reported on the electronic CRFs beginning with the first dose of study therapy until 30 days following the last dose of study therapy (or until the patient begins another therapy). The investigator will evaluate all adverse events and suspected adverse reactions as to their severity and relationship to Marqibo® as well as the regimen as a whole. Serious adverse events and suspected adverse reactions will require expedited reporting to the TACL Operations Center as described below.

11.3 Reporting Serious Adverse Events or Serious Suspected Adverse Reactions

11.3.1 <u>The following serious adverse events or serious suspected adverse reactions requires expedited reporting:</u>

- All Grade 5 events regardless of causality.
- All Grade 4 events that are possibly, probably or definitely related to Marqibo® or the regimen as a whole. Exclude reporting of hematologic toxicity as a serious adverse event unless the event meets the criteria of hematologic dose limiting toxicity per protocol section 4.2.1.2: The absence of peripheral blood count recovery (ANC > 500/µL and platelet count > 20,000/µL) 7 weeks (49 days) after the start of chemotherapy in the absence of persistent leukemia or documented myelosuppressive infection.
- All unexpected Grade 3 events that are possibly, probably or definitely related to Marqibo® or the regimen as a whole.

11.3.2 Steps for Reporting

Step 1: Identify the adverse event or suspected adverse reaction using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded at **http://evs.nci.nih.gov/ftp1/CTCAE/About.html**.

Step 2: Grade the event using the NCI CTCAE version 4.03.

Step 3: Determine if the adverse event or suspected adverse reaction meets the criteria of being "serious".

Step 4: Determine whether the adverse event or suspected adverse reaction is related to the protocol therapy.

The investigator will assess the causal relationship between the investigational product and the regimen as a whole and the adverse event. The investigator will use his/her clinical expertise and judgment to select the attribution category below that best fits the circumstances of the AE.

Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Unrelated:
- The adverse event is *clearly unrelated* to the investigational agent(s).
- Does not follow a known response pattern to the suspect investigational product (if response pattern is previously known).
- Can be explained by the known characteristics of the patient's clinical state or therapy administered to the patient.

Unlikely:
- The adverse event is *doubtfully* related to the investigational agent(s).
- May or may not follow a reasonable temporal sequence from administration of the investigational product.

- Likely explained by the known characteristics of the patient's clinical state or other therapy administered to the patient.

Possibly Related:
- The adverse event *may be* related to the investigational agent(s).
- Follows a reasonable temporal sequence from administration of the investigational product.
- May also be reasonably explained by the patient's clinical state or therapy administered to the patient.
- May follow a known response pattern to the investigational product (if response pattern is previously known)

Probably Related:
- The adverse event *is likely* related to the investigational agent(s).
- Follows a reasonable temporal sequence from administration of the investigational product.
- May follow a known response pattern to the investigational product (if response pattern is previously known)
- Could not be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient, if applicable;

Definitely Related:
- The adverse event is *clearly related* to the investigational agent(s).
- Follows the temporal sequence from administration of the investigational product
- Follows a known response pattern to the investigational product.
- Cannot be explained by the known characteristics of the patient's clinical state or other therapy administered to the patient.
- Is confirmed by improvement of symptoms on stopping or slowing administration of the investigational product and re-emergence of symptoms on restarting administration of the investigational product, (if applicable).

Step 5: Determine if the adverse event or suspected adverse reaction is "unexpected".

Step 6: Notify the TACL Operations Center by telephone or email

The following information should be submitted within 24 hours of event notification by either telephone (323) 361-3022 or Email TACL@chla.usc.edu.

1. Patient TACL study ID and initials
2. Event description
3. Severity (CTCAE Grade)
4. Onset date
5. Reason event is considered serious

6. Dose of study drug and dates of administration
7. Investigator opinion of relationship to DRUG and the regimen as a whole
8. Name and phone number of physician in charge of the case
9. Name and phone number of CRA or Research nurse working with the case

Step 7: Submit a written report to the TACL Operations Center

Complete the TACL SAE Notification Form within 72 hours of learning of the event. The completed form can emailed to TACL@chla.usc.edu. The form may also be faxed to 323-361-4505. A follow-up SAE Notification Form must be submitted upon resolution of the event or interimly (prior to resolution) as requested by the study committee and/or TACL Operations Center. Please confirm via email or phone that the TACL Operations Center has received this notification. These serious adverse events will be reported to the FDA by the TACL Operations Office using the MedWatch form as required per federal regulations.

11.4 Institutional Reporting to the IRB

All SAEs should be reported to the treating institution's IRB or Ethics board per institutional guidelines. The TACL Operations Center will also report SAE's to the CHLA IRB as required. The TACL Operations Center will distribute SAE's to all TACL sites as appropriate for submission to their institutional IRB or Ethics board.

12.0 DATA AND SAFETY MONITORING

12.1 Data Submission

All study data will be submitted via electronic data capture forms using the DataLabs/TACL Website. All toxicities grades 1-5, heme and non-heme with grade fluctuations should be reported in the eCRF. Please refer to the TACL web site https://tacl.chla.usc.edu) for T2012-002 CRF Completion Guide or contact the TACL Operations Center at (323) 361-3022 if you need assistance.

The following are required to be submitted to the Operations Center for all patients entered:

Copies of following**:** Roadmaps and Bone Marrow Reports (include both aspirate and biopsy reports). These de-identified forms are to be emailed to the TACL Operations Office at tacl@chla.usc.edu at the end of the study course.

12.2 Weekly Safety Review

The TACL Operations Center (TOC) conducts weekly (as needed) patient safety and review meetings with the protocol chair, protocol vice-chair, research coordinators and other administrative TACL team members to review all data submitted, non-serious adverse events and other correspondence pertaining to patients. Serious adverse events will be immediately evaluated by the study team and determination regarding notification of participating sites will be made. All serious adverse events will be sent to the CHLA IRB and DSMC if required. Any interim

results that would affect patient safety would be immediately communicated to all participating TACL sites. All correspondence with sites will be transmitted via email, and all information also being posted on a member's only section of the TACL website.

12.3 Data Safety and Monitory Committee

This study will be monitored by the CHLA Hematology/Oncology/BMT Data and Safety Monitoring Committee (DSMC), which meets every six months to review progress and safety of studies under its purview. In advance of the DSMC meetings, a study progress report will be prepared by the TACL Operations Center, study statistician and study PI detailing patient accrual, toxicities, deaths on study, current study status, responses, summary of amendments to protocol/consent, lists of any publications from study, and plans for study in coming year. Any publications from the study (abstract or manuscript) will be attached to the DSMC report. After DSMC review, the DSMC will issue a confidential report to the study PI and TACL Operations Center.

Not more than 8 weeks after the DSMC meeting, a DSMC public report will also be created after approval of the confidential report and resolution of any issues by the PI. The public report will provided to the participating sites, and can be filed at the IRB at each site if required per local IRB guidelines.

13.0 REFERENCES

1. Ko RH, Ji L, Barnette P, Bostrom B, Hutchinson R, Raetz E *et al.* Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. *J Clin Oncol* 2010; **28**(4)**:** 648-654. e-pub ahead of print 2009/10/21; doi: JCO.2009.22.2950 [pii]10.1200/JCO.2009.22.2950

2. Weiden PL, Wright SE. Vincristine neurotoxicity. *N Engl J Med* 1972; **286**(25)**:** 1369-1370. e-pub ahead of print 1972/06/22;

3. Webb MS, Harasym TO, Masin D, Bally MB, Mayer LD. Sphingomyelin-cholesterol liposomes significantly enhance the pharmacokinetic and therapeutic properties of vincristine in murine and human tumour models. *Br J Cancer* 1995; **72**(4)**:** 896-904. e-pub ahead of print 1995/10/01;

4. Shah NN, Cole DE, Lester-McCully CM, Wayne AS, Warren KE, Widemann BC. Plasma and cerebrospinal fluid pharmacokinetics of vincristine and vincristine sulfate liposomes injection (VSLI, marqibo(R)) after intravenous administration in Non-human primates. *Invest New Drugs* 2016; **34**(1)**:** 61-65. doi: 10.1007/s10637-015-0311-x

5. Thomas DA, Kantarjian HM, Stock W, Heffner LT, Faderl S, Garcia-Manero G *et al.* Phase 1 multicenter study of vincristine sulfate liposomes injection and dexamethasone in adults with relapsed or refractory acute lymphoblastic leukemia. *Cancer* 2009; **115**(23)**:** 5490-5498. e-pub ahead of print 2009/08/27; doi: 10.1002/cncr.24632

6. U.S. Food and Drug Administration, FDA News Release, Aug. 9, 2012. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm315027.htm. In.

7. O'Brien S, Thomas DA, Heffner LT, Stock W, Messerschmidt GL, Hagey A *et al.* Marqibo(R) (vincristine sulfate liposomes injection; VSLI) In the Treatment of Adult Patients with Advanced, Relapsed/Refractory Acute Lymphoblastic Leukemia (ALL): A Combined Analysis of the VSLI-06 and RALLY Studies. *ASH Annual Meeting Abstracts* 2010; **116**(21)**:** 2143.

8. Herzog CE, Russo ML, Kuttesch J. Phase II Study of Sphingosomal Vincristine (SV), in Pediatric Malignancies (American Society of Pediatric Hematology/Oncology 18th Annual Meeting Abstract, #393). *Pediatr Blood Cancer* 2005; **44**(Supplement 6)**:** 540.

9. Shah NN, Merchant MS, Cole DE, Jayaprakash N, Bernstein D, Delbrook C *et al.* Vincristine Sulfate Liposomes Injection (VSLI, Marqibo(R)): Results From a Phase I Study in Children, Adolescents, and Young Adults With Refractory Solid Tumors or Leukemias. *Pediatr Blood Cancer* 2016; **63**(6)**:** 997-1005. doi: 10.1002/pbc.25937

10. Parker C, Waters R, Leighton C, Hancock J, Sutton R, Moorman AV *et al.* Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. *Lancet* 2010; **376**(9757)**:** 2009-2017. e-pub ahead of print 2010/12/07; doi: 10.1016/S01406736(10)62002-8

11. Abelev B, Adam J, Adamova D, Adare AM, Aggarwal MM, Aglieri Rinella G *et al.* Production of muons from heavy flavor decays at forward rapidity in pp and PbPb collisions at sqrt[s(NN)]=2.76 TeV. *Phys Rev Lett* 2012; **109**(11)**:** 112301. epub ahead of print 2012/09/26;

12. Sun W, Orgel E, Malvar J, Sposto R, Wilkes JJ, Gardner R *et al.* Treatmentrelated adverse events associated with a modified UK ALLR3 induction chemotherapy backbone for childhood relapsed/refractory acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2016; **63**(11)**:** 1943-1948. doi:

10.1002/pbc.26129

13. Raetz EA, Borowitz MJ, Devidas M, Linda SB, Hunger SP, Winick NJ *et al.* Reinduction platform for children with first marrow relapse of acute lymphoblastic Leukemia: A Children's Oncology Group Study[corrected]. *J Clin Oncol* 2008; **26**(24)**:** 3971-3978. e-pub ahead of print 2008/08/20; doi: 10.1200/JCO.2008.16.1414

14. Horton TM, Sposto R, Brown P, Reynolds CP, Hunger SP, Winick NJ *et al.* Toxicity assessment of molecularly targeted drugs incorporated into multiagent chemotherapy regimens for pediatric acute lymphocytic leukemia (ALL): review from an international consensus conference. *Pediatr Blood Cancer* 2010; **54**(7)**:** 872-878. e-pub ahead of print 2010/02/04; doi: 10.1002/pbc.22414

15. Jeha S, Gaynon PS, Razzouk BI, Franklin J, Kadota R, Shen V *et al.* Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *J Clin Oncol* 2006; **24**(12)**:** 1917-1923. e-pub ahead of print 2006/04/20; doi: 10.1200/JCO.2005.03.8554

16. Messinger YH, Gaynon PS, Sposto R, van der Giessen J, Eckroth E, Malvar J *et al.* Bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Study. *Blood* 2012; **120**(2)**:** 285-290. e-pub ahead of print 2012/06/02; doi: 10.1182/blood-2012-04-418640

17. Wexler LH. Ameliorating anthracycline cardiotoxicity in children with cancer: clinical trials with dexrazoxane. *Semin Oncol* 1998; **25**(4 Suppl 10)**:** 86-92.

18. Woodlock TJ, Lifton R, DiSalle M. Coincident acute myelogenous leukemia and ischemic heart disease: use of the cardioprotectant dexrazoxane during induction chemotherapy. *Am J Hematol* 1998; **59**(3)**:** 246-248.

19. Herman EH, Zhang J, Rifai N, Lipshultz SE, Hasinoff BB, Chadwick DP *et al.* The use of serum levels of cardiac troponin T to compare the protective activity of dexrazoxane against doxorubicin- and mitoxantrone-induced cardiotoxicity. *Cancer Chemother Pharmacol* 2001; **48**(4)**:** 297-304.

20. Bernitsas E, Wei W, Mikol DD. Suppression of mitoxantrone cardiotoxicity in multiple sclerosis patients by dexrazoxane. *Ann Neurol* 2006; **59**(1)**:** 206-209. doi: 10.1002/ana.20747

21. Feijen EA, Leisenring WM, Stratton KL, Ness KK, van der Pal HJ, Caron HN *et al.* Equivalence Ratio for Daunorubicin to Doxorubicin in Relation to Late Heart Failure in Survivors of Childhood Cancer. *J Clin Oncol* 2015; **33**(32)**:** 3774-3780. doi: 10.1200/JCO.2015.61.5187

22. Bedikian AY, Silverman JA, Papadopoulos NE, Kim KB, Hagey AE, Vardeleon A *et al.* Pharmacokinetics and Safety of Marqibo (Vincristine Sulfate Liposomes Injection) in Cancer Patients With Impaired Liver Function. *The Journal of Clinical Pharmacology* 2011; **51**(8)**:** 1205-1212. doi: 10.1177/0091270010381499

14.0 SAMPLE INFORMED CONSENT

Local IRB changes to this document are allowed. Changes within the document should not substantially alter the meaning or intent of the consent document. If the institution or IRB insists on making deletions or more substantive modifications to the consent, especially in the risks sections, they should be reviewed and approved by the TACL Operations Center.

SAMPLE INFORMED ASSENT*/CONSENT DOCUMENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH *Assent for patients >13 years of age *Assent for patients <13 years of age should be written per institutional guidelines

TACL Protocol T2012-002: A Pilot Study of Vincristine Sulfate Liposome Injection (Marqibo®) in Combination with UK ALL R3 Induction Chemotherapy for Children, Adolescents, and Young Adults with Relapse of Acute Lymphoblastic Leukemia
IND 128316

Subject Name:	
Medical Record #:	
Physician:	

When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

This study is being carried out by the Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Consortium. TACL is a group of Universities and Children's Hospitals that are working together to find treatments for children with leukemia and lymphoma. Funding for this research is provided by Acrotech Biopharma and Gateway for Cancer Research.

You are being asked to take part in this research study because your acute lymphoblastic leukemia or lymphoma (ALL) has relapsed. Relapse means your leukemia has come back after treatment. Marqibo® is a drug approved by the FDA (Food and Drug Administration) for the treatment of ALL in adults. This study is being done to find out if Marqibo® can be safely given during treatment with standard chemotherapy drugs.

It is important for you to know why this study is being done before you decide to take part in this research study. This consent will tell you about the study. This consent will also tell you about risks and side effects that might happen to you if you take part in this study. You also need to know you do not have to take part in this study. You can talk to your doctor about other cancer treatments. Because all of the drugs used in this study are each available to doctors, it is possible for you to receive these drugs without taking part in this study. Taking part in this study is voluntary.

Why is this study being done?

The goals of this study are:

- To evaluate the side effects (good and/or bad) of giving Marqibo® with other chemotherapy using the standard drugs dexamethasone, pegaspargase and mitoxantrone.
- To evaluate the pharmacokinetics of Marqibo® when it is given with other chemotherapy agents
- To measure how effective the combination Marqibo® with standard chemotherapy drugs is at treating children and young adults with relapsed ALL

How many people will take part in this study?

It is expected that approximately 25 – 38 children and young adults will take part in this study.

What will happen if I take part in this research study?

Before you begin the study…

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of your regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. The results of these tests will be reviewed. It is possible that after these tests are reviewed, you will not be able to take part in the study. If you are not able to take part in the study, your doctor will discuss with you the reasons why.

- A medical history
- Physical exam with vital signs
- Bone marrow test to check your cancer (see Tests on the Bone Marrow, below)
- Lumbar puncture to test the fluid in your spinal cord (see Lumbar Punctures, below)
- Blood tests to check your organ (liver, kidneys) function

- Tests to make sure you are not pregnant (if you are a female and old enough to become pregnant) or have certain types of infections
- Echocardiogram (ECHO) which uses sound waves to test heart function
- EKG a test to measure the electrical activity in your heart

Tests on the Bone Marrow

Examinations of the bone marrow will be performed routinely and may be done at the discretion of your study doctor. You have already had many tests of your bone marrow for your previous treatment of ALL. Many children receive some form of sedation or anesthesia during this procedure. A small area over your hipbone on the back will be cleaned and numbed with lidocaine and/or with an anesthetic cream. Approximately 2 teaspoons of bone marrow will be withdrawn through a needle inserted into the bone. The test is painful, especially when the bone marrow is withdrawn. There is also a small risk of bleeding or infection from this procedure. An optional research test to evaluate for the smallest amounts of leukemia detectable in the bone marrow (minimal residual disease) may be sent on your sample if you agree.

Lumbar Punctures ("L.P.s", "spinal taps")

You are familiar with spinal taps since they were done during your initial therapy for ALL. Whether you decide to participate or not on this study, additional spinal taps will need to be done to give medicines, which are necessary to prevent the leukemia from spreading to the spinal fluid. Many children receive some form of sedation or anesthesia during this procedure. Spinal taps are painful and may cause headaches. The skin at the site of needle insertion is usually numbed with an anesthetic cream or lidocaine before the procedure is performed. Approximately 1 teaspoon of spinal fluid will be withdrawn prior to injection of the medicine (methotrexate).

Treatment

There are three groups in which you may enroll and you and your doctor will discuss which regimen is best for you and your disease.

Treatment cohort A of this study consists of approximately 4 weeks of re-induction chemotherapy. You will receive 4 weekly doses Marqibo®. The other standard chemotherapy will start on day 1 and continue until day 19. The table below outlines the therapy you will receive.

Treatment cohort B is the same as Cohort A except it is a milder regimen that does not use one of the drugs called anthracycline (e.g. mitoxantrone).

Treatment cohort C is the mildest version of this regimen and consists of a cycle of 1 dose of Marqibo and a standard chemotherapy regimen of 2 weeks. This cycle may be repeated a second time if you and your doctor decide to do so.

Cohort A: UK ALL R3/Marqibo

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 29
Marqibo®	●					●	●					●	Response Evaluation
Dexamethasone	●	●	●	●	●		●	●	●	●	●		
Mitoxantrone	●	●											
Pegaspargase			●						●				
IT Therapy	●					●							

[#] Erwina asparaginase or Rylaze ® may be substituted for pegaspargase if patient has a PEG allergy.

Cohort B: **UK ALL R3/Marqibo without anthracycline (e.g. mitoxantrone)**

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 16	Day 17		Day 18	Day 19	Day 22	Day 29
Marqibo®	●					●	●						●	Response Evaluation
Dexamethasone	●	●	●	●	●		●	●	●		●	●		
Pegaspargase			●						●					
IT Therapy	●					●								

Cohort C: **Modified Maintenance with Marqibo®**

Cycle 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Daily through day 13	Day 14
Marqibo®	●							Response Evaluation
Dexamethasone	●	●	●	●	●			
Methotrexate (PO)	●					●		
Mercaptopurine (PO)	●	●	●	●	●	●	●	
IT Therapy as needed no more than once weekly								

Various methods will be used to give drugs:

- PO – Drug is given by tablet or liquid swallowed through the mouth
- IV – Drug is given using a needle or tubing inserted into a vein. It can be given by IV push over several minutes or by infusion over minutes to hours
- IM – Drug is given using a needle injected into the muscle (IM shot)
- IT – Drug used to treat the brain and spinal cord and given using a needle inserted into the spinal canal

Medical Tests During Treatment

Whether you are on this study or not the following medical tests will be done to monitor for response to treatment as well as side effects related to treatment. These include:

- Physical exams with vital signs
- Blood tests to check your organ function including
  - CBC to look at your blood cells
  - Chemistries to look at elements and minerals in your blood
  - Blood tests to look at your liver, pancreas and kidney function
- Bone Marrow Tests
- Lumbar Punctures
- EKG a test to measure the electrical activity in your heart

You will have regular medical appointments throughout treatment.

Tests for research purposes:

In addition to the routine tests listed above, we would like to do other tests while you are enrolled on the study.

- **Marqibo® Drug Levels (Pharmacokinetics)**

Mandatory: Pre-Dose 1, 2 and 3 samples for arm A and B. Arm C would only have pre-dose 1 and day 8 trough levels during each cycle for patients that continue on to have a second cycle. These samples can be drawn from a central line, or the same line that is being used to give your chemotherapy.

Optional: Dose 1 samples for Arm A and B. If you do not agree to have these samples taken, you can still receive treatment as part of this study. These samples must be obtained from a separate line that is not being used for infusion of Marqibo®. (e.g., peripheral IV)

Doctors have developed tests to determine the levels of Marqibo® in the body. During therapy, researchers would like to draw an extra ½ teaspoon (2.5-3mL) of blood to measure the levels of Marqibo® in your body. Any leftover blood that is not used for this test will be destroyed. Samples will be drawn on the following schedule.

Mandatory Arm A & B: (May be collected from same line as Marqibo® infusion line or a central line.)	**Optional for Arm A, B and C**: (Must be collected from separate line than Marqibo® infusion line.)
• 30 minutes before start of infusion (SOI) prior to Dose #1 • Pre Dose #2[1] • Pre Dose #3 (Not required for Arm C)	• End of infusion (EOI) • 3 hours (EOI + 2 hours) • 25 hours (EOI + 24 hours)
Mandatory (Arm C): (May be collected from same line as Marqibo® infusion line or a central line.) • Pre-dose 1 • Day 8 trough level	• End of infusion (EOI) • 3 hours (EOI + 2 hours) • 25 hours (EOI + 24 hours)

1. For Arm C, each course will have only one dose of Marqibo, but on Day 8 there will be a trough level.

Final Study Visit

Within 30 days after you finish *the last dose of study drugs,* your doctor will need to check to see how you are doing. The doctor will ask you how you feel, if you have trouble doing your daily routine, and what drugs you are taking. You will also have the following tests done:

- Physical exam, weight, and vital signs
- CBC and chemistry blood tests
- EKG a test to measure the electrical activity in your heart

Follow-up Tests

After completing the treatment on this study we would like to continue to collect some medical information about how you are doing for as long as you are willing to let us. We will collect information on how your ALL is doing, what kind of therapy you may be getting and if you have any long term side effects.

What are my responsibilities?

- During the study you will be asked to take all your chemotherapy drugs as prescribed. It is very important that you follow your doctor's instructions regarding when and how to take your study medications. Be sure to ask your study doctor or nurse if you have any questions about taking your study medications.

- If you experience any unusual side effects as explained by your study doctor, you should contact the study center immediately. You should also contact your study doctor if you are hospitalized for any reason during the study or within 30 days after completion of therapy.

How long will I be in the study?

You will be in the study for one course of therapy which will last approximately 1 month if you are in Cohort A or B. If you are in Cohort C, you will be in the study for 2 weeks if you receive 1 cycle and 1 month if you receive 2 cycles. After completing the study therapy, your doctor will discuss with you the options for additional treatment. These options will vary depending on whether or not your leukemia responded to the therapy. Additionally, after participating in the study, you will continue to be followed to evaluate for any late effects and overall outcomes. We will primarily obtain this information from your primary team, although the study committee may contact you in the future for any additional questions.

Can I stop being in the study?

Yes. You can decide to stop at any time. Your clinical care will not be affected by your decision to withdraw. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. You will be asked to visit the hospital or clinic for some follow-up tests to make sure all the side effects you may have experienced have gone away.

It is important to tell your doctor if you are thinking about stopping so any risks from the study treatment and chemotherapy drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your doctor may stop you from taking part in this study at any time without your permission if he/she believes it is in your best interest; if you do not follow the study rules; if you become pregnant or begin to breast feed; or if the study is stopped.

What side effects or risks can I expect from being in the study?

All people who receive cancer treatment are at risk of having side effects. In addition to killing leukemia cells, chemotherapy drugs can damage normal tissues and produce side effects. Side effects are usually reversible when the medication is stopped, but occasionally can persist and cause serious complications or death. The therapy used in this clinical trial is made stronger so that it can kill cancer cells quickly before they can become resistant to treatment. Protocols used to treat relapsed leukemia are more intense than are those to treat newly diagnosed disease. It is not possible to predict whether the side effects listed below, or other rare side effects may occur. Side effects can be increased when chemotherapy drugs are combined. It is possible that this re-induction therapy will prove better than past therapies for relapsed ALL, but it may be no better or worse than other treatments. Any or all of the agents used alone or in combination with other agents could lead to life-threatening complications and other side effects.

Protocol Updates:
As of 12/3/2021, a total of 23 subjects have been treated on study. 13 were treated on Cohort A, 7 were treated on Cohort B and 3 were treated on Cohort C. At Dose Level 1 Cohort A, there were 8 patients who were treated, and 2 patients developed infection with recovery from the infection. The most common side effects were low blood counts. At Dose Level 2 Cohort A, there were two patients with serious infections and delay in recovery of blood counts. In one patient, infection was the cause of death. Therefore, it was determined that Dose Level 2 was too high for Cohort A, which is the most intensive regimen. All future patients enrolled on Cohort A will be treated at Dose Level 1. 7 patients have been treated on Cohort B and 3 patients on Cohort C at this time, and due to the lower intensity of this regimen, Cohorts B and C patients were treated at Dose Level 2 with a plan to decrease to Dose Level 1 if this level is found to be too high. Due to the development of toxicities, the last 5 patients in Cohort B were treated at Dose Level 1. As of Protocol Amendment #3, future patients on Cohort B will be treated at Dose level 1. On Cohort C,

future patients will be treated at Dose Level 2. This may change depending on new information we get as more patients are treated on this study.

Infection

There is a serious risk of developing an infection while being treated on this research study. This could lead to life-threatening complications, including heart failure, severe infection or death. Because of the intensity of Cohort A, risks of infection may be higher.

To reduce the risk of developing an infection, you will be required to take antifungal medication if you are enrolled onto Cohort A or B. You may need to be hospitalized for part of the treatment so that your doctors and nurses can monitor you very carefully for any signs or symptoms of infection.

If you experience any of the following signs or symptoms while you are being treated on this research study, it is very important to call your doctor or nurse right away.

- Fever
- Pain (earache, sore throat, headache, pain with urination or with bowel movement)
- Redness, swelling, pain, or pus at the site of your central catheter

Common side effects include nausea, vomiting, hair loss and fatigue. The risks from having your blood taken are minimal, but can include an infection or a blood clot. There may be pain and or bruising at the site where the needle is inserted to draw your blood. Chemotherapy causes temporary bone marrow depression. Red blood cell and platelet transfusions may be required. Bone marrow depression means that your bone marrow may make:

- Less red blood cells causing anemia;
- Less platelet, causing bruising and an increased chance of bleeding;
- Less white blood cells, causing a risk for serious infections.

Each drug will have a unique set of side effects. Side effects related to drugs occur in people at different rates or frequencies.

In a study of Marqibo in 21 children and adolescents with refractory malignant disease, at least one out of five children and adolescents reported the following adverse events:

- Changes in blood test results of electrolytes (salts) and other chemistries including increases in liver enzymes, glucose, triglycerides, bilirubin, cholesterol, magnesium, and uric acid and decreases in potassium, calcium, magnesium, albumin, sodium, and phosphorus
- Fatigue
- Decreases in blood counts including red blood cells (anemia), white blood cells, platelet count, and neutrophil count
- Abdominal pain
- Fast heart rate
- Diarrhea

- Nausea, vomiting
- Fever
- Prolonged bleeding time
- Bruising, nose bleeds
- Reduced appetite
- Constipation
- Low blood pressure
- Infections
- Back pain, headache, pain, muscle pain
- The sensation of numbness, tingling or burning on the skin
- Itching
- Rash

In general, the safety profile of Marqibo has been similar to that of vincristine.

Marqibo ®

Likely (Happens to 21-100 children out of 100)	**Less Likely (Happens to 5-20 children out of every 100)**	**Rare (Happens to <5 children out of every 100)**
• Constipation • Hair loss • Reversible nerve problem that may affect the way you walk or the feelings in your fingers or toes • Loss of deep tendon reflexes (such as the "knee jerk") noted only on physical exam • Insomnia • Headache • Nausea • Vomiting • Diarrhea • Anorexia	• Jaw pain • Muscle weakness • Pain and bloating in your abdomen • Numbness and tingling • Wrist or foot drop • Abnormal walk with foot slapping • A drop in white blood cells, red blood cells and platelets in the blood • A low number of red blood cells can make you feel tired and weak. • A low number of white blood cells can make it easier to get infections. • A low number of platelets can make you bruise and bleed more easily. • Electrolyte (salt and mineral) abnormalities due to breakdown of tumor • High blood pressure	• Complete stoppage of your intestinal activity which can result in intestinal blockage • If the drug leaks out of the vein when being administered it can cause damage to nearby tissue • Seizures • Vocal cord paralysis • Difficulty breathing and respiratory failure • Inability to walk • Decreased ability to hear clearly • Dizziness • Difficulty with urination or increase desire to urinate • Drooping eyelids • Double vision, difficulty seeing at night • Life-threatening infection which can lead to significant complications including death • Weight loss

Likely (Happens to 21-100 children out of 100)	**Less Likely (Happens to 5-20 children out of every 100)**	**Rare (Happens to <5 children out of every 100)**
		• Worsening of graft versus host disease

Dexamethasone (given orally)

Likely (Happens to 21-100 children out of 100)	Less Likely (Happens to 5-20 children out of every 100)	Rare (Happens to <5 children out of every 100)
• Overeating • Difficulty sleeping or falling asleep • Decreased ability of the body to fight infection • Personality changes with mood swings • Changes in hormone • production that cause weight gain especially around the abdomen and shoulders, puffy cheeks, muscle • weakness and make your body less able to deal with stress • Pimples	• Upset and irritated stomach with heartburn • High blood sugar which may • require treatment • Red face • Poor wound healing • Infections • Fluid retention • Stretch marks and easy bruising of the skin • Muscle weakness • Lessening of calcium in the bones making them more susceptible to fracture • Cataracts which are usually more reversible in children	• Abnormal amounts of • uric acid in the blood • Inflammation of the pancreas • Increased pressure in the eyes High blood pressure • Serious changes in mood, personality and/or severe depression • Dizziness • Headache • Bone Fractures • Slowed growth • Stomach ulcers • Stomach and intestinal tract bleeding from ulcers Increased pressure in the brain which can lead to difficulty seeing, pressure in the eyes and headache • Damage to the joints which can result in pain and loss of motion usually involving the joints of the hip and knee

Mercaptopurine (given orally)

Likely (Happens to 21-100 children out of every 100)	Less Likely (Happens to 5-20 children out of every 100)	Rare (Happens to <5 children out of every 100)
• Condition where bone marrow activity is decreased so that there are fewer red blood cells, white blood cells, and cells involved in blood clotting (L)	• Poor appetite • Nausea • Vomiting • Diarrhea • General feeling of being unwell • Red rash (L) • Low concentration of sperm	• Hives • High level of molecule called uric acid in the blood • White layer of film in the mouth • Inflammation of the liver (L) • Increased liver enzymes • Increased darkening of the skin (L) • Inflammation of the pancreas • Fibrosis of the liver (L) • High levels of a molecule called bilirubin in the blood • Fibrosis of the lungs • Cancer caused by this therapy
Birth defects caused by mercaptopurine have been noted in animals. Women receiving mercaptopurine in the first trimester of pregnancy have an increased chance of having an abortion. It is unknown whether the drug is excreted in breast milk.		

(L) Toxicity may also occur later.

Methotrexate (orally)

Likely (Happens to 21-100 children out of 100)	Less Likely (Happens to 5-20 children out of every 100)	Rare (Happens to <5 children out of every 100)
• Elevation in the blood of certain enzymes found in the liver	• Nausea • Vomiting • Decreased appetite • Low blood counts • Oral ulcers • Fatigue • Learning disability	• Allergic reactions • Blurred vision • Severe skin reactions • Hair loss • Kidney damage • Neurologic toxicity (headache, blurred vision, difficulty moving, speaking or seeing)

Likely (Happens to 21-100 children out of 100)	Less Likely (Happens to 5-20 children out of every 100)	Rare (Happens to <5 children out of every 100)
		• Diarrhea • Inflammation of the lungs and/or heart

Mitoxantrone (given into the vein)

Likely (Happens to 21-100 children out of 100)	Less Likely (Happens to 5-20 children out of every 100)	Rare (Happens to <5 children out of every 100)

• Nausea
• Vomiting
• Diarrhea
• Fever
• Loss of Appetite
• Blue or blue green color to urine and the white of the eye
• Fewer white blood cells, red blood cells and platelets in the blood.
  • A low number of red blood cells can make you feel tired and weak
  • A low number of white blood cells can make it easier to get infections
  • A low number of platelets causes you to bruise and bleed more easily
• Inflammation and/or sores in the mouth, throat and/or esophagus
• Increase chance of infection
• Temporary hair loss
• Tiredness
• Absence of or irregular menstrual cycles (periods)
	• Abdominal or back pain
	• Headache
	• Swelling of the veins
	• Constipation
	• Elevation in the blood of certain enzymes found in the liver
	• Rash and/or itching and dryness of the skin which can lead to flakey skin
	• Decrease in your hearts ability to pump blood
	• Damage to the heart muscle which may not be noticeable or may make you feel tired, weak, feel short of breath, and retain fluid
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• Increased fluid around the heart
		• An irregular heart beat which is usually slower than normal
		• Seizures
		• Damage to the skin if the medication leaks from a vein which can lead to pain and inflammation
		• The rapid death of large numbers of tumor cells which can cause the potassium and phosphate salts and the uric acid in the blood to rise quickly and this could lead to a life-threatening irregular heart beat or damage to the kidneys.
		• Swelling and redness of the eyes
		• Ulceration or bleeding of the lower intestinal tract

Likely (Happens to 21-100 children out of 100)	Less Likely (Happens to 5-20 children out of every 100)	Rare (Happens to <5 children out of every 100)
• Temporary decrease in the number of sperm which may temporarily decrease the ability to have children		• Damage or inflammation of lung tissue which may make you short of breath • Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid and may require treatment • Liver damage • A new cancer or leukemia resulting from this treatment.

Methotrexate (given into the spinal fluid)

Likely (Happens to 21-100 children out of 100)	Less Likely (Happens to 5-20 children out of every 100)	Rare (Happens to <5 children out of every 100)
▪ Nausea ▪ Headache	▪ Abnormally high number of cells in the spinal fluid ▪ Learning disability ▪ Vomiting ▪ Fever ▪ Rash ▪ Drowsiness ▪ Stiff neck ▪ Irritation of tissues in the brain/spinal cord ▪ Unsteady walk	▪ Seizures ▪ Partial paralysis ▪ Damage to brain tissue ▪ Increasingly poor nervous system function ▪ Fewer red and white blood cells and platelets in the blood • a low number of red blood cells can make you feel tired and weak • a low number of white blood cells can make it easier to get infections • a low number of platelets causes you to bruise and bleed more easily

Pegaspargase (given into the muscle)

Likely (Happens to 21-100 children out of 100)	Less Likely (Happens to 5-20 children out of every 100)	Rare but serious (Happens to <5 children out of every 100)
• An increase in the level of ammonia that is found in the blood • A decrease in levels of factors in the blood that help your blood to clot normally • A feeling of extreme tiredness not relieved by sleep • Weakness • Diarrhea	• Rashes, hives, swelling of the lips • Feeling short of breath or shortness of breath • Some sort of allergic reaction such as a rash, hives or fever that may require pretreatment with antihistamines prior to the injection • Puffiness or swelling around the eyes • Fluid build-up in the tissues or Fluid retention • High levels of sugar in the blood that may require treatment • Elevation in the blood of certain enzymes or bilirubin found in the liver which may mean liver irritation or damage • High levels of uric acid in the blood which could damage the kidneys • Headache • Dizziness • Chest pain • A fast heartbeat which may cause pain in the chest • A decrease or an increase in blood pressure • Loss of desire to eat or appetite • Weight loss • Mild nausea and/or vomiting • Muscle and joint aches and pains • Numbness and tingling in the fingers and toes • Chills and fever • Changes in your mood such that you feel depressed, irritable, confused or have	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever • Irritation of the small airways of your lungs that can make you cough and wheeze • Seizures • Coma • Sudden damage to the red blood cells (hemolytic anemia) which could cause a rapid decrease in the number of red blood cells such that you would be tired and weak and feel short of breath and may require a blood transfusion • Temporary decrease in blood to the brain which can lead to temporary loss of consciousness • A bleeding disorder that can lead to bleeding from many areas of the body or excessive clotting in blood vessels including those that lead to the brain • Damage to the bladder which can lead to large amounts of blood in the urine, pain and the urge to urinate frequently and also scarring of the bladder • High levels of nitrogen and/or a chemical (creatinine) in the blood which may indicate that the kidneys are not working as well as normal • Severe kidney damage • Severe damage to the liver which can lead to a fatty and

Likely (Happens to 21-100 children out of 100)	Less Likely (Happens to 5-20 children out of every 100)	Rare but serious (Happens to <5 children out of every 100)
	hallucinations (see or hear things that are not there) • An increase in the levels of lipids (fats) in your blood which if prolonged could lead to heart problems later in life • Shakiness or tremor which may cause jerky movements • Pain in the abdomen (belly) • Too much gas produced in the intestines • Inflammation of the pancreas (an organ in the abdomen which produces insulin and certain digestive chemicals) which may affect the function of the pancreas and which may cause pain in the abdomen (belly)which can be severe and may increase the blood sugar • Elevations of certain chemicals in the blood which may indicate damage to the pancreas • Fewer white blood cells, red blood cells and platelets in the blood o a low number of white blood cells can make it easier to get infections o a low number of red blood cells can make you feel tired and weak o a low number of platelets causes you to bruise and bleed more easily	enlarged liver, inflammation and/or scarring which could lead to a yellow appearing skin, and fluid collection in the abdomen (belly) which makes it look larger • Reduced ability of the body to fight infection which can lead to infections including severe blood infections which will need to be treated and may be life threatening, infections of the valves in the heart, the bladder and other areas of the body

Erwinia Asparaginase (given into the muscle)

If you develop an allergic reaction to pegaspargase, you may be treated with

Erwinia L-asparaginase (Erwinaze® or Erwinase®). This preparation has been given to hundreds of children over many years and many of the side effects are similar to those that occur with the other forms of asparaginase. Six injections of Erwinia L-asparaginase are required to substitute

for each injection of pegaspargase and one injection of Erwinia L-asparaginase for each injection of asparaginase.

Another alternative if you are not able to take Pegasparagase is Erwinia chrysanthemi (recombinant)-rwyn (Rylaze ®) (given into the muscle). The side effects are the same as Erwinia asparaginase.

Likely (Happens to 21-100 children out of 100)	Less Likely (Happens to 5-20 children out of every 100)	Rare But Serious (Happens to <5 children out of every 100)
	• Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing. • Allergic reaction which can be life-threatening and potentially fatal. This reaction requires immediate medical treatment. It may include fever, chills and skin rash. Less commonly wheezing, shortness of breath, swelling of the throat, drop in blood pressure, and rapid heart rate may occur. • Hives; red and sometimes itchy bumps on the skin. • Local allergic reactions including rashes and hives around the site of the injection	• Inflammation of the pancreas (an organ in the abdomen which makes insulin and certain digestive chemicals) which causes severe pain in the abdomen (belly) and back and may increase the blood sugar • Formation of blood clots that plug blood vessels and can lead to pain and swelling in the area of the clot. Such clots may break loose and travel to another area. They can cause damage or be life-threatening depending on where they go. • Excessive or uncontrolled bleeding which can occur in the head, stools, the nose, urine and other parts of the body. • Sudden and temporary loss of blood flow and oxygen to the brain causing problems with vision, dizziness, weakness and numbness (especially in one side of the body), and trouble speaking. Also called mini stroke. • A bleeding disorder in which small blood clots develop throughout the bloodstream blocking small blood vessels and depleting platelets and clotting factors needed to control bleeding. This condition can lead to bleeding from many areas of the body and can be life-threatening.

Likely (Happens to 21-100 children out of 100)	Less Likely (Happens to 5-20 children out of every 100)	Rare But Serious (Happens to <5 children out of every 100)
		• Fever • Abnormal control of blood sugar level • Increase in the blood level of certain enzymes or bilirubin (a waste product that passes through the liver) which could indicate liver irritation or damage • High blood sugar which may require treatment with insulin • An increase in the level of ammonia that is found in the blood • Vomiting • Nausea • Belly pain • Headache • Diarrhea • Weight loss • Seizures; sudden, uncontrolled muscle spasm and loss of consciousness resulting from abnormal brain function.

Reproductive risks

Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse a baby while on this study. It is a condition of this study that adequate birth control methods be used by all participants and/or their sexual partners while enrolled in the study. Examples of these include total abstinence (no sex), oral contraceptives ("the pill"), an intrauterine device (IUD), Levonorgestrol implants (Norplant), or medroxyprogesterone acetate injections (Depo-provera shots). If one of these methods of birth control cannot be used, contraceptive foam with a condom is recommended. Ask your doctor about counseling and more information about preventing pregnancy.

If you become pregnant/father a child during this study, contact your doctor immediately to discuss the requirements for pregnancy outcome follow-up. Female subjects will be given instructions for discontinuation of study medication.

Confidential Information

Because the sponsor of this study is outside of your medical center there is the potential small risk of accidental release of confidential information when sending out any research documentation. Please see the "Will my medical information be kept private?" section of this document for more details.

Developing a Second Cancer

It is possible that you may develop a second form of cancer as a result of this treatment. Experience so far suggests that the chance of this happening is very small. Not enough information has been gathered in children to be able to give an accurate prediction, although it may be in the range of one in every 50 to 800 children treated.

Are there benefits to subjects taking part in the study?

Participation on this study may or may not benefit you. Participating in this study will not cure your relapsed leukemia. Based on experience with the drugs used in the treatment plan, researchers believe this therapy may cause your leukemia to stop growing or go into remission for a period of time. Your cancer may not have any response to the therapy received while participating in this study.

Are there benefits to society?

It is hoped that the information learned from this study may help future children or young adults with relapsed ALL.

What other choices do I have if I do not take part in this study?

You do not have to participate in this study to receive treatment for recurrent leukemia. There is no "standard" therapy for recurrent leukemia. Most treatment plans have used drugs similar to those used in this protocol, although these drugs may be given in different combinations, and at different times. You can receive other combinations of chemotherapy without participating in this study.

As an alternative to this study, you may decide you don't want additional treatment for your relapsed leukemia. You will always receive medicines to help you feel more comfortable and deal with problems caused by your cancer or treatment whether you participate in this study or not.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Members of the research team and, if appropriate, your primary care physicians and nurses will know that you are a research subject. All results will be kept confidential, but may be made available to you, and/or your physician if you wish. Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately. You may read your medical record. The records are available to those caring for you at this hospital.

Organizations that may inspect/or copy your research records for quality assurance and data analysis include:

- Therapeutic Advances in Childhood Leukemia Consortium (TACL)
- The United States Food and Drug Administration (FDA)
- The United States Department of Health and Human Services (DHHS)
- The Institutional Review Board (IRB) of Children's Hospital Los Angeles (CHLA)
- Acrotech Biopharma (the makers of Marqibo®)
- DSMC (CHLA)

As a result, these organizations may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

Reasonable steps will be taken to protect your right to privacy. No information about you, or provided by you during the research, will be shared with others without your written permission, except as explained below:

If necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or
if required by law (i.e., child abuse, reports of certain infectious diseases).

The information collected will be used to meet the purpose of this clinical study. In addition, this information may be used to support applications to market the studied drug in the United States and in other countries. It may also be used in reports of the study or for scientific publications and presentations that will not identify study participants by name.

A description of this clinical trial will be available on http://www.clinicaltrials.gov , as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at anytime.

What are the costs of taking part in this study?

The health care costs during your participation in this study that are considered part of the standard treatment of your disease will be billed to your insurance or other third-party payer. This includes blood tests, hospitalizations, procedures that will be done and medications.

You will not have to pay for the following tests that will be done for research purposes only.

- Tests to measure Marqibo® levels

Your family is responsible for other costs which may result from your participation in the study, such as, but not limited to, time off of work, car fare, baby sitter fees, food purchased while at the hospital, etc. You will not receive any type of payment for participating in this study. Taking part in this study may lead to added costs to your insurance company. Please ask about any expected added costs or insurance problems.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at *http://cancer.gov/clinicaltrials/understanding/insurance-coverage* . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is voluntary. You may choose not to participate in this study. If you decide not to participate, you will not be penalized and you will still receive the standard treatment.

If you choose to participate, you may discontinue your participation in the study at any time. If you discontinue participation in the study, physicians and hospital personnel will still take care of you.

You also have the right to know about new information that may affect your health, welfare, or your willingness to participate in the study. You will be provided with this information as soon as it becomes available.

Whether you participate or not, you will continue to get the best medical care this hospital can provide.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[*name of center*] Institutional Review Board (a group of people who review the research to protect your rights) at* _____ *[*telephone number*].*
*[*Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.*]*

Where can I get more information?

Call the National Cancer Institute's Cancer Information Service:
1-800-4-CANCER (1-800-422-6237) OR 1-800-332-8615 (for the hearing impaired)

- You will be given a copy of this consent form.
- You will be given a copy of this treatment plan upon request.
- The National Cancer Institute web site: www.cancer.gov. It contains peer-reviewed summaries on cancer treatment, screening, prevention, and supportive care; a registry of about 1,700 open and 10,300 closed cancer clinical trials from around the world; and directories of physicians, genetic counselors, and organizations that provide cancer care.
- ClinicalTrials.gov: https://clinicaltrials.gov/. ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.
- Visit the TACL Consortium Website at https://tacl.chla.usc.edu

CONSENT FOR OPTIONAL STUDIES FOR RESEARCH

THESE TESTS ARE OPTIONAL. YOU MAY STILL PARTICIPATE IN THE STUDY EVEN IF YOU DO NOT AGREE TO THESE TESTS.

Marqibo® Drug Levels (Pharmacokinetics)-Optional studies

During therapy, researchers would like to draw an extra ½ teaspoon (2.5-3mL) of blood at each time point. Samples will be drawn on the following schedule. You will not get a copy of the results of this testing.

- End of infusion (EOI) after dose #1 of Marqibo®
- 3 hours (EOI + 2 hours)
- 25 hours (EOI + 24 hours)

YES, I agree to have blood drawn for Marqibo® levels with the first dose of Marqibo®

_____ initials of subject (if subject is 14 years or older)

_____ initials of parent/legal guardian (if subject is a minor)

_____ initials of parent/legal guardian (if subject is a minor)

NO, I do not agree to have blood drawn for Marqibo® levels with the first dose of Marqibo®

_____ initials of subject (if subject is 14 years or older) _____ initials of parent/legal guardian (if subject is a minor)

_____ initials of parent/legal guardian (if subject is a minor)

Pre-treatment bone marrow sample for minimal residual disease

Before you start treatment, researchers may take some of the bone marrow that is normally taken for your medical care and send it to be tested to evaluate for the smallest amount of leukemia in the bone marrow (minimal residual disease).

YES, I agree to have this sample sent

_____ initials of subject (if subject is 14 years or older)

_____ initials of parent/legal guardian (if subject is a minor)

_____ initials of parent/legal guardian (if subject is a minor)

NO, I do not agree to have this sample sent

_____ initials of subject (if subject is 14 years or older)

_____ initials of parent/legal guardian (if subject is a minor)

_____ initials of parent/legal guardian (if subject is a minor)

SIGNATURE PAGE

Use your own institutional signature page.

APPENDIX 1: PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria Karnofsky and Lansky performance scores are intended to be multiples of 10					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.

	self-care. Totally confined to bed or chair.	10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX 2: GUIDANCE FOR DETERMINING PREVIOUS CUMULATIVE ANTHRACYCLINE DOSE

Total Anthracycline Calculation Worksheet

Instructions:

In order to calculate the total anthracycline received by a patient, you will need to review the patient's previous treatment. You will need to document **each dose** of anthracycline chemotherapy prescribed and received by the patient.

Step 1: Indicate which drug the patient received (Contact TACL Operations if drug not listed)

Step 2: Enter the prescribed dose for that drug per the chemotherapy roadmap/orders. Be sure to list all doses.

Step 3: Enter the corresponding conversion factor for the drug given.

Step 4: Multiply the prescribed dose by the conversion factor and enter the result in the "Total Anthracycline" column.

Step 5: After you have completed this worksheet for all doses, add all the total doses to obtain the Total Cumulative Dose.

Drug	Prescribed Dose The prescribed dose is the dose of chemotherapy written in the protocol. It will be listed as mg/m^2. (It is not the actual dose received by the patient)	Conversion Factor Doxorubicin = 1 Daunorubicin = 1 Idarubicin = 4 Mitoxantrone = 4	Total Anthracycline
☐ Doxorubicin ☐ Daunorubicin ☒ Idarubicin ☐ Mitoxantrone	**EXAMPLE:** **10 mg/m^2**	**4**	**40 mg/m^2**
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone			
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone			
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone			
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone			
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone			

☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone			
Total Cumulative Dose			

APPENDIX 3: PARTIAL LIST OF CONCOMITANT MEDICATIONS KNOWN TO INTERACT WITH CYTOCHROME P450-3A4 ISOENZYMES AND/OR P-GLYCOPROTEIN (TO BE USED WITH CAUTION)

Please note that this is not a comprehensive listing and other medications should be reviewed with the PI.

- Atazanavir
- Atorvastin
- Azithromycin
- Carbamazepine
- Chlorpheniramine
- Cimetidine
- Ciprofloxacin
- Clarithromycin
- **Clotrimazole***
- Cyclosporine
- Dexamethasone^
- Digoxin
- Diltiazem
- Ergotamine
- Erythromycin
- **Fluconazole***
- Grapefruit Juice
- Haloperidol
- Indinavir
- **Itraconazole***
- **Ketoconazole***
- Lidocaine
- Lovastatin
- **Miconazole***
- Nefazodone
- Nelfinavir
- Norfloxacin
- Orphenadrine
- Paroxetine
- Phenobarbital
- Phenytoin
- **Posaconazole***
- Progesterone
- Rapamycin
- Rifabutin
- Rifampin
- Rifapentine
- Ritonavir
- Rosiglitazone
- Saquinavir
- Sertraline
- Simvastatin
- St. John's Wort
- Tacrolimus
- Tamoxifen
- Telithromycin
- Toremfine
- Trazadone
- Verapamil
- **Voriconazole***
- Zafirlukast

*** No azole-based antifungal therapy is permitted without PI approval.**

^ Dexamethasone has been used in combination with standard vincristine in the UK ALL R3 regimen (Parker et al. Lancet 2010) and in combination trials with Marqibo®in adults (Thomas et al. Cancer 2009) with an acceptable toxicity profile. Dexamethasone *will* be used on this trial.

APPENDIX 4: NEUROLOGICAL EXAM

TACL Registration #: _____ TACL Protocol #: _____

TACL Subject ID : _____ Enrollment Date: _____

Assessment Date: _____

If Pretreatment or Off Study Neurological Exam Section must be completed.

☐ Pretreatment ☐ Dose 3
☐ Dose 1 ☐ Dose 4
☐ Dose 2 ☐ Off Study

Performance Status: Lansky: _____ Karnofsky: _____

Neurological Status :

General: ☐ No neurological findings ☐ Stable
☐ Improved ☐ Worse ☐ Resolved

Any Change from baseline: ☐ Yes ☐ No *If Yes, go to Neuro exam; If no to both then assessment is complete.*

Any Change from previous assessment: ☐ Yes ☐ No

Neurological Exam:

Mark Normal or Abnormal with an X.
If abnormal, record a brief description of the current abnormality.
Record ND for any examination not done.

	Normal	Abnormal	Description of abnormality
Muscle Tone & Strength: (weakness)			
Reflexes: (Brachioradialis, biceps, knee, ankle)			
Gait:			
Postural Hypotension:			
Sensory: (Pain, jaw pain, numbness, paresthesias, constipation, vibration first toe)			
Stretch-extension of wrist:			
Stretch-dorsiflexion of foot:			

Comments:

MD Signature Date

APPENDIX 5: NEUROLOGIC TOXICITY GRADING

Grade	Peripheral Motor Neuropathy (CTCAEv4.03)	Peripheral Sensory Neuropathy (CTCAEv4.03)
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Asymptomatic; loss of deep tendon reflexes or paresthesia
2	Moderate symptoms; limiting instrumental ADL	Moderate symptoms; limiting instrumental ADL
3	Severe symptoms; limiting self care ADL; assistive device indicated	Severe symptoms; limiting self care ADL;
4	Life-threatening consequences; urgent intervention indicated	Life-threatening consequences; urgent intervention indicated
5	Death	Death

Peripheral motor neuropathy: A disorder characterized by inflammation or degeneration of the peripheral motor nerves.

Peripheral sensory neuropathy: A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.

APPENDIX 6: BOWEL PROPHYLAXIS AND MANAGEMENT GUIDELINES

- A diet high in bulk fiber, fruits and vegetables, and adequate fluid intake may help minimize constipation.
- Bowel regimen may be held if diarrhea develops.

Level I: Prophylaxis

All subjects must receive a concomitant stool softener, or equivalent agents (e.g., Miralax®), during and for at least 7 days post discontinuation of Marqibo®. Stool softeners may be held if diarrhea develops.

- Docusate; or
- Lactulose; or
- Docusate/sennosides A and B (US Peri-Colace®).

Level II: Active Intervention

To be initiated if a patient is constipated per definition below, with institution of one of the following options, or equivalent agents:

- Substitution of Docusate/sennosides A and B (US Peri-Colace®) for one dose of docusate; or
- Increase dose and/or frequency of lactulose or Docusate/sennosides A and B (US PeriColace®); or
- Provide a dose of milk of magnesia at bedtime.

Level III: Escalated Intervention

To be initiated if the patient is still constipated per definition after 2 days with active intervention, with the addition of one of the following options, or equivalent agents:

- Bisacodyl tablets; or
- Mineral oil orally; or
- Phosphate buffered solution orally.

Level IV: Aggressive Intervention

To be initiated if the patient is still constipated as per definition after 2 days of escalated intervention, with the addition of one of the following, or equivalent agents:

- Magnesium citrate oral solution; or
- Bisacodyl suppository (NOT with neutropenia); or
- Phosphate enema (NOT with neutropenia); or
- Mineral oil enema (NOT with neutropenia).

Definition of Constipation: Change in the usual pattern of elimination including two or more of the following symptoms:

- Decrease frequency of stool and/or < 3 times per week
- Difficulty passing stool
- Passage of hard stool

Agent Schedules and Doses

Docusate

- Adults and children older than 12 years of age: **50 to 360 mg orally daily**
- Children 2 to 12 years of age: **50 to 150 mg orally daily**
- Children Younger than 2 years of age: **25 mg orally daily**

Alternatively, children 3 to 6 years of age may receive oral docusate sodium dosages of 20 to 60 mg daily and children younger than 3 years of age may receive 10 to 40 mg daily. Doses at the higher end of these dosage ranges may be required initially.

Lactulose

- **Adults:** initial dosage is 10 to 20 g orally daily; may be increased to 40 g daily if necessary.
- **Children:** 5 to 7.5 g orally daily, usually given as a single dose after breakfast.

Docusate/sennosides A and B (US Peri-Colace®).

- **Adults:** 1 or 2 capsules orally at bedtime, or as indicated. In severe cases, dosage may be increased to 2 capsules twice daily, or 3 capsules at bedtime.
- **Children:** 1 to 3 teaspoons of syrup orally at bedtime, or as indicated. Peri-Colace syrup may be given in a 6 oz. to 8 oz. glass of milk or fruit juice or in infant's formula to prevent throat irritation.

Milk of Magnesia

- **Adults and children older than 12 years of age:** 30 to 60 mL orally daily, given as a single dose or in divided doses.
- **Children 6 to 11 years of age:** 15 to 30 mL orally daily, given as a single dose or in divided doses.
- **Children 2 to 5 years of age:** 5 to 15 mL orally daily, given as a single dose or in divided doses.

Bisacodyl

- **Adults and children 12 years of age and older:** 5 to 15 mg orally daily as a single dose

SOP Development

- Update protocol deviation SOP

Mineral Oil Orally

- **Adults and children 12 years of age and older:** 15 to 45 mL orally daily, given as a single dose (minimum dose of 15 mL) or in divided doses.
- **Children 6 to 11 years of age:** 5 to 15 mL orally daily, given as a single dose (minimum dose of 5 mL) or in divided doses.

Phosphate Buffered Solution Oral

- **Adults and children 12 years of age and older:** 20 to 45 mL orally (4 to 9 teaspoons).
- **Children 10 and 11 years of age:** 10 to 20 mL orally (2 to 4 teaspoons).
- **Children 5 to 9 years of age:** 5 to 10 mL orally (1 to 2 teaspoons).
- **Children under 5 years:** Physician discretion

****DO NOT TAKE MORE THAN THIS AMOUNT IN A 24 HOUR PERIOD**

Magnesium Citrate Oral Solution (1.745 gm/30mL)

- **Adults and children 12 years of age and older:** 11 to 25 g orally daily, given as a single dose or in divided doses.
- **Children 6 to 11 years of age:** 5.5 to 12.5 g orally daily, given as a single dose or in divided doses.
- **Children 2 to 5 years of age:** 2.7 to 6.25 g orally daily, given as a single dose or in divided doses.

Bisacodyl Suppository (**NOT WITH NEUTROPENIA)

- Adults and children 12 years of age and older: **10 mg daily, given as a single dose**
- **Children 2 to 11 years of age:** 5 to 10 mg (one-half to one suppository) daily, given as a single dose
- **Children younger than 2 years of age:** 5 mg (one-half suppository daily, given as a single dose

Phosphate Enema (**NOT WITH NEUTROPENIA)

- Adults and children 12 years of age and older: **118 mL (one bottle) daily as a single dose**
- **Children 2 to 11 years of age:** 59 mL (one bottle of Fleet enema for children) daily as a single dose

Mineral Oil Enema (**NOT WITH NEUTROPENIA)

- Adults and children 12 years of age and older: **118 mL (one bottle) daily as a single dose**
- **Children 2 to 11 years of age:** 59 mL (one half bottle) daily as a single dose

Dosing information from 2001 edition of the American Hospital Formulary Service's Drug Information book or the 2001 edition of the Physician's Desk Reference.

APPENDIX 7: PHARMACOKINETIC WORKSHEET – T2012-002 MARQIBO® Study

TACL Registration #: _____ BSA (m2): _____

Height (cm): _____ Assigned Dose (mg/m^2): _____

Weight (kg): _____ Actual dose (mg): _____

Dose 1:

Date of Administration	Infusion Start Time	Infusion End Time
_____	_____	_____

Dose 2 (arm C will have a trough level but no dose administered[1]):

Date of Administration	Infusion Start Time	Infusion End Time
_____	_____	_____

Dose 3 (Not required for Arm C)

Date of Administration	Infusion Start Time	Infusion End Time
_____	_____	_____

1.Complete a second form if there is a second cycle of Arm C

Sample #	Day	Date	Hour	Target Time	Time obtained	Comments

1	1		All: Pre-Dose			
2*	1		Arm A/B: End of Infusion (EOI)			
3*	1		Arm A/B: EOI + 2 hours			
4*	1		Arm A/B:EOI + 24 hours			
5	8		All: Pre dose #2 (trough level for Arm C)			
6	15		Arm A/B: Pre dose #3			

EOI = End of infusion. * Obtain sample, if feasible, in consenting patients from a line separate than the one used to infuse Marqibo®

Blood Sample Collection and Processing

1. For non-mandatory samples, a peripheral or central access device may be used for collection of the PK samples. This must be a separate line from that used for Marqibo® infusion.

2. Mandatory PK samples may be collected through the line used for Marqibo® infusion.

3. If blood samples are taken via an indwelling central venous cannula, an appropriate amount of fluid should be removed from the cannula to clear the line before each blood sample is taken.

4. Blood samples of 3 mL will be collected in lavender-top (EDTA) vacutainers at each of the time points indicated above. Invert the lavender-top vacutainer 10 times to mix completely.

5. Complete the labels using a waterproof pen and apply to the Vacutainer tubes. Complete information requested on this PK sheet for each sample. Remember to record all sampling times (use the 24 hour clock; for example, 1:00 PM = 13:00). Add comments, as necessary. Place the samples on ice until centrifugation.

6. Plasma: should be separated by centrifugation at 10°C (10 min at 1000 g or 2500 rpm) within four hours after collection. Separated plasma should be transferred to screw capped polyproplyene tubes (i.e. Nunc 3.6 ml #379189, 366524 or equivalent) and labeled with the TACL registration number, date and time of sampling, and sample number. Plasma samples should be stored in the dark at -70° C.

7. Shipment: Participating sites should ship samples on dry ice using priority Federal Express (contact TACL Operations for a FedEx label to be used for sample shipments.) Samples should be shipped Monday, Tuesday or Wednesday only. Lab receives samples Tuesday

through mid-Friday. Samples should not be sent on the day preceding a holiday. All samples should be batched per patient. Send a notification email to **marqibo@mail.nih.gov** when sending samples.

Ship samples to:

Figg Lab
Clinical Pharmacology Program
National Cancer Institute
9000 Rockville Pike
Building 10, Room 5A08
Bethesda, MD 20892
(O) 240-760-6180
(F) 301-402-8606

8. Please notify the PK team by e-mail (marqibo@mail.nih.gov) or phone (301-402-6642) with questions regarding sample handling and shipment.

Appendix 8: Mercaptopurine Dosing Guidelines (As per Children's Oncology Group AALL1131 Trial

MERCAPTOPURINE 75 mg/m2

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.60 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / day	350 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.79 - 0.83	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab /d x 1	500 mg/wk
0.98 - 1.02	1½ tab / day	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / day	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.46 – 1.49	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.50 – 1.54	2½ tab/ d x 4; 2 tab / d x 3	800 mg/wk
1.55 – 1.59	2½ tab/ d x 5; 2 tab / d x 2	825 mg/wk
1.60 – 1.64	2½ tab/ d x 6; 2 tab / d x 1	850 mg/wk
1.65 – 1.69	2½ tab/ d	875 mg/wk
1.70 – 1.73	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
1.74 – 1.78	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
1.79 – 1.83	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
1.84 – 1.88	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
1.89 – 1.92	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
1.93 – 1.97	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
1.98 – 2.02	3 tab/ d x 7	1050 mg/wk
2.03 – 2.07	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.08 – 2.11	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.12 – 2.16	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
2.17 – 2.21	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.22 – 2.26	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.27 – 2.30	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk
2.31 – 2.35	3½ tab/ d x 7	1225 mg/wk
2.36 – 2.40	3½ tab/ d x 6; 4 tab / d x 1	1250 mg/wk
2.41 – 2.45	3½ tab/ d x 5; 4 tab / d x 2	1275 mg/wk
2.46 – 2.49	3½ tab/ d x 4; 4 tab / d x 3	1300 mg/wk
2.50 – 2.54	4 tab/ d x 4; 3½ tab / d x 3	1325 mg/wk
2.55 – 2.59	4 tab/ d x 5; 3½ tab / d x 2	1350 mg/wk
2.60 – 2.64	4 tab/ d x 6; 3½ tab / d x 1	1375 mg/wk
2.65 – 2.69	4 tab/ d x 7	1400 mg/wk
2.70 – 2.73	4 tab/ d x 6; 4½ tab / d x 1	1425 mg/wk
2.74 – 2.78	4 tab/ d x 5; 4½ tab / d x 2	1450 mg/wk
2.79 – 2.83	4 tab/ d x 4; 4½ tab / d x 3	1475 mg/wk
2.84 – 2.88	4½ tab/ d x 4; 4 tab / d x 3	1500 mg/wk
2.89 – 2.92	4½ tab/ d x 5; 4 tab / d x 2	1525 mg/wk
2.93 – 2.97	4½ tab/ d x 6; 4 tab / d x 1	1550 mg/wk
2.98 – 3.00	4½ tab/ d x 7	1575 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*