

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202497Orig1s000

MEDICAL REVIEW(S)

Clinical Review

Ashkan Emadi, MD, PhD (Primary Reviewer)

Qin Ryan, MD, PhD (Team Leader)

NDA 202497

Marqibo (Vincristine Sulfate Liposome Injection)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202497
Priority or Standard	Standard
Submit Date(s)	July 12, 2011
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PDUFA Goal Date	May 12, 2012
Division / Office	Division of Hematology Products (DHP), Office of Hematology and Oncology Products (OHOP)
Reviewer Name	Ashkan Emadi, MD, PhD
Clinical Team Leader	Qin Ryan, MD, PhD
Review Completion Date	April 17, 2012
Established Name	Vincristine Sulfate Liposomal Injection (VSLI)
(Proposed) Trade Name	Marqibo
Therapeutic Class	Vinca Alkaloid
Applicant	Talon Therapeutics (formerly Hana Biosciences)
Formulation(s)	Vincristine Sulfate Liposomes Injection (Marqibo Kit) contains 3 drug product components: 1) Vincristine Sulfate Injection USP (5 mg/5 mL), 2) Sphingomyelin / Cholesterol Liposomes Injection (103 mg/mL), 3) Sodium Phosphate Injection (14.2 mg/mL)
Dosing Regimen	2.25 mg/m ² IV every 7 days as a 60 minutes infusion
Indication	Treatment of adult patients with Philadelphia Chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy
Intended Population	As mentioned above in Indication

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List of Abbreviations

AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ANC	Absolute Neutrophil Count
BM	Bone Marrow
BMBx	Bone Marrow Biopsy
BSA	Body Surface Area
CBC	Complete Blood Count
CI	Confidence Interval
CR	Complete Remission
CRi	Complete remission with incomplete blood count recovery
CRp	Complete remission with incomplete platelet recovery
CRF	Case Report Form
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HI	Hematologic Improvement
HSCT	Hematopoietic Stem Cell Transplantation
IRRC	Independent Response Review Committee
ITT	Intent-to-Treat
IV	Intravenous
IWG	International Working Group
K-M	Kaplan-Meier
6-MP	6-Mercaptopurine
MRC	Medical Research Council
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
NHL	Non-Hodgkin's Lymphoma
ODAC	Oncologic Drugs Advisory Committee
OS	Overall Survival
Ph-	Philadelphia Chromosome Negative
PR	Partial Remission
PS	Performance Status
SAE	Serious Adverse Event
SCLI	Sphingomyelin/Cholesterol Liposomes Injection
SD	Stable Disease
SPA	Special Protocol Assessment
SPI	Sodium Phosphate Injection
Std	Standard Deviation
VCR	Vincristine
VSLI	Vincristine Sulfate Liposomal Injection (Marqibo)
WBC	White Blood Cell

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 202497 submission is seeking accelerated approval for Marqibo for the treatment of adult (age ≥ 18 years) patients with Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy. Marqibo is administered at a dose of 2.25 mg/m² IV every 7 days as a 60 minute infusion for a 28-day course of treatment. The clinical evidence of safety and efficacy to support this claim was based on a single arm trial.

This reviewer acknowledges that the decision on recommendation on regulatory action for this NDA is not straightforward. However, based on following discussion and risk-benefit assessment, this reviewer recommends accelerated approval of Marqibo for the proposed indication with implementation of postmarket requirement to be performed with due diligence with respect to the conduct of the confirmatory study.

This recommendation was based on

- a 15% CR+CRi rate
- a median CR+CRi duration of 28 days between two confirmed CR or CRi and 56 days from the first documented CR or CRi until the next therapy including HSCT
- an 8% subsequent stem cell transplant rate after achievement of CR or CRi after single agent Marqibo
- a reasonable safety profile which does not appear to be different than vincristine based on the literature

1.2 Risk Benefit Assessment

1.2.1 Executive Summary

Marqibo is a liposomal formulation of vincristine, which has been developed with the intention to increase the tolerable dose of the active moiety, vincristine, while reducing its dose limiting neurotoxicity. Marqibo's NDA 202497 is a 505(b)(2) submission based on the results of a phase 2 single arm study, HBS407, supported by a phase 1/2 single arm dose finding study, VSLI-06. Study HBS407 was an international, multicenter, open-label, single-arm trial to evaluate the effect of Marqibo in adult patients with Ph-ALL in second or greater relapse, or Ph- ALL who failed two or greater number of treatment lines of anti-leukemia chemotherapy. The primary efficacy endpoint of Study HBS407 was the proportion of the patients who achieved CR+CRi.

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The review of NDA 202497 by this reviewer revealed that the rate of CR+CRi in the study HBS407 was 15.4% (10 out of 65) with 3 CRs and 7 CRis. Due to the lack of subsequent bone marrow evaluations, two of the Applicant's reported responses were not confirmed.

Some patients received subsequent therapies without documentation of their disease status prior to initiating post Marqibo therapies. Hence, durations of response are difficult to characterize. Three different methods for assessment of CR/CRi durations were considered and used by this reviewer:

- 1 FDA has provided guidance for Industry for clinical trial endpoints for the approval of cancer drugs and biologics when assessments of response are missing. This assessment of response duration is based on the first date of CR or CRi to the date of the last available assessment of the same response when a subsequent assessment was missing. The median response duration based on this definition was 28 days.
- 2 Another way to assess the response duration is from the first date of CR or CRi to date of documented relapse, death or subsequent chemotherapies including HSCT. Some may consider this as leukemia free survival until the next therapy. The median response duration based on this definition was 56 days.
- 3 The Applicant's duration of response used time from first CR or CRi until recorded (or inferred) relapse which includes the period after transplant or other subsequent chemotherapies. This assessment of response duration is confounded since it attributes the therapeutic effects of other drugs including stem cell transplantation to Marqibo. The median response duration was 144 days by applicant for 11 reported CRs or CRis.

Twelve patients in study HBS407 received hematopoietic stem cell transplantations (HSCT) after receiving Marqibo. Of these 12 patients, 5 achieved CR or CRi with Marqibo treatment and underwent HSCT. However, "bridge to transplant" in study HBS407 was not positively correlated with CR/CRi status after Marqibo. Seven of 12 patients' disease did not achieve CR or CRi following Marqibo. These patients were anticipated to have poor tolerance for multi-agent chemotherapy at the time of enrollment. Nevertheless, 6 of these 7 patients whose disease did not achieve CR or CRi received multi-agent chemotherapy regimens pre-transplant and underwent subsequent HSCT.

The Applicant reported other endpoints including overall survival. Overall survival analysis in a single arm study is exploratory and difficult to interpret because the result may be heavily influenced by other non-drug factors. Furthermore, this reviewer did not find any association between long-term (more than one year) survivorship and response or lack of response to Marqibo.

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The long-standing clinical experience with standard vincristine has demonstrated a safety profile most notable for peripheral sensory and motor neuropathy as well as autonomic polyneuropathy and myelosuppression. The evaluation and interpretation of neuropathy in a single arm study involving patients who received prior multi-agent chemotherapies including vincristine is complicated. Neuropathy-associated adverse events during Marqibo treatment period were reported in 72 out of 83 (86.7%) patients who received 2.25 mg/m² of Marqibo, and neuropathy AEs of Grade ≥3 in 27 (32.5% of the 83 treated with 2.25 mg/m²). Eleven (13.3% of the 83 treated with 2.25 mg/m²) patients reported serious AEs related to neuropathy. In study HBS407, 15 (23.1%) patients died during the treatment period (i.e. from the first dose infusion date through last dose date plus 30 days). Overall, 96.4% of patients who received 2.25 mg/m² of Marqibo reported AEs of Grade ≥3 and 75.9% of patients reported any serious AE.

1.2.2 Risk-Benefit Analysis

The risk benefit assessment of this NDA is complex and has limitations. The major limitations arise from the single arm nature of the main trial as well as lack of standard treatment for this heavily pre-treated heterogeneous patient population with ALL.

Efficacy analysis is limited to response rate. Because the only recommended treatment with curative intent for this population is HSCT, the definition of response duration becomes convoluted when patients undergo HSCT. Time-to-event endpoints such as overall survival cannot be adequately interpreted in a single arm study. Finally, a comprehensive safety evaluation is not possible in this single arm trial because it does not allow for attribution of adverse events, where the majority of patients had a history of neuropathy and other chemotherapy-related toxicities.

Regarding the risks, due to lack of randomized study comparing Marqibo to vincristine, it is difficult to support any advantage in safety of Marqibo without a direct comparison to vincristine. Applicant's claim of the better tolerability of Marqibo compared to vincristine can be questioned by 21% missed doses, 22% dose reduction and the fact that 30% of patients completed cycle 2, and only 5% completed cycle 3. A total of 96% of patients had an adverse event of Grade 3 or higher, 76% of patients reported serious AEs, 29% of patients had AEs with outcome of death and 28% had AEs leading to discontinuation. Moreover, with regard to neuropathy, 87% of patients reported neuropathy of any grade, 33% reported neuropathy related AEs of grade 3 or higher which impair activities of daily living, 13% had a serious adverse event of neuropathy, and 10% discontinued study treatment due to peripheral neuropathy. Although, these adverse events are important and non-negligible and they don't support advantage over other cytotoxic chemotherapies in general and vincristine in particular, they are considered common and manageable by most oncologists who treat acute leukemias especially in patients whose disease relapsed after first or second lines of therapy.

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With respect to benefit, the CR+CRi rate was approximately 15-20% (range, based on the reviewer analysis and the applicant's claim). In 2003, an International Working Group (IWG) proposed several categories of response to treatment in acute (myelogenous) leukemia. Although, there is no published data on the value of CRi in assessing efficacy of chemotherapy in patients with ALL, the literature suggests that CR is of unique value in the therapy of AML. In patients with AML CR provides a survival advantage over CRp, even after accounting for other covariates. This advantage does not seem to reflect differences in therapy given once initial therapy has failed. However, AML patients who achieve CRp appear to live longer than patients who do not achieve CRp. There is no data available on the value of CRi with the lack of neutrophil recovery in assessing efficacy.

Protocol of study HBS407 clearly indicated the need for confirmatory bone marrow examination 4 weeks after documentation of CR or CRi. The 2003 report by IWG acknowledged physicians desire to re-treat once CR has been observed and eliminated the requirement that the requisite blood counts and marrow findings be maintained for at least 4 weeks before CR is declared. This makes the assessment of durability of response challenging when subsequent therapy, including HSCT, is administered without the confirmation of CR or CRi. This brings up another argument that as long as these patients were able to undergo HSCT, as the only curative treatment modality, the duration of CR or CRi may not indicate the clinical benefit.

As mentioned above, the data from study HBS407 indicate that patients whose disease did not achieve a CR or CRi after Marqibo were candidates for other therapy. Patients underwent HSCT regardless of achieving CR or CRi after Marqibo administration. This reviewer acknowledges the lack of positive correlation between achievement of CR or CRi after Marqibo and bridge to HSCT, nevertheless, this reviewer considers the 8% (5 out of 65) rate of subsequent HSCT after CR or CRi with single agent Marqibo as an important clinical benefit in this heavily pre-treated patients. This was a shift in treatment paradigm from palliative to potentially curative mode with a single agent which was administered in outpatient setting.

These results were presented to ODAC committee. After extensive discussion about risk-benefit ratio of Marqibo (outlined in section 10.1), the panel voted that the clinical benefit of Marqibo in the treatment population outweighs the risk.

Based on above discussion, the analysis of risk benefit by this reviewer favors benefit over the risk in this patient population with ALL. However, the following PMR and PMC are required to confirm the clinical benefit of Marqibo in a randomized clinical trial.

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1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

See DMEPA review.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical recommendation for postmarket requirements and commitments is to conduct an adequate and well-controlled clinical trial or trials to compare the efficacy and safety of Marqibo with vincristine in the induction, intensification, and maintenance phases of combination chemotherapy in the treatment of patients with newly diagnosed acute lymphoblastic leukemia, under FDAAA 901 and 21 CFR 314.55(b).

We are uncertain about the feasibility of the proposed confirmatory trial based on the following concerns:

- The proposed chemotherapy regimen includes administration of asparaginase for three consecutive months to older patients with ALL. This regimen appears to be too toxic for this patient population. This was acknowledged by the applicant's expert consultant during ODAC and some of the ODAC members.
-  (b) (4)
- 

At this time, we are investigating the mechanisms based on which the Agency can effectively and closely monitor due diligence and performance, by setting up a schedule of interim reports on enrollment numbers and careful proactive tracking and documentation of missed or delayed dates. FDAAA gives FDA authority to apply civil monetary penalties to sponsors who do not complete accelerated approval confirmatory trials in a timely manner. These mechanisms need to include any or all of penalties, fines, and even declaring lack of due diligence if enrollment fails to meet the plan. The final decision on any milestone for percentages of enrollment by dates is pending.

For other PMR/PMC related to other disciplines including CMC, microbiology and DMEPA, see the corresponding reviews.

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2 Introduction and Regulatory Background

Drug Established Name: Vincristine Sulfate Liposomal Injection (VSLI)

Proposed Trade Name: Marqibo

Drug Class: Vinca Alkaloid, Mitotic Inhibitor

Applicant:

Talon Therapeutics Inc. (formerly Hana Biosciences)

2207 Bridgepointe Parkway Suite 250

San Mateo, CA 94404

Telephone: 650-228-5066

Facsimile: 650-228-5067

Proposed Indication:

Marqibo is indicated for the treatment of adult (age ≥ 18 years) patients with Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy.

Proposed Dose and Schedule:

Marqibo is administered at a dose of 2.25 mg/m² intravenously every 7 days as an one hour infusion. Each course (or cycle) of treatment is 28 days.

The Marqibo was granted Orphan Drug status (January 8, 2007) and Fast Track designation (August 20, 2007) by the United States Food and Drug Administration (FDA). Because of the granted Orphan status to Marqibo (under CFR316, subpart C), no pediatric waiver request will be required according to CFR316 (d) exemption for orphan drugs.

2.1 Product Information

The active ingredient of the drug substance is vincristine sulfate. Vincristine is a natural product belonging to the class of compounds commonly known as vinca alkaloids. It is isolated from the periwinkle plant (*Vinca rosea* Linn.) and prepared as the sulfate salt.

Marqibo (VSLI), which is packaged in a kit, is a sphingomyelin/cholesterol liposome-encapsulated formulation of vincristine. Marqibo kit is comprised of three vials: 1) active ingredient: vincristine sulfate injection, USP (5 mg/5ml) (VSI), 2) liposomes: sphingomyelin/cholesterol liposome injection (103 mg/ml) (SCLI), 3) buffer: sodium phosphate injection (14.2 mg/ml) (SPI).

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2.2 Epidemiology and Biologic Features of Adult ALL

Of the estimated 43,000 new cases of leukemia in the United States in 2010, there were 5300 new cases of ALL.¹ While ALL represents approximately 75% of leukemia cases in childhood, it is relatively uncommon in adulthood where acute myelogenous leukemia (AML) and chronic lymphocytic leukemia (CLL) are more common. Of 5300 new cases of ALL annually in the U.S., approximately 3300 are childhood ALL and approximately 2000 are adult (age ≥ 18 years) ALL. Seventy percent (1400 subjects) of new annual cases of adult ALL in the U.S. are Ph-.¹

Prevalence of ALL in the U.S. in 2009 was approximately 61000 cases, qualifying the disorder as an orphan disease under the U.S. Rare Drug Act of 2002. The incidence of ALL has strong age dependence, with a peak incidence at 3 to 6 years of age, declining until late adulthood when it gradually rises. Approximately 95% (~57,000) of those with ALL are under the age of 30. The biphasic age incidence suggests biological differences between ALL in children and adults.

ALL in adults is a highly heterogeneous disease comprised of many subgroups. Figure 1 demonstrates the estimated frequency of specific genotypes of ALL in adults.² In many situations, this information is more predictive for children than for adults, which underscores the challenge to extrapolate many of the pediatric-derived prognostic data to adult population. The most frequent (15 to 30%) and clinically important chromosome structure abnormality in adult ALL is translocation t(9;22)(q34;q11) (Philadelphia chromosome [Ph]) with the *BCR-ABL1* fusion. Of note, only 3% of ALL in children are Ph+. Adult patients with Ph+ ALL are usually older, present with higher white blood cell and blast counts and frequently show some myeloid markers on the blasts. The prognosis of Ph+ ALL used to be dismal, however, the availability of the 1st and the 2nd generations of tyrosine kinase inhibitors and their combination with cytotoxic chemotherapies have demonstrated promising results for management of Ph+ ALL.

Figure 1. Estimated Frequency of Specific Genotypes of ALL in Adults
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Source: Literature Search (Reference 2)

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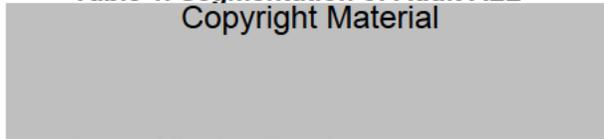
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Segmentation of adult ALL based on cell lineage and presence or absence of Philadelphia chromosome is shown in Table 1. As summarized in the Table, 85% of adult ALLs are arising from B-lineage lymphoblasts and 15% are T-lineage.

Table 1. Segmentation of Adult ALL
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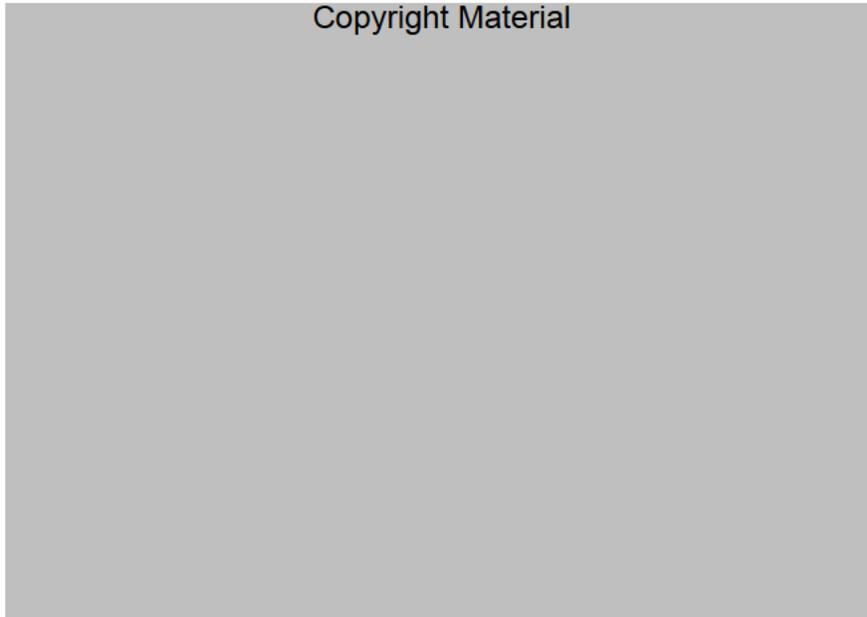
A large grey rectangular area redacting the content of Table 1.

Source: Literature Search

Figure 2 illustrates an estimation of the response, relapse and refractory rates after administration of different lines of therapies in adult patients with Ph- ALL in the US. Treatment response and treatment-related mortality rates were derived from retrospective analyses, which suggested that approximately 450 patients annually in the U.S. are in second or greater relapse and require second or greater salvage therapy.³⁻⁵ The unfavorable prognostic predictors for first remission duration include age ≥ 30 years, WBC $\geq 30 \times 10^9/L$, immunophenotype of mature B-cell or early T-cell, karyotypes of t(4;11), t(1;19), hypodiploid, -7, +8, and persistent MRD following induction.

Figure 2. Adult Patients with Ph- ALL in the U.S.

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Thomas et al. 1999, Tavernier et al. 2007, O'Brien et al. 2008

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2.3 Treatments for Adult ALL

2.3.1 Treatments for the Proposed Indication

There is no approved drug for the proposed indication of the treatment of adult patients with Ph- ALL in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy. There is no randomized study published in the Ph- adult ALL in salvage setting. The NDA under this review included results from single arm trials to support the proposed indication (See Section 5 for sources of clinical data that were used to support this NDA).

2.3.2 FDA Approved Therapies for ALL

2.3.2.1 Conventional Chemotherapies

Vincristine, cyclophosphamide, doxorubicin, daunorubicin, methotrexate, cytarabine, etoposide, 6-MP, and corticosteroids have been used in different combinations to treat acute leukemias in adults or children.

2.3.2.2 Asparaginase Products

- In 1994, the FDA approved Elspar (L-asparaginase) as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL.
- In 2006, the FDA approved Oncaspar (a modified form of L-asparaginase with longer serum half-life) as a component of a multi-agent chemotherapeutic regimen for first line treatment of patients with ALL, and ALL with hypersensitivity to asparaginase.
- In 2011, the FDA approved Erwinaze (asparaginase *Erwinia chrysanthemi*) as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL who have developed hypersensitivity to *E. coli*-derived asparaginase.

2.3.2.3 Accelerated Approvals

- In 2004, the FDA approved Clolar (clofarabine) for the treatment of relapsed or refractory ALL in children. Clofarabine has been used off-label and in clinical trials for the treatment of adults with acute leukemia in the up-front as well as relapsed or refractory settings. The clinical benefit of clofarabine in adult leukemia has not established.

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- In 2005, Arranon (nelarabine) was approved by the FDA for the treatment of adults and children with relapsed or refractory T-cell ALL (T-ALL).

2.3.2.4 Tyrosine Kinase Inhibitors for Ph+ ALL

- In 2006, the FDA approved Gleevec (imatinib) for treating patients with Philadelphia chromosome-positive ALL.
- In 2006, the FDA approved Sprycel (dasatinib) for treating patients with Philadelphia chromosome-positive ALL.

2.3.3 Available Therapies for Patients with ALL

According to literature, combination chemotherapy regimens including vincristine, anthracyclines (daunorubicin, doxorubicin, idarubicin and mitoxantrone), cyclophosphamide, cytarabine, etoposide, methotrexate, 6-mercaptopurine and corticosteroids are effective chemotherapy backbone for ALL treatment. Rituximab has been used off-label for treatment of CD-20⁺ ALL.

Asparaginase products, including L-asparaginase, Pegaspargase and Asparaginase Erwinia chrysanthemi, were given *regular approval* as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL. Hence, these agents are considered available therapies for ALL. The use of asparaginase for the treatment of adult patients with ALL depends on the choice of multi-agent regimen. In Cancer and Leukemia Group B (CALGB) study 9511, pegasparaginase 2000 U/m² was given to untreated adult patients with ALL during each of the first 3 courses.⁶ Asparagine was depleted in 80% of patients and was correlated positively with disease-free and overall survival.

Nelarabine was given *accelerated approval* for the treatment of relapsed or refractory T-cell ALL in 2005. Also, clofarabine received *accelerated approval* in 2004 for the treatment of pediatric patients with relapsed ALL. Because these products are under accelerated approval, they are not considered available therapy for ALL.

2.3.4 Current First-line Therapies

Significant success in the treatment of ALL in pediatric patients has been built on combinations of multiple anti-leukemic drugs that are delivered in a sequence of extended courses. A similar strategy has been proposed for the first line treatment of ALL in adult patients. This strategy includes administration of different chemotherapeutic agents in different phases including induction, early intensification, CNS prophylaxis, late intensification and prolonged maintenance. Figure 3 shows

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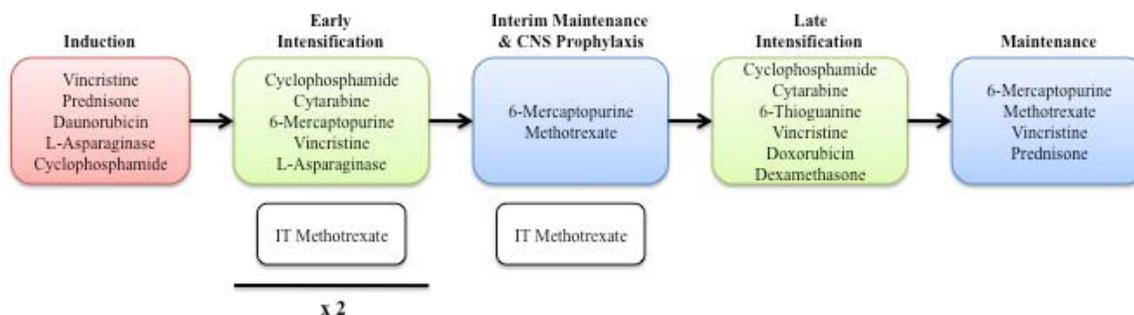
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Protocol CALGB 8811, which has been widely used as front-line therapy for Ph- adult ALL since 1995.⁷ This protocol has been used by the applicant as the backbone regimen for the randomized trial comparing Marqibo to vincristine.

Maintenance chemotherapy regimen is of relatively low intensity but delivered for an extended period of time. It usually consists of daily 6-mercaptopurine, weekly methotrexate, and monthly vincristine and prednisone administered for 2 to 3 years.

Figure 3. Protocol CALGB 8811 (Larson Regimen) as Front-line Therapy for Ph- ALL in Adults



Source: NDA 202497 Based on Reference 7

Another commonly used chemotherapy regimen for adult patients with ALL is hyper-CVAD, which consists of two combinations of drugs (courses A and B) given alternatively. Hyper refers to the hyperfractionated nature of the chemotherapy, which is given in smaller doses but more frequent to minimize side effects. Drugs used in course A include: cyclophosphamide, vincristine, doxorubicin, and dexamethasone. Course B consists of methotrexate and cytarabine. Table 2 summarizes commonly used regimens for the treatment of adult patients with Ph- ALL.⁸

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Table 2. Regimens for Treatment of Adult ALL

Regimen	Induction	Consolidation	Maintenance	CR Rate, %	5-Year DFS Rate, %
LALA-94 ⁹	P, V, C, D, or Ida	Ara-C, MTZ, or C, Ara-C, 6-MP based on risk	HSCT or MTX/6-MP or additional chemo based on risk	84	30
Hyper-CVAD ¹⁰	Hyper C, V, A, and D alternating with MTX and Ara-C × 8 cycles	See induction	Allo HSCT or 6-MP, V, MTX, P	92	38
UCSF 8707 ¹¹	P, V, D, and L-Asp	V, P, D, A, Ara-C, VM-26, MTX	6-MP, MTX	93	52
GMALL 05/93 ¹²	Induction 1: P, V, D, MTX, L-Asp; Induction 2: C, Ara-C, 6-MP	HD Ara-C, MTZ, HD MTX, L-Asp, 6-MP	6-MP, MTX	83	35-40
CALGB 8811 ⁷	P, V, C, D, L-Asp	C, subq Ara-C, 6-MP, V, L-Asp	6-MP, MTX	85	39 (Ages 30-59 y); 69% (aged <30 y) ^a

CR = complete remission; DFS = disease-free survival; LALA = adult acute lymphoblastic leukemia; P = prednisone; V = vincristine; C = cyclophosphamide; D = daunorubicin; Ida = idarubicin; Ara-C = cytarabine; MTZ = mitoxantrone; 6-MP = 6-mercaptopurine; HSCT = hematopoietic stem cell transplantation; Hyper-CVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MD = moderate dose; Allo = allogeneic; UCSF = University of California-San Francisco; L-Asp = asparaginase; VM-26 = teniposide; GMALL = German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; HD = high-dose; CALGB = Cancer and Leukemia Group B; subq = subcutaneous.

(a) Overall survival at 3 years.

Source: NDA 202497

Table 3 summarizes the induction regimens in clinical trials involving adults with ALL since 1993. It shows the chemotherapy component of each regimen as well as vincristine dose utilized in each regimen. Vincristine dose ranged from 1.3 - 2 mg/m². In several, but not all, regimens, vincristine dose capped at 2 mg per each day of injection.

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Table 3. Chemotherapy Regimens and Vincristine Dosages Used in Clinical Trials in Adults with ALL Since 1993

Group/Study	Induction Regimen	Vincristine Dosing
GMALL 01	V-P-A-D-C-AC-M-MP	2.0 mg d1, 8, 15, 22
GMALL 02	V-P-A-D-C-AC-M-MP	2.0 mg d1, 8, 15, 22
UK-ALL IX	V-P-A-MP-M-D	1.5 mg/ m ² (max 2) d1, 8, 15, (22, 36)
SAKK	V-P-D-M-A-AC-VP	2.0 mg d1, 8, 15, 22
BGMT	V-P-A-D-C-AC-MP	1.5 mg/ m ² d1, 8, 15, 22
CALGB 8811	V-P-A-D-C	2.0 mg d1, 8, 15, 22
GIMENA 0183	V-P-A-D	1.5 mg/ m ² (max 2) d1, 8, 15
HOVON	V-P-A-D	1.5 mg/m ² (max 2.5) d1, 8, 15, 22, 29
UKALL XA	V-P-D-A	1.5 mg/m ² d1, 8, 15, 22
CALGB 9111	V-P-D-A-C	2.0 mg d1, 8, 15, 22
LALA-87	V-P-D-C-AC	1.5 mg/m ² d1, 8, 15, 22
GMALL 05/93	V-P-D-A-C-AC-MP	1.5 mg/m ² (max 2) d1, 8, 15, 22
GIMENA 0496	V-P-D-A	1.4 mg/m ² (max 2) d1, 8, 15, 22, 36
Sweden	V-C-D-AC-BM	2.0 mg d1
JALSG-ALL93	V-AD-P-A-C	1.3 mg/m ² (max 2) d1, 8, 15, 22
UCSF, USA	V-P-D-A	1.4 mg/m ² (max 2) d1, 8, 15, 22
GIMENA ALL 0288	V-P-A-D-C	2.0 mg/m ² d1, 8, 15, 22
MRC/ECOG	V-P-D-A-C-AC-MP	1.4 mg/m ² d1, 8, 15, 22
MD Anderson	V-AD-DX-C	2.0 mg d4, 11
GOELAMS-GOELAL02	V-P-I-A	1.5 mg/m ² d1, 8, 15, 22
LALA-94	V-P-C-D-IDA	2.0 mg d1, 8, 15, 22
EORTC ALL-3	V-P-D-C	1.5 mg/m ² d1, 8, 15, 22
PETHEMA ALL-93	V-P-D-A-C	2.0 mg d1, 8, 15, 22

A = asparaginase

C = cyclophosphamide

IDA = idarubicin

P = prednisone

AC = cytarabine arabinoside

D = daunorubicin

M = methotrexate

V = vincristine

AD = doxorubicin

DX = dexamethasone

Mi = mitoxantrone

VP = etoposide

BM = betamethasone

I = ifosfamide

MP = 6-mercaptopurine

Source: NDA 202497

2.3.5 Postremission Therapy Including HSCT

Postremission therapy for ALL includes intensified consolidation and maintenance therapy or HSCT. The optimal regimen and duration of postremission therapy, the role of dose intensification and the optimal time of HSCT are not well established. The

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potential benefit of more intense and more prolonged postremission chemotherapy comes with trade-offs including higher rates of toxicities and worse complications.

Allogeneic HSCT has been investigated in Ph- adult ALL in the following settings:

1. Relapsed ALL following achievement of second or higher CR, or primary refractory ALL in CR following salvage therapy: Allogeneic HSCT is the only curative option for adult patients with relapsed or refractory ALL based on current available therapy.
 - A retrospective analysis of allogeneic HSCT performed between 1990 and 2002 at 9 transplant centers on 264 adult patients in different disease states at the time of transplant showed an overall 5-year disease-free survival of 28%, including 23% of 54 patients transplanted in the second CR.¹³
2. First CR for high-risk category Ph- ALL, such as t(4;11) and t(1;19): It has been proposed that in this setting allogeneic HSCT provides superior outcomes compared to chemotherapy alone.
 - In the French LALA-87 study, in which patients with high risk genetic features were randomized to receive HLA-matched sibling HSCT versus chemotherapy, 10 year disease-free survival rates were 44% for HSCT compared to 11% for chemotherapy alone.¹⁴
3. After achievement of the first CR and after intensification in standard-risk ALL patients: The benefit of allogeneic HSCT in this setting is not universally accepted among leukemia centers.
 - The large MRC UKALL XII / ECOG E2993 trial included 1929 patients ages 15-59 years. After induction chemotherapy and high-dose methotrexate intensification, all patients who had HLA-matched sibling donor and were ≤ 55 years were assigned to allogeneic HSCT, whereas all others were randomized to chemotherapy versus autologous HSCT. High-risk patients were defined by age >35 years, leukocytosis ($\geq 30 \times 10^9/L$ for B-lineage ALL and $100 \times 10^9/L$ for T-lineage ALL), and Ph+ ALL. The 5-year survival rate was 53% for Ph- patients who had a donor compared with 45% for those who had no donor ($P = 0.02$). The 5-year survival rate for standard-risk patients was superior for patients who had a donor compared with those who had no donor (62% vs 52%; $P = 0.02$). The 5-year survival rate for high-risk patients was not significantly different whether patients had a donor or not (41% vs 35%; $P = 0.2$). Postremission chemotherapy produced superior event-free and overall survival compared with autologous HSCT ($P = 0.02$ and $P = 0.03$, respectively). The results of this study was not consistent with the results of previous studies, in which, allogeneic HSCT was favorable only for high-risk patients.¹⁵

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Allogeneic HSCT with reduced-intensity non-myeloablative conditioning regimens have been tested in small series of adult patients with ALL. Low transplant-related mortality rates and approximately 30% overall survival at 3 years were reported in some studies.^{16, 17}

2.3.6 Salvage Therapies

In a large case series from MD Anderson Cancer Center (MDACC), 76% of patients relapsed after front-line induction remission while receiving active consolidation or maintenance phase therapy.³ Remission rates ranging from 21 to 83% have been reported in adults with refractory ALL or after the first relapse of ALL.^{3, 18} These rates primarily come from small reports. Remissions as a result of first salvage therapy, when achieved, are usually short-lived with median durations ranging from 2 to 7 months and shorter than any prior remission duration.^{3, 18} Adults with relapsed Ph- ALL have an expected 5-year survival of approximately 7%.^{4, 19}

First salvage therapy for Ph- ALL in adults may consist of a patient's original front-line induction regimen with or without additional drugs including high- or intermediate-dose cytarabine-based regimens, methotrexate combined with asparaginase, dose-intensified anthracycline-based regimens, or a single agent treatment. There have been many proposed first salvage therapy regimens, but none has emerged as definitive and standard therapy. In a study by Thomas and colleagues from the MDACC, following first relapse, approximately 30% of the patients who had achieved an initial remission were able to achieve a second CR as a result of first salvage therapy with approximately 20% deaths during attempted first salvage induction.³

The median duration of remission and overall survival in responders to first salvage therapy is approximately 6 months. The majority (~70%) of patients who achieve a CR due to first salvage subsequently relapse and become candidates for second salvage therapy. There are approximately 450 patients in need of second salvage therapy annually in the United States.

In 2008, O'Brien and colleagues reported a retrospective assessment of the outcomes of 288 adults with ALL after second salvage therapy delivered at MDACC. In this study, the median age was 33 years (range, 14-76 years), and 42 patients (15%) were aged ≥60 years. A CR after frontline induction therapy was observed in 224 patients (78%), a CR after first salvage therapy was observed in 99 patients (34%), and 37 patients (13%) never achieved a prior CR.

Second salvage therapy was highly heterogeneous and probably guided by different factors such as a patient's past anti-leukemic drug exposure and response, perceived ability to tolerate intensive multi-agent second salvage therapy, and the availability of an

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investigational protocol at the time. The major second salvage therapies that these patients received are listed in Table 4.⁵

Table 4. Major Second Salvage Therapy Regimens in O'Brien Review

Second Salvage Therapy	No. of Patients (%)	No. of CRs (%)
VAD or hyper-CVAD	61 (21)	17 (28)
Cytarabine combinations	54 (19)	17 (32)
Allogeneic HSCT	22 (8)	9 (41)
Methotrexate-asparaginase combinations	52 (18)	3 (6)
Other combinations	29 (10)	4 (14)
Single agents	70 (24)	3 (4)

VAD = vincristine, doxorubicin, and dexamethasone, hyper-CVAD = hyper-fractionated cyclophosphamide and VAD alternating with methotrexate and cytarabine.

Overall, 53 patients (18%) achieved a CR. The median remission duration was reported as 7 months and the median survival as 3 months. The remission rates based on different categories of relapse and refractory histories ranged from 13% to 33%. The remission rates with different second salvage chemotherapy regimens ranged from 4% to 41% (Table 4).

Twenty-two (8%) patients underwent allogeneic HSCT as second salvage for active disease with preparative regimens, including total body irradiation (TBI) in 11 patients and non-TBI regimens in 11 patients. The donor was a related matched sibling for 20 patients and a matched unrelated donor in 2 patients. Overall, 9 patients (41%) achieved a CR and the 1-year survival rate was 18%, which was not different from the outcome of other patients ($P = .096$). Of the 53 patients who achieved a CR, 7 underwent allogeneic stem cell transplantation in third CR, and all 7 patients developed recurrent disease after a median of 4.5 months (range, 2–19.5 months).

It was reported that remission re-induction rates were approximately 4% following single-agent treatment with no further reported detail of these agents except for five patients who received single-agent clofarabine with no reported CR.

Early death (<2 weeks) and induction-related mortality were reported in 27 (9%) and 39 (14%) of the patients. Resistant disease were observed in 169 (59%) of patients.

This study has several problems. The issues that are germane to this NDA review include 1) different categories of CRs, including CR_p and CR_i, were not reported in this retrospective single institution study, 2) the method for calculation of duration of remission was not clear, 3) the names of single agents were not provided for all patients. It was not reported whether or not patients received single-agent vincristine.

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2.4 Applicant's Rationals for the Drug Development Program

The applicant provided the following rationals to demonstrate the importance of development of liposomal formulation of vincristine:

- Adult patients with advanced, relapsed and/or refractory Ph- ALL poorly tolerate multi-agent salvage re-induction regimens, hence, development of an active drug that can be used as a single agent is beneficial to this heavily pretreated ALL patients,
- According to *in vitro* and non-clinical studies reported by the applicant, altering vincristine formulation to sphingomyelin-based liposomal formulation may widen its therapeutics window and may enhance its anti-cancer activity without significant exacerbation of the toxicity by enhancing vincristine penetration and concentration in tumors
- An exploratory clinical evaluation of biweekly, single-agent VSLI at a dose of 2.0 mg/m² in heavily pre-treated, relapsed and refractory lymphoid malignancies including refractory adult ALL (Study DM97-162) demonstrated, according to the applicant, an unexpected anti-leukemia activity
- VSLI is administered at 2.25 mg/m² based on actual weight and height without dose capping, which may provide an opportunity for a patient to receive higher doses of vincristine as an active anti-leukemia therapy.

2.5 Availability of Proposed Active Ingredient in the United States

Marqibo kit is not marketed in the United States or elsewhere.

2.6 Important Safety Issues With Consideration to Related Drugs

ALL is a serious, life threatening disease. If untreated, patients usually succumb to the leukemia rapidly. For this reason, several of the safety issues such as myelosuppression, mucositis, moderate to severe infectious complications are considered expected and manageable by hematologists and oncologists who treat acute leukemia. Nevertheless, because ALL is potentially a curable disease, long term sequelae of chemotherapies should be taken into account in patients with prolonged survivorship.

Vinca alkaloids including vincristine cause mitosis arrests in metaphase by binding to tubulin dimers and inhibiting assembly of microtubule structures. Therefore, the vinca alkaloids affect rapidly dividing cancer cells as well as intestinal epithelium and bone marrow. In addition to myelosuppression and mucositis, the other main side effect of vincristine is neuropathy. Neurotoxicity of vincristine includes peripheral sensory and motor neuropathy as well as central and autonomic neuropathy. Peripheral neuropathy

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secondary to vinca alkaloids can be severe, and may commonly results in dose reduction, or termination of the use of vincristine or other vinca alkaloids. Symptoms of neuropathy include but not limited to hypoesthesia, hyperesthesia, paresthesia, hyporeflexia, areflexia, neuralgia, jaw pain, decreased vibratory sense, cranial neuropathy, ileus, burning sensation, arthralgia, myalgia, muscle spasm or weakness, orthostatic hypotension, foot drop, fine motor neuron disturbances such as difficulty in writing or in buttoning shirts, and numbness. Constipation, hyponatremia, and hair loss are common.

2.7 Summary of Regulatory Activity Related to NDA 202497

Talon Pharmaceuticals (formerly Hana Biosciences) obtained the rights to develop Marqibo from Inex on May 6, 2006 (see below for the prior history of the drug development program). Talon had the following meetings with the Agency since then:

- October 31, 2006 (Type B Clinical meeting): The proposed Phase 2 study design for Marqibo for treatment of ALL was discussed.
- January 8, 2007: Orphan drug designation status for the treatment of ALL was granted to Marqibo.
- June 27, 2007 (Type A SPA meeting): Agreement that Marqibo qualifies for Fast Track Designation. *The Agency did not agree with the proposed SPA based on the Phase 2 study.*
- August 20, 2007: Fast track designation was granted for vincristine liposomes injection for the treatment of adult patients with Ph- ALL in second relapse or whose disease progressed after two lines of prior therapy.
- March 26, 2009 (Type C Clinical meeting): FDA and Applicant discussed DSHNHL 2009-1 lymphoma study. Agency agreed upon QT/QTc assessment plan, and that a clinical assessment of mass balance was not required.
- April 20, 2010 (Type B Clinical Pre-NDA meeting): FDA and Applicant discussed general drug development plan.
- November 8, 2010 (Type B Pre-NDA meeting): Content and format of proposed NDA were discussed.
- Applicant provided responses to Agency's Quality and Clinical Pharmacology / Biopharmaceutics questions mentioned in the non-approval letter (IND 59056 amendments, SN#255, December 17, 2009 (Quality), SN#260, February 2, 2010 (Quality) and SN#261, February 11, 2010 (Pharmacology / Biopharmaceutics)).
- May 13, 2011: Talon requested an SPA for the proposed confirmatory study TTX404 entitled, "A Phase 3, Multicenter, Randomized Study to Evaluate the Substitution of Marqibo (Vincristine Sulfate Liposomes Injection, VSLI) for

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Standard Vincristine Sulfate Injection (VSI) in the Induction, Intensification, and Maintenance Phases of Combination Chemotherapy in the Treatment of Patients \geq 60 Years Old with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL)".

- July 12, 2011 (NDA Submission): Talon submitted the current NDA 202497 seeking accelerated approval for Marqibo for the aforementioned indication.
- August 26, 2011: SPA Agreement Letter was issued by the Agency (IND 59056) for study TTX404 (See Section 9).
- October 6, 2011 (Teleconference, Review Timeline): Agency and the applicant discussed the results of the preliminary review of the NDA. Agency reminded Applicant the guidance from Map 6020.3. Together, these supported the Agency's decision for Standard Review Timeline. This decision was communicated with Talon.
- March 21, 2012 (ODAC meeting): ODAC members discussed the risk / benefit profile of Marqibo based on the results of the phase 2 study HBS407.
- April 2, 2012: The Agency communicated its concerns with the Applicant regarding CMC, microbiology, medication errors and feasibility of the proposed confirmatory trial. Based on Applicant's response, a Major Amendment will apply to this NDA to extend the review time for 3 months. Applicant agreed to submit a thorough and comprehensive results with respect to serious concerns that were raised by CMC, Microbiology and DMEPA. Applicant also performed a presentation to demonstrate the feasibility of the proposed confirmatory study (TTX404).

2.8 Other Relevant Background Information

- The original IND 59056 for Marqibo was submitted in September 30, 1999 by Inex Pharmaceuticals (now Tekmira Pharmaceuticals).
- In September 29, 2003, NDA 21600 was submitted by Inex Pharmaceuticals for accelerated approval of Marqibo for the proposed indication of "the treatment of patients with aggressive non-Hodgkin's Lymphoma (NHL) that is refractory to, or relapsed after two prior combination chemotherapy regimens".
- Tekmira sought the indication based primarily on results from an international, multicenter, open-label, single arm study (CA99002) of Marqibo in patients with relapsed, aggressive NHL. The NDA submission included 2 single arm studies. The primary study endpoint was best response rate. The secondary endpoints included duration of response, time to progression, and survival.
 - The study enrolled 119 patients with relapsed NHL. Based on central pathology review and FDA analysis of incomplete baseline staging for NHL, only 72 patients were eligible for evaluation.

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- *In FDA's analysis the response rate was 21% (95% CI 12-32), with a CR rate of 1%. The duration of response could not be adequately determined because two thirds of the patients dropped out prior to tumor progression. In the Agency's analysis, median duration of response in the 11 confirmed responders who were histologically eligible and had no major protocol violations was 85 days.*
- The supportive study (DM-97-J 62) was a single center, open-label, single arm study of Marqibo in patients with relapsed and refractory acute lymphoblastic leukemia and NHL. There were multiple problems with this study, including lack of an independent review of pathology and radiology results, incomplete documentation of two-dimensional measurements, and no information provided on duration of response.
- ODAC discussed the results of this trial on December 1, 2004. The committee unanimously voted that these results were not predictive of clinical benefit and should not be the basis of approval under Subpart H.
 - For a drug to be approved under subpart H, the drug must demonstrate an improvement over available therapy. Per the ODAC discussion and committee voting, Marqibo did not demonstrate an improvement over available therapy. ODAC recommended randomized clinical trials to demonstrate clinical benefit of Marqibo in NHL.
- A non-approval letter was sent to the applicant on January 14, 2005 (INEX January 14, 2005 NDA 21-600 Action Letter).
- Since the 1999 IND, no randomized clinical trial has been done with Marqibo in any disease setting.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

NDA 202497 was an electronic submission filed in the FDA electronic Document Room at <\\Cdseub1\evsprod\NDA202497>. The entire NDA and relevant literature and regulatory history were reviewed.

3.2 Compliance with Good Clinical Practices

The applicant stated that the studies were conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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3.3 Financial Disclosures

The applicant provided document related to the clinical investigators participating in studies HSB-407 and VSLI-06. The disclosure information was tabulated by center, principal investigator, study facility and address. Talon provided a letter certifying that no Marqibo investigators were employees of Talon. No investigators in the two studies noted above claimed any interests, investments, or payments that required certification and disclosure in FDA Form 3455. FDA Form 3454 is included for the two studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 505(b)(2) Application

The current NDA 202497 is a 505 (b)(2) application relying on publically available information regarding vincristine sulfate.

A 505(b)(2) application is an application for which one or more investigations relied upon for approval were not conducted by the applicant, and the applicant has not obtained a right of reference from the person who conducted the investigations. This regulatory pathway allows FDA to rely on data that was not developed by the applicant for NDA approval.

For a 505(b)(2), an applicant can rely on published literature, if necessary for approval, and/or the Agency's previous finding of safety and/or effectiveness for a drug. Relying on the Agency's previous finding of safety and/or effectiveness is intended to encourage innovation without requiring duplicative studies to demonstrate what is already known about a drug while protecting patent and exclusivity rights for the approved drug.

For changes to a previously approved drug, an applicant may rely on the Agency's finding of safety and effectiveness of the previously approved product, coupled with information needed to support the change from the approved product. Additional information could be new studies conducted by the applicant or published data, if appropriate.

A previous example of 505(b)(2) approval was Abraxane, an albumin-bound nano-particle formulation of paclitaxel. The approval was based on response rate in a randomized controlled trial of 460 metastatic breast cancer patients comparing Abraxane to paclitaxel.

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4.2 Chemistry Manufacturing and Controls

Figure 5 illustrates the presumed structure of Marqibo based on liposomal (sphingomyelin / cholesterol) encapsulation of vincristine (Source: NDA 202497, summary of clinical safety, page 21). Marqibo kit contains 3 vials including vincristine sulfate injection, sphingomyelin/cholesterol liposome injection, and sodium phosphate injection. Pharmacist compounds Marqibo by mixing vials of vincristine and sphingomyelin/cholesterol liposome into the sodium phosphate buffer. The vial is inverted 5 times, the floatation ring is attached, then kept in 65°C water bath for 10 minutes. The appropriate dose is withdrawn and added into an infusion bag. For further detail see CMC Review.



4.3 Clinical Microbiology

See Microbiology and DMEPA Review.

4.4 Preclinical Pharmacology/Toxicology

See Non-Clinical Toxicology Review.

4.5 Clinical Pharmacology

See Clinical Pharmacology Review.

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4.5.1 Mechanism of Action

Marqibo is a liposomal formulation of vincristine, hence belongs to vinca alkaloids family of chemotherapeutics. Vinca alkaloids bind to tubulin and inhibit the assembly of tubulin into microtubules during M phase of the cell cycle and cause cell cycle arrest and apoptosis. The vinca alkaloids include vincristine, vinblastine, vinorelbine, vindesine.

4.5.2 Pharmacodynamics

See Clinical Pharmacology Review.

4.5.3 Pharmacokinetics

See Clinical Pharmacology Review.

5 Sources of Clinical Data

The clinical data germane to this NDA is from two single arm studies (HBS407 and VSLI-06), which enrolled a total of 101 adult patients with Ph- ALL in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy.

Efficacy Population: Study HBS407 included 65 patients who received at least one dose of Marqibo. These 65 patients formed the “treated population” based on whom the efficacy analyses were performed by this reviewer for the NDA. Because patients in study VSLI-06 received concomitant dexamethasone, the isolated effect of VSLI could not be ascertained. Hence, the patients in study VSLI-06 were not included in the efficacy population.

Evaluable Population The primary efficacy data used by Talon to support the proposed indication included study HBS407 Intent-to-Treat (ITT) Population (N = 65) and Independent Response Review Committee (IRRC) Evaluable Population (N = 53). Because study HBS407 was a single arm study, the use of intent-to-treat and IRRC population terminology is inappropriate. We used treated population as mentioned above.

Safety Population: A total of 83 patients treated with weekly VSLI at the dose of 2.25 mg/m² in studies HBS407 and the supportive phase 1 study VSLI-06 provided the primary safety data.

Table 5 summarized the design of HBS407 and VSLI-06 trials.

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5.1 Tables of Studies/Clinical Trials

Table 5. Summary of Marqibo Clinical Trials Related to ALL (Studies HBS407 and VSLI-06)

Study (Status)/ Study Report Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients Treated (Male/Female)	Diagnosis of Patients
HBS407 (Complete) / m5.3.5.2	Primary: CR+CRi rate Key Secondary: 1) the duration of CR+CRi, 2) overall survival, 3) number and proportion of patients who received post-VSLI HSCT	Phase 2, international, multicenter, open-label, single-arm study.	VSLI IV at a dose of 2.25 mg/m ² infusion over 1 hour every 7 days on Days 1, 8, 15, 22 (±3 days) of a 28-day course. Four weekly doses constituted one course.	65 patients (33/32)	Adult patients with Ph- ALL who were in 2 nd relapse or whose disease progressed after 2 lines of anti-leukemia chemotherapy, and who achieved a CR to at least one prior anti-leukemia therapy as defined by a leukemia-free interval of ≥90 days.
VSLI-06 (Complete) / m5.3.5.2	Primary: To determine MTD of VSLI given with pulse dexamethasone Key Secondary: To determine the efficacy of VSLI given with dexamethasone, To evaluate safety and tolerability	Phase 1-2, multicenter, open-label, dose escalation study.	VSLI IV (7 dose cohorts: 1.5, 1.825, 2.00, 2.25, 2.4, 2.6 and 2.8 mg/m ²) every 7 days and dexamethasone 40 mg daily orally or IV on Days 1 to 4 and Days 11 to 14 of a 28-day course. T Four weekly doses constituted one course.	36 patients (24/12)	Patients with previously treated, relapsed or refractory ALL (including lymphoblastic lymphoma or Burkitt's-like subtypes) with measurable disease.

Other studies not-related to ALL include 1) HBS408 (phase 2 single-arm metastatic malignant uveal melanoma), 2) VSLI-12 (phase 1-2 single-arm metastatic melanoma), 3) VSLI-11 (phase 1 metastatic non-choroidal melanoma), 4) VSLI-13 (phase 1 metastatic cutaneous or non-choroidal melanoma), 5) IDP93-C01 (phase 1 refractory cancer), 6) CA00001 (phase 2 small cell lung cancer relapsed after etoposide and platinum), 7) CA95002 (phase 2 metastatic colorectal carcinoma), 8) CA95001 (phase 2 pancreatic cancer), 9) CA99002 (phase 2 relapsed NHL), 10) DM97-162 (phase 2 relapsed / refractory NHL), 11) VSLI-05 (phase 2 relapsed / refractory Hodgkin's disease), 12) P99-401 (phase 2 pediatric patients with relapsed malignancies), 13) CA00004 (phase 2 previously untreated aggressive NHL), 14) CA00005 (US) - 01/010 (UK) (phase 1-2 relapsed aggressive NHL), 15) VSLI-01-NHL (US) – EV1 (UK) (phase 2 relapsed / refractory aggressive NHL), and 16) VSLI-02 (compassionate use for pediatric patients with relapsed malignancies).

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5.2 Review Strategy

Clinical review of efficacy for this NDA was primarily based on the efficacy data of study HBS407, which were relevant to the proposed indication. Clinical review of safety for this NDA was based on the safety data of study HBS407 and the data for 18 patients who were treated with VSLI at the proposed dose of 2.25 mg/m² in the supportive study VSLI-06. The electronic submission, with the CSRs, and other relevant portions of studies HBS407 and VSLI-06 were reviewed and analyzed.

The key review materials and activities are outlined below:

- Electronic submission of the NDA including:
 - Clinical overview, Summary of Clinical Efficacy, Summary of Clinical Safety in Module 2
 - Integrated Summary of Efficacy (ISE, 5.3.5.3.27) and Integrated Summary of Safety (ISS, 5.3.5.3.28) in Module 5
 - Data sets for study **VSLI-06** (with data definition document) located in Module 5 <\\Cdsub1\evsprod\NDA202497\0000\m5\datasets\vsli-06\analysis\datasets>
 - Data sets for study **HBS407** (with data definition document) located in Module 5 <\\Cdsub1\evsprod\NDA202497\0000\m5\datasets\hbs-407\analysis\datasets>
 - A comprehensive review of all CRFs for patients claimed to achieve CR, CRp or CRi.
- Relevant published literature
- Relevant prior regulatory history
- Sponsor presentations to the FDA
- Major efficacy and safety analyses reproduced or audited using the SAS and JMP9 datasets.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 VSLI-06 Study

Study VSLI-06, as the supportive study for this proposed indication, was a Phase 1/2, multicenter, open-label, dose escalation study of VSLI combined with dexamethasone. Patients were required to have relapsed or refractory ALL, lymphoblastic lymphoma or Burkitt's leukemia/lymphoma and to have measurable disease. Study VSLI-06 was designed to be conducted in 2 phases. The Phase 1 portion of the study was to define the maximum tolerated dose (MTD) of VSLI. Seven sequential escalating dose cohorts (1.5, 1.825, 2.0, 2.25, 2.4, 2.6, and 2.8 mg/m²) were planned, with 3 to 7 patients in each cohort. Escalation to the next higher dose cohort was allowed to proceed only if there were an absence of non-hematologic dose-limiting toxicities (DLT) observed. The Phase 2 portion of the study had a Simon 2-stage design and was designed to

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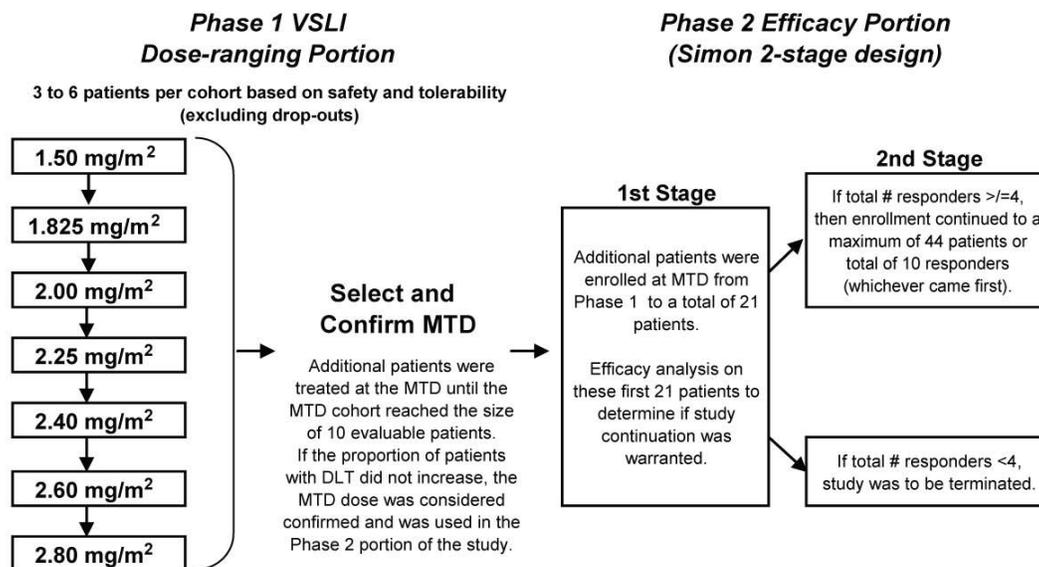
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determine the efficacy of the VSLI at MTD dose in a larger cohort of patients. Patients from the first phase could be included in the second phase analysis. The study design is represented in Figure 5.

Figure 5. Study VSLI-06 Design



Source: NDA 202497

In order to be included in the MTD evaluation, patients had to receive at least 1 course of VSLI, consisting of 4 weekly infusions at the assigned dose with a 2-week minimum observation after the last VSLI dose. Patients who received fewer than four infusions were replaced for the MTD evaluation.

Each patient received VSLI intravenously over one hour on Days 1, 8, 15, and 22 (± 2 days) and dexamethasone 40 mg daily either orally or IV on Days 1 to 4 (± 2 days) and Days 11 to 14 (± 2 days) of each 28-day course. Patients with stable disease or a response were allowed to receive up to three courses (12 doses total) of study therapy. Protocol-stipulated dose delays were permitted for up to 30 days to enable resolution of toxicity. In addition, patients could have up to 3 protocol-specified dose reductions for toxicity. Patients were followed for safety for 30 days following the last dose of study drug. Patients with a CR at the end-of-treatment visit were followed periodically until relapse or death.

Study VSLI-06 included a heterogeneous population of relapsed and/or refractory patients with ALL. Study VSLI-06 also included one patient with Ph⁺ ALL, two patients with Burkitt's lymphoma/leukemia, and patients in need of first salvage (38.9%).

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A total of 36 patients were enrolled in the study and received at least 1 dose of VSLI plus dexamethasone. Of the 36 patients enrolled, 26 patients (72.2%) were included in the MTD evaluable population.

Because of DLTs at the 2.4 mg/m² dose level, the 2.25 mg/m² dose administered weekly was declared the MTD. DLTs included motor neuropathy of Grade 3, grand mal seizure of Grade 4, and elevated AST and hyperbilirubinemia of Grade 4 in three patients. Table 6 demonstrates the number of patients in each dosing group in Study VSLI-06.

Table 6. Number of Patients in Each VSLI Dose Group in Study VSLI-06

VSLI Dose Group	N (%)
1.5 mg/m ²	5 (13.9%)
1.825 mg/m ²	3 (8.3%)
2.0 mg/m ²	3 (8.3%)
2.25 mg/m ²	18 (50.0%)
2.4 mg/m ²	7 (19.4%)

Source: NDA 202497

Applicant reported an overall response rate (CR+PR) of 22.2% (4 out of 18 patients in the 2.25 mg/m² dose cohort, 95% CI: 6.4 - 47.6) and a CR rate of 16.7% (3 out of 18 patients, 95% CI: 3.6 - 41.4) in this Study. On the basis of these results from the phase 1 portion of the study, applicant decided to open a different Phase 2 clinical trial (Study HBS407) instead of continuing with the Phase 2 portion of Study VSLI-06.

As mentioned above, because of the use of concomitant intermediate to high-dose dexamethasone and its contribution to the observed therapeutic activity, the anti-leukemic effect of VSLI cannot be isolated from results of study VSLI-06. Hence, these results were used for efficacy analysis of Marqibo for NDA 202497.

It is worth mentioning that no long-term follow-up was conducted for Study VSLI-06.

5.3.2 HBS407 Study

Design:

Study HBS407 was a Phase 2, international, multicenter, open-label, single-arm trial to evaluate the effect of Marqibo in adult patients with Ph- ALL or lymphoblastic lymphoma in second or greater relapse, or patients with Ph- ALL or lymphoblastic lymphoma

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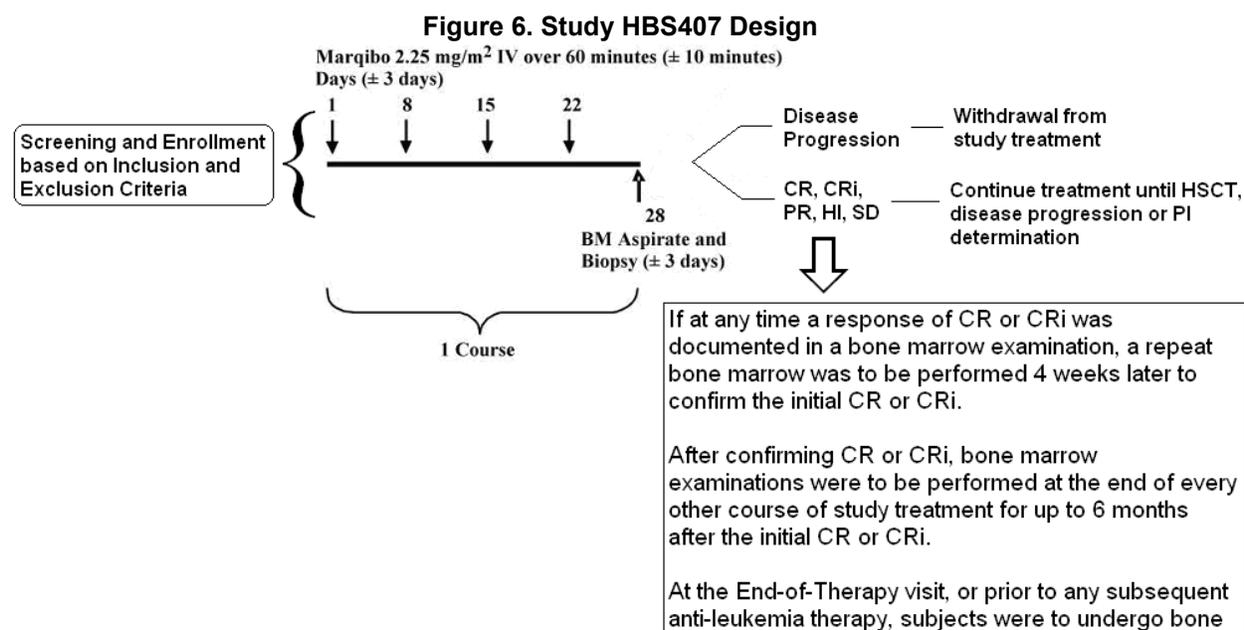
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whose disease progressed after 2 or greater treatment lines of anti-leukemia chemotherapy.

The key inclusion and exclusion criteria:

Patients had to be 18 years of age or older with ECOG performance status of zero to three and with Ph- ALL who were in second or greater relapse or whose disease progressed after two treatment lines of anti-leukemia therapy. Patients had to have achieved a CR to at least 1 prior, but not necessarily the immediately prior, anti-leukemia chemotherapy, defined by a leukemia-free interval of ≥ 90 days. Patients had to be ineligible for immediate HSCT at the time of screening and enrollment. According to the applicant, patients were enrolled into this single-agent Phase 2 study because of anticipated intolerance of multi-agent therapy (e.g., poor marrow reserves or poor performance status), a lack of standard of care in the salvage setting, refractoriness to prior multi-agent therapy, relapse following multi-agent therapy and a relatively short remission duration, or relapse following HSCT and a relatively short remission duration. The HBS407 study design is represented in Figure 6.



Source: Reviewer Drawing Based on NDA 202497

Treatment:

Corticosteroids were prohibited in study HBS407 in order to assess the efficacy of VSLI alone. Systemic corticosteroids, if employed, must have been tapered off, preferably before the start of study treatment, but no later than by Day 5 of Course 1. From Day 6

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of Course 1 through the end of study participation, systemic corticosteroids as ALL treatment were not allowed.

Eligible patients received IV Marqibo at 2.25 mg/m² (MTD in the phase 1/2 supporting Study VSLI-06), based on actual BSA over one hour. Dosing was administered every 7 days (± 3 days) on Days 1, 8, 15, and 22 with no less than 4 days between dosing. Four weekly doses of VSLI constituted 1 course (cycle) of study treatment. Before each scheduled dose of VSLI, the patient was to be evaluated for possible toxicities, particularly neurotoxicity, that may have occurred after the previous doses.

Response Assessment Schedule:

Bone marrow aspirate and biopsy were to be performed on Day 28 of designated study treatment cycles. For those patients with $<10\%$ bone marrow blasts and evaluable extramedullary disease, imaging and/or biopsy of the extramedullary disease site should have been obtained in addition to BM aspirate and biopsy. Those patients who had a CR, CR with incomplete hematologic recovery (CRi), bone marrow blast (BMB) response (morphologic remission without blood platelet count and neutrophil recovery), PR, hematologic improvement (HI) or stable disease (SD) without unacceptable study treatment-related toxicity were eligible for continued VSLI treatment until HSCT, disease progression, or PI determination that VSLI treatment was no longer beneficial.

If at any time a response of CR or CRi was documented in a bone marrow examination, a repeat bone marrow aspirate and biopsy were to be performed 4 weeks later on Day 28 of the next study treatment course to confirm the initial CR or CRi. After confirming CR or CRi, bone marrow aspirate and biopsy were to be performed at the end of every second course of study treatment (Day 28 \pm 3 days) for up to 6 months after the initial CR or CRi assessment. At the End-of-Therapy Visit (30 days [+5 days] after the last VSLI dose), or prior to any subsequent anti-leukemia therapy, patients were to undergo bone marrow aspirate and biopsy assessments.

Patients who, at the time of discontinuation from study treatment, did not achieve CR or CRi were to complete the End-of-Therapy Visit. They were to be followed monthly for survival from the EOT visit through Month 12, then every 3 months through Month 24, and every 6 months through Month 60. Patients who, at the time of discontinuation from study treatment, achieved CR or CRi were to complete the EOT visit and were to be followed for CR+CRi duration and any subsequent anti-leukemia therapy monthly from the EOT visit through Month 12 or until relapse if it occurred before Month 12. In addition, these patients were to be followed for survival every month from the EOT visit through Month 12, then every 3 months through Month 24, and after that, every 6 months through Month 60.

Endpoints:

The primary efficacy endpoint of Study HBS407 was the proportion of patients who achieved CR+CRi, as determined by IRRC and PI using IWG Criteria.²⁰ The key

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secondary efficacy endpoints included 1) CR+CRi duration defined by the applicant as “time, in days, from first CR or CRi until recorded (or inferred) relapse”, 2) time to CR or CRi, 3) OS, 4) leukemia-free survival, and 5) number and proportion of patients who received post-VSLI HSCT.

Two analysis datasets were utilized by the applicant for the analysis of efficacy: 1) Treated Analysis Set which included all patients who received at least one dose of study drug and had histologically and molecularly proven Ph- ALL that was confirmed by a central hematopathologist, 2) IRRC Evaluable Analysis Set that included patients who had reviewable data for IRRC to assess and determine response or lack of response. In order to have less biased and more accurate evaluation of this single arm study, this reviewer used “Treated Population” to analyze the efficacy.

Two IRRC members were [REDACTED] (b) (4)

[REDACTED] These members completed their assessments independently without internal discussion and without knowledge of the PI determined response. If the assessments by both reviewers agreed, then this was the final IRRC response assessment. If the 2 IRRC members differed in their response assessment, the case was sent to a third IRRC member ([REDACTED] (b) (4)) who adjudicated the final response determination.

Applicant claimed that based on the advanced disease status of the target population and reported 4% CR rate for single-agent second salvage therapies,⁵ a priori definition of success was achievement of CR or CRi in 16% of patients while maintaining a predictable and manageable safety profile. Again, this review does not concur with such assumption and definition of success.

6 Review of Efficacy

6.1 Efficacy Summary

6.1.1 CR+CRi Rates

The Applicant reported, based on PI assessment, the number of CR+CRi was 13 and based on IRRC assessment, the number of CR+CRi was 11 (8 CRs and 3 CRis). The PI assessment included two cases of CR+CRi which were morphologic bone marrow blast responses, which represent CR without recovery of both neutrophil and platelet counts, by IRRC assessment. The FDA CR+CRi rates based on case report forms (CRFs) in treated patient population from Study HBS407 are summarized in Table 7.

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Table 7. FDA Review of CR+CRi Rates Based on Review of CRFs (Treated Population)

	CR+CRi FDA Reviewer Assessment Based on CRFs Review (N=65)	
	Confirmed	Confirmed + Unconfirmed*
Complete Remission (CR) [n(%)] 95% CI	2 (3.1) (0.4, 10.7)	3 (4.6) (1.0, 12.9)
CRi (including CRp) [n(%)] 95% CI	6 (9.2) (3.5, 19.0)	7 (10.8) (4.5, 21.0)
CR+CRi [n(%)] 95% CI	8 (12.3) (5.5, 22.8)	10 (15.4) (7.6, 26.5)

*Unconfirmed - no repeat bone marrow evaluation to confirm the response

Source: NDA 202497 – Case Reports Forms (Module 5)

The FDA response assessment that included all patients who received at least one dose of study drug was not in complete agreement with the applicant's. FDA's assessment found that 10 patients' disease status was a CR or CRi with treatment.

FDA review of the CRFs provided in the initial submission suggested that one patient's (0193-0692) bone marrow persistently contained >5% blasts, hence could not be considered as CR or CRi. The review team queried the Applicant regarding this one case. The Applicant stated that "Course 1 Day 28 and Course 3 Day 28 case report forms appear to have been misfiled in a manner that could lead one to conclude that there was reviewer discordance where there was actually none".

Table 8 summarizes the bone marrow assessments for this patient. Compared to the initial submission, in the amended submission the central pathology reviews were switched between course 1 and course 3. The dates on which bone marrow examinations were performed are not indicated on the central pathology review forms.

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Table 8. Summary of Bone Marrow Assessments of the Patient for Whom FDA Reviewer Does Not Concur with the Applicant on CR Status

Bone Marrow Assessments by Pathologists	Course 1, Day 28 (June 2008)		Course 2 Day 28 (July 2008)	Course 3, Day 28 (Aug 2008)		Course 4 Day 28 (Sep 2008)
	Initial Submission	Amended Submission		Initial Submission	Amended Submission	
Local Marrow Blast (%)	2	2	20	3	3	30
Central Marrow Blast (%)	2	25	11	25	2	22
Adjudicator Marrow Blast (%)	10	10	-	-	-	19
Status based on Initial Submission	No CR	-	No CR	No CR	-	No CR
Status based on Subsequent Submission	-	No CR	No CR	-	CR	No CR

Local, Central and Adjudicator bone marrow blast percentage was based on the highest blast percentage derived following any microscopic, immunohistochemical, and flow cytometry examination of bone marrow aspirate and biopsy based on the initial submitted and amended Case Reports Forms of this patient (NDA 202497, Module 5).

No additional documentation was provided by the applicant regarding this case. For the following reasons this reviewer does not concur with the applicant on CR status of this patient:

1. Based on subsequent submission, the bone marrow assessments at the end of Cycles 1, 2, and 4 showed persistently >5% blasts (i.e. no CR). The claimed CR at the end of Cycle 3 was not confirmed 4 weeks later. In fact patient was taken off the study due to disease progression at the end Cycle 4.
2. The bone marrow specimen at the end of Cycle 3 reported as inadequate (no spicules/particles present) by the central pathology review.
3. It is not clear why this patient was kept on the study after Cycle 2 which showed disease progression compared to Cycle 1. According to the protocol, this patient should have been withdrawn from the study.
4. Patient's platelet count did not rise above $100 \times 10^9/L$ at the end of Cycle 3. This was indicated by IRRC review too. So, this patient's status at best at the end Cycle 3 was CRp.

Reviews of local, central and adjudicator pathology reports, CBC results, transfusion histories and subsequent anti-leukemic therapies by the FDA, demonstrated that out of 10 CR+CRi, 3 were CRs and 7 were CRis (including CRps). For 8 patients, the initial documented CR+CRi responses were confirmed by at least a subsequent bone marrow aspirate or biopsy and complete blood count (CBC) examinations. Two patients only had one bone marrow biopsy without subsequent biopsies to confirm the initial CR or CRi. For more details about these 10 patients, see sections 6.4.9 and Table 26 below.

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Out of the 8 confirmed CR+CRis, 2 were CRs and 6 were CRis. Based on reviews of local and central pathology reports, CBC results, transfusion histories and subsequent anti-leukemic therapies, this reviewer was able to confirm only 2 CRs. For the rest of the 6 patients the best confirmed responses were CRis (including CRps).

6.1.2 CR+CRi Rates in Patients Who Received Prior Asparaginase

As mentioned in the available therapy section, 22 (34%) of patients in the treated population did not receive asparaginase products as an available therapy prior to enrollment into Study HBS407. Of the 10 CR+CRi patients, 7 (70%) received asparaginase and 3 (30%) did not receive asparaginase in prior lines of treatment. Of 43 patients who received prior asparaginase, 6 (14%) achieved confirmed CR+CRis. The CR+CRi rates based on prior asparaginase treatment are summarized in Table 9. There was no clear association between prior asparaginase exposure and age of patients at the time of initial diagnosis or subsequent relapse.

Table 9. CR+CRi Rates in Population who Received Available Therapy

Patients	n (%)
Total	43 (100)
Confirmed CR+CRi	6 (14)
Unconfirmed CR+CRi	1 (2.3)

Source: FDA reviewer's analysis

6.1.3 Duration of CR or CRi

Some patients received subsequent therapies without documentation of their disease status prior to initiating post Marqibo therapies. Hence, durations of response are difficult to characterize. Three different methods for assessment of CR/CRi durations were considered and used by this reviewer:

- 1 FDA has provided guidance for Industry for clinical trial endpoints for the approval of cancer drugs and biologics when assessments of response are missing. This assessment of response duration is based on the first date of CR or CRi to the date of the last available assessment of the same response when a subsequent assessment was missing. The median response duration based on this definition was 28 days.
- 2 Another way to assess the response duration is from the first date of CR or CRi to date of documented relapse, death or subsequent chemotherapies including HSCT. Some may consider this as leukemia free survival until the next therapy. The median response duration based on this definition was 56 days.

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- 3 The Applicant's duration of response used time from first CR or CRi until recorded (or inferred) relapse which includes the period after transplant or other subsequent chemotherapies. **This assessment of response duration is confounded since it attributes the therapeutic effects of other drugs including stem cell transplantation to Marqibo.**

Table 10 shows Applicant's and FDA assessed CR or CRi duration by the 3 definitions mentioned above. The median response duration was 144 days by applicant for 11 reported CRs or CRis and 28 days by FDA for 8 confirmed CRs or CRis. By FDA assessment, five out of 8 confirmed CRs or CRis had response duration less than one month. The median response duration from the first documented CR or CRi until next treatment, relapse, or death was 56 days.

Table 10. Duration of CR/CRi Assessment

Patients	Response By FDA	CR/CRi Duration (days)		
		FDA	Until next treatment/relapse/death	Applicant
1 (0063-0010)	CRi	7	23	42
2 (0026-0393)	CRi	26	50	135
3 (0022-0031)	CR	28	61	162
4* (0107-0093)	CR	28	146	166
5 (0192-0211)	CRi	28	62	210
6 (0217-0781)	CRi	36	39	463
7 (0026-0391)	CRi	63	65	162
8 (0193-0694)	CRi	144	144	144
9 (0063-0004)	CR	Unable to assess	35	35
10 (0063-0003)	CRi	Unable to assess	9	132
11 (0193-0692)	-	Unable to assess	-	32
Median (95% CI)		28 (7 , 36)	56 (9 , 65)	144 (35 , 166)

*Extramedullary ALL in kidney, negative bone marrow examination

Source: FDA reviewer's analysis

The difference between median response durations of 28 or 56 days would not substantially change the risk/benefit assessment of Marqibo. However, the Applicant's response duration includes the effects of subsequent therapies, hence, overestimating the response duration.

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6.1.4 Proportion of Patients Who Received Post-VSLI Subsequent Hematopoietic Stem Cell Transplantation

Twelve patients in study HBS407 received hematopoietic stem cell transplantations (HSCT) after receiving Marqibo. Of these 12 patients, 5 achieved CR or CRi with Marqibo treatment and underwent HSCT. This means 8% or 5 out of these 65 heavily pre-treated patients were able to undergo HSCT after single agent Marqibo. As discussed by ODAC members, this was a shift in treatment paradigm from palliative to potentially curative mode and was considered a meaningful clinical benefit.

However, “bridge to transplant” in study HBS407 was not positively correlated with CR/CRi status after Marqibo. Seven of 12 patients did not achieve CR or CRi following Marqibo (Table 11). These patients were anticipated to have poor tolerance for multi-agent chemotherapy at the time of enrollment. Nevertheless, 6 of these 7 patients who did not achieve CR or CRi received multi-agent chemotherapy regimens pre-transplant and underwent subsequent HSCT (Table 12). Further information on subsequent treatment for one patient who underwent HSCT was not available. These data indicate that patients whose disease did not achieve a CR or CRi after Marqibo were candidates for other therapy. Patients underwent HSCT regardless of achieving CR or CRi after Marqibo administration.

Table 11. Subsequent Hematopoietic Stem Cell Transplantation

Marqibo Response	Number of Patients Received HSCT
Total	12
CR/CRi	5
No CR/CRi	7

Source: FDA reviewer’s analysis

Table 12 summarizes subsequent anti-leukemia chemotherapies post-Marqibo and pre-transplant for the 6 patients whose disease did not achieve CR/CRi after Marqibo. These Patients were able to receive other combination chemotherapies prior to HSCT within a few weeks after the last dose of Marqibo, hence anticipation of having poor tolerance for multi-agent chemotherapy at the time of enrollment by applicant, at least for these patients, was questionable.

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Table 12. Subsequent Anti-Leukemia Therapy Post-Marqibo and Pre-HSCT for Patients Whose Disease Did not Achieve a CR or CRi after Marqibo

Patient ID	Last Marqibo Dose Date	Anti-Leukemia Therapy	Start Date of Anti-Leukemia Therapy	Stop Date of Anti-Leukemia Therapy	Subsequent HSCT Therapy Date
0063-0008	(b) (6)	CLOFARABINE CYCLOPHOSPHAMIDE CLOFARABINE METHOTREXATE PEG ASPARGASE	(b) (6)	(b) (6)	(b) (6)
0106-0812		CYCLOPHOSPHAMIDE CLOFARABINE CYCLOPHOSPHAMIDE			
0192-0212		CYTARABINE ETOPOSIDE HYDROCORTISONE METHOTREXATE MITOXANTRONE PREDNISONE			
0063-0009		n/a			
0026-0399		MITOXANTRONE ETOPOSIDE IFOSFAMIDE ASPARAGINASE CYTARABINE ETOPOSIDE IFOSFAMIDE VINCRIStINE			
0034-0121		CYTARABINE ETOPOSIDE MITOXANTRONE			
0193-0691		CYCLOPHOSPHAMIDE DOXORUBICIN VINCRIStINE VINCRIStINE METHOTREXATE CYTARABINE METHOTREXATE DEXAMETHASONE METHOTREXATE VINCRIStINE			

Source: Applicant's Response to FDA Information Request

To answer the question whether achievement of CR/CRi after Marqibo positively affected post-HSCT survival, we analyzed the survival data for 12 patients who received subsequent HSCT. Table 13 summarizes survival after Marqibo followed by HSCT. The first five patients achieved CR/CRi after administration of Marqibo. The next seven patient did not achieve CR or CRi after Marqibo, nevertheless underwent HSCT. The sample size for this analysis was small, but the data suggest that survival after HSCT was not related to the response or lack of response to Marqibo; two of the three longest survivors did not achieve CR or CRi after Marqibo.

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Table 13. Survival after Marqibo and after HSCT in Patients with or without CR/CRi Achievement

Patient ID	Response to Marqibo before HSCT	Duration of Response before HSCT (days)	Duration of CR/CRi after HSCT and before subsequent relapse / death (days)	Survival form the first day of response to Marqibo (days)
Patients with CR/CRi after Marqibo who underwent HSCT				
0026-0393	CRi	55	84	139
0026-0391	CRi	65	124	189
0192-0211	CRp	65	147	237
0063-0003	CRi	9	122	289
0217-0718	CRi	39	Patient was alive at study completion (follow up visit month 21, (b) (6))	699
Patients without CR/CRi achievement after Marqibo who underwent HSCT				
0063-0008	None	-	40	40
0106-0812	None	-	42	42
0192-0212	None	-	64	64
0063-0009	None	-	128	128
0026-0399	None	-	135	135
0034-0121	None	-	Patient was alive at study completion (follow up visit month 12, (b) (6))	490
0193-0691	None	-	Patient was alive at study completion (follow up visit month 24 (b) (6))	760 (patient died on (b) (6))

Source: FDA reviewer's analysis

6.2 Indication

Marqibo is indicated for the treatment of adult (age ≥ 18 years) patients with Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy.

6.3 Methods

See Section 5.3.2, HBS407 Study.

6.4 Results

6.4.1 Demographics

In study HBS407, the original enrollment target was approximately 56 patients. Per a protocol amendment, enrollment was increased from 56 to 65 to facilitate PK sample

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capture. The actual number of consented patients was 68, and 65 enrolled patients received study treatment, which constituted “treated population”.

For 12 patients the protocol specified assessment of disease response to VSLI was not performed. These patients were not included in the IRRC evaluable analysis reported by the applicant. The most common reason for the lack of assessment was death secondary to infection. Table 14 summarizes these patients for whom protocol specified bone marrow examinations and other assessments to document a response or lack of response to Marqibo were absent. Ten of these 12 patients died within 40 days on treatment.

Table 14. Patients for Whom the Protocol Specified Assessment of Disease Response to VSLI Was Not Performed

Subj#	VSLI Doses	Days on Treatment	On-Study Response Assessment	Reason(s) for Not Undergoing an On-Study ALL Response Assessment
395	2	9	No	Death related to suspected infection and intestinal bleeding
397	1	18	No	Death related to Pseudomonas pneumonia
398	1	30	No	Withdrawn consent due to worsening epistaxis and gum bleeding
451	2	25	No	Death related to pneumonia
482	1	2	No	Death related to suspected sepsis and multi-organ system failure
691	1	31	No	Terminated from study because of concomitant steroids
721	3	40	No	Death related to Pseudomonas sepsis and pneumonia
751	2	31	No	Death related to progressive graft versus host disease
783	4	42	No	Death
813	2	27	No	Death related to vancomycin resistant enterococcus pneumonia
814	3	21	No	Death related to suspected fungal pneumonia
961	3	20	No	Death related to sudden cardiac arrest

Source: Module 5, HBS407 CSR, 5.3.5.3.27. ISE Ad Hoc Tables Listing, Table 9014

The patients’ demographic characteristics are shown in Table 15. In study HBS407, approximately 45% of patients were less 30 years old, 43% were between 30 and 60 years old and 12% were older than 60 years of age. Approximately 50% of patients were female. The male to female ratio appears to be similar to the US ALL patient population. The majority of the treated patient were white. At baseline, mean weight in the treated population was 77.8 kg (\pm 19.3) with a range of 45 to 120 kg. Median BSA was 1.89 m² with a range of 1.44 to 2.45 m².

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Table 15. Demographic Characteristics of Patients in Study HBS407

Variable at baseline	Treated Population, N=65
Age group (range 19-83 years old)	N (%)
18-29 years	29 (44.6)
30-59 years	28 (43.1)
≥60 years	8 (12.3)
Gender	N (%)
Female / Male	32 (49.2) / 33 (50.8)
Race	N (%)
White	56 (86.2)
Black or African American	4 (6.2)
Asian	2 (3.1)
Other	3 (4.6)

Source: Module 5, HBS407 CSR, Tables 14.1.6.1 through 14.1.6.2

Table 16 shows the baseline characteristics of patients in Study HSB407. Two patients were allowed into the study with relapsed ALL and <10% bone marrow blasts because of biopsy positive extramedullary disease (lymphoblastic lymphoma-like relapse presentation). In study HBS407, approximately 85% of treated patients had B-cell ALL. Ten patients had T-cell ALL. The median time since diagnosis of ALL was 1.8 years ranging less than a year to 15 years. The majority (85%) of patients did not have extramedullary disease. Approximately 77% of patients had ECOG performance status of zero or one. Fifteen patients had ECOG of 2 or 3. Sixty percent of treated patients had baseline platelet count of less than 50,000 per microliter of blood.

Table 16. Baseline Characteristics of Patients in Study HBS407

Baseline Parameter	HBS407 (ITT), N=65
Type of ALL (based on Central Reviewer)	n (%)
Precursor B-lymphoblastic leukemia	55 (84.6)
Precursor T-lymphoblastic leukemia	10 (15.4)
Time Since Diagnosis of ALL (Years)	Years
Mean (std dev)	2.7 ± (2.80)
Median (Min, Max)	1.8 (< 1, 15)
Presence of Extramedullary Disease	n (%)
No	55 (84.6)
Yes	10 (15.4)
ECOG Performance Status [n (%)]	n (%)
0 - 1	50 (76.9)
2 - 3	15 (23.1)
Platelet Count	
≤ 50 × 10 ⁹ /L	39 (60.0)
> 50 × 10 ⁹ /L	26 (40.0)

Source: Module 5, HBS407 CSR, Tables 14.1.6.1 through 14.1.7.2, Tables 14.1.7.5 through 14.1.7.7, and Table 14.1.7.10

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6.4.2 Immunophenotype Classification

In the treated population the majority of patients displayed markers (CD10 [70%], CD19 [77%], CD20 [37%] or CD22[39%]) consistent with precursor B-cell ALL. CD13 [31%], CD15 [23%], and CD33 [33%], which are commonly detected myeloid antigens in adult ALL were also detected. CD34, which was reported to adversely affect outcome by the CALGB study group, detected in 62% of the Study HBS407 populations.

6.4.3 Cytogenetics Characteristics

In study HBS407, 31% of patients had normal cytogenetics. Approximately 51% of patients had unfavorable cytogenetics, of which 29% had complex karyotypes. For 9 or 14% of patients cytogenetic data were missing. None of the patients were reported to have had favorable cytogenetics. This pattern of cytogenetics is consistent with the relapsing and/or refractory disease natural history in these populations. Approximately one third of patients had complex karyotypes. Table 17 summarizes the baseline cytogenetics in study HBS407.

Table 17. Baseline Cytogenetics of Patients in Study HBS407

Findings	Treated Population, N = 65
Intermediate Cytogenetics n (%)	23 (35.4)
Normal	20 (30.8)
del and -Y	3 (4.6)
Unfavorable Cytogenetics n (%)	33 (50.8)
complex karyotypes	19 (29.2)
-7/del(7q)	2 (3.1)
+8	1 (1.5)
-7/del(7q)+8	1 (1.5)
del (5q)/-5q	1 (1.5)
abnl 11q	2 (3.1)
abnl 21q	2 (3.1)
abnl 17p	1 (1.5)
abnl 9q	2 (3.1)
abnl 21q and abnl 17p	1 (1.5)
abnl 21q and abnl 9q	1 (1.5)
Missing	9 (13.9)
t(9;22) (Philadelphia chromosome)	0 (0.0)

Source: Module 5, HBS407 CSR, Table 14.1.7.4 and Table 14.1.7.9

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6.4.4 Prior Anti-leukemia Therapy

Prior anti-leukemia therapy received by patients in study HBS407 is summarized in Table 18. All of the treated patients in study HBS407 had at least two prior lines of anti-leukemia treatment. Approximately 37% of patients had three, 11% of patients had four, and 1 patient received 6 lines of prior anti-leukemia treatment.

In 95% of treated patients, the best response to prior induction therapies was complete remission. The median duration of best response to prior induction therapy for 51 patients for whom these data were available was 334 days ranging from one month to eleven years.

Approximately 52% of treated patients did not have prior hematopoietic stem cell transplantation. Approximately 45% of patients had undergone one prior transplant and 2 patients had two previous transplant.

Table 18. Study HBS407 - Prior Anti-leukemia Therapy (Treated population)

Therapy Type	Treated Population, N = 65
Number of Prior Lines of Anti-Leukemia Tx (%)	n (%)
2	33 (50.8)
3	24 (36.9)
4	7 (10.8)
6	1 (1.5)
Best Response to Prior Induction Therapy	n (%)
Complete Remission (CR)	62 (95.4)
Progressive Disease and No Response	2 (3.1)
Unknown	1 (1.5)
Duration of Best Response to Prior Induction Therapy*	Days
Median (Min, Max)	334 (32, 4050)
Prior HSCT	n (%)
None	34 (52.3)
One Prior HSCT	29 (44.6)
Two Prior HSCT	2 (3.1)

*The data for duration of best response to prior induction therapy were missing for 14 patients
Source: NDA 202497, Module 5, HBS407 CSR, Table 14.1.8.1 and Table 14.1.8.3

6.4.5 Prior Anti-leukemic Agents

6.4.5.1 Conventional Cytotoxic Agents

All patients (100%) had received prior vincristine as part of their first-line treatment. Most patients (93.8%) also received standard VCR as part of their second-line treatment. Other frequently reported first-line drugs included cyclophosphamide (93.8%), methotrexate (92.3%), cytarabine (89.2%), and doxorubicin (89.2%). Other frequently reported second-line therapies included cytarabine (84.6%),

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cyclophosphamide (81.5%), methotrexate (78.5%), and doxorubicin (72.3%). Table 19 summarizes the most commonly previously received cytotoxic agents in the treated population of study HBS407.

Table 19. Study HBS407 - Prior Anti-leukemic Agents (Treated population)

Chemotherapy used	first-line	second-line
vincristine	100%	93.8%
cyclophosphamide	93.8%	81.5%
methotrexate	92.3%	78.5%
cytarabine	89.2%	84.6%
doxorubicin	89.2%	72.3%

Source: NDA 202497, Module 5, HBS407 CSR, Table 14.1.8.2

The majority (60/65, 92.3%) of patients were in need of a second or third salvage therapy. Marqibo was given as 1st, 2nd, 3rd, and 4th salvage therapy to 5, 43, 15, and 2 patients, respectively, in study HBS407. The median duration of best response to prior induction therapy was approximately 11 months (334 days).

Approximately half of the patients (48%) received prior HSCT included those who received 1 prior HSCT (44.6%), and 2 prior HSCT (3.1%). Twenty-seven HSCT were in remission as a component of remission consolidation therapy and 4 HSCT were a component of salvage therapy.

6.4.5.2 Asparaginase or pegylated asparaginase

Approximately 34% (22 out of 65) of patients did not receive asparaginase or peg-asparaginase prior to enrollment which is an approved and therefore available therapy for the treatment of Ph- ALL. The ID for these patients were 0063-0002, 0063-0004, 0063-0005, 0063-0007, 0063-0010, 0063-0011, 0022-0031, 0022-0032, 0022-0033 (peg. asp.), 0194-0061, 0194-0062, 0107-0091, 0107-0092, 0107-0093, 0107-0095, 0034-0121, 0097-0181, 0097-0182 (peg. asp.), 0026-0391, 0026-0394 (peg. asp.), 0026-0396, 0026-0398, 0026-0399, 0025-0421 (peg. asp.), 0025-0422 (peg. asp.), 0186-0482, 0186-0483, 0182-0541, 0193-0691, 0193-0692, 0193-0693, 0193-0694, 0193-0696, 0129-0721, 0216-0751, 0217-0781, 0217-0782, 0217-0783, 0106-0815, 0106-0816, 0229-0991, 0229-0992, 0233-1021. Five patients (0022-0033, 0097-0182, 0026-0394, 0025-0421, and 0025-0422) received pegylated asparaginase. (Source: Module 5, 5.3.5.2.12. Demographic Data Listing)

6.4.5.3 Nelarabine

Three patients (0063-0007, 0026-0396 and 0228-0961) with prior T-cell ALL received nelarabine as one of their prior anti-leukemic therapy before enrollment into the study HSB407. (Source: Module 5, 5.3.5.2.12. Demographic Data Listing)

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6.4.6 Concomitant Corticosteroid

In Study HBS407, Corticosteroid use was prohibited during the study and patients had to be tapered off of systemic steroids by Day 5 of Course 1. Systemic steroids were prescribed beyond Day 5 of Course 1 for 16 patients (16/65, 24.6%), including 4 patients with CR+CRi assessed by PI. Overall, 6 different corticosteroids were used after Day 5 of Course 1 at varying doses including:

1. Methylprednisolone IV or PO at doses ranging from 12 to 125 mg
2. Hydrocortisone IV at doses ranging from 20 to 100 mg
3. Dexamethasone IV or PO at doses ranging from 1 to 40 mg
4. Prednisone PO at a dose ranging from 5 to 40 mg
5. Prednisolone IV at a dose of 50 mg
6. Budesonide inhaled at a dose of 90 mcg

Table 20 shows the concomitant corticosteroid use in study HBS407.

Table 20. Concomitant Corticosteroid Use (including Taper Off by Day 5)

	Concomitant Corticosteroids	n	percent
1	Dexamethasone + Dexamethasone sodium phosphate	17+2=19	26.2+3.1=29.2
2	Hydrocortisone + Hydrocortisone sodium succinate	18+6=24	27.7+9.2=39.9
3	Methylprednisolone + Methylprednisolone sodium acetate	5+9=14	7.7+13.8+21.5
4	Prednisolone + Prednisolone acetate	1+1=2	1.5+1.5=3
5	Prednisone	17	26.2
6	Budesonide inhaled	1	1.5

Source: ISS Tables, Table 1.8.1

In response to FDA's Information Request about the use of concomitant corticosteroid and the time of tapering off in the study HBS407, applicant provided the following information: "The majority (39/65, 60%) of the HBS407 subjects received no corticosteroid whatsoever. Twenty-six (40%) subjects were prescribed and may have received at least 1 dose of 1 corticosteroid drug."

Reviewer's Information Request: *How many of the concomitant corticosteroids were tapered before Cycle 1 Day 5? How many continued during the study?*

Applicant Response: Nine subjects (9/26, 35%) who received steroid therapy during study HBS407 had their steroid therapy tapered and curtailed completely by Cycle 1 Day 5. Seventeen subjects (17/26, 65%) were prescribed steroids beyond Cycle 1 Day 5, of whom 1 subject received solely inhaled steroids for airway disease. Thus, 16 subjects out treated population of 65 (25%) had potentially relevant pharmacologic steroid exposure.

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The following descriptions demonstrates the use of each type and dosages of corticosteroids that was used by the patients in study HBS407 beyond cycle 1 day 5.

Subjects who did not achieve a CR or CRi assessed by the PI:

- Subjects 0063-0006 and 0063-0010 were prescribed hydrocortisone 25 or 50 mg on an as needed (PRN) basis.
- Subject 0054-0242 completed a prednisone taper with a 5 mg PO dose on Cycle 1 Day 6.
- Subject 017-0783 completed a dexamethasone taper with a 1 mg IV dose on Cycle 1 Day 7.
- Subject 0233-1021 completed a prednisone taper with a 5 mg PO dose on Cycle 1 Day 12.
- Subject 0063-0005 received a single IV dose of methylprednisolone 125 mg on Study Day 53 due to a reported adverse event (non-neutropenic fever).
- Subject 0129-0721 received a single IV dose of prednisolone 50 mg on Study Day 9.
- Subject 0107-0091 received 3 individual and isolated doses of IV hydrocortisone 50 mg on Study Days 37, 44, and 50 due to reported adverse events (hives).
- Subject 0063-0011 received a single IV dose of hydrocortisone 25 mg on Study Day 36 due to a reported adverse event (neutropenic fever) and 1 week of PO methylprednisolone 16 mg QID on Study Days 43 to 50 because of an adverse event (bone pain).
- Subject 0107-0094 received a single IV dose of hydrocortisone 25 mg on Study Day 50 because of an adverse event (hives) and daily dose (5-10 mg) of PO prednisone because of reported decreased appetite for an unknown duration of time.
- Subject 0026-0395 received daily PO prednisone 15 mg with an unknown start date and continuing until Cycle 1 Day 8 as well as methylprednisolone IV 12 mg daily beginning on Cycle 1 Day 9 with an unknown duration.
- Subject 0217-0782 received daily PO dexamethasone 10 mg; start/end date unknown.

For 4 CR+CRi patients assessed by PI the following corticosteroid use were reported:

- Subject 0106-0817 received 3 individual and isolated IV doses of hydrocortisone 20 mg, 25 mg, and 100 mg respectively on Study Days 3, 31, and 33 as well as daily PO prednisone 20 mg from Study Days 42 to 64 because of increased pain.
- Subject 0107-0093 received a low-dose (20 to 5 mg) PO prednisone taper from Study Days 22 to 43 to ameliorate anorexia.
- Subject 0192-0212 received 5 days of daily IV dexamethasone 1 mg from Study Days 12 to 16 to ameliorate nausea.
- Subject 0217-0781 received 4 days of daily PO dexamethasone 6 mg from Study Days 5 to 8 because of reported fever.

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6.4.7 Cumulative Dose of Marqibo Received by Treated Population

6.4.7.1 Cumulative Dose of Marqibo During the First Cycle

To evaluate the tolerability of Marqibo at the proposed dose with no capping, we analyzed the cumulative dose of Marqibo received by patients in treated population. Table 21 shows the total cumulative dose in milligram and based on BSA (i.e. mg/m^2). During cycle 1, if patients received full dose, the cumulative dose should have been 9 (2.25×4) mg/m^2 . The data indicate that majority of the patients could tolerate the full dose of Marqibo in cycle 1.

Table 21. Cumulative Dose of Marqibo Received by Patients in Cycle 1

	n	Mean (SD)	Median	Range
Cumulative dose (mg)	65	14.0 (4.9)	15	(3.5, 20.88)
Cumulative dose (mg/m^2)	65	7.4 (2.3)	9	(2.25, 9.0)

Source: FDA reviewer's analysis

Five patients received more than 5 mg of Marqibo per injection (the maximum of Marqibo in one kit) in cycle 1 (Table 22).

Table 22. Patients Who Received More Than 5 mg of Marqibo Per Injection

Patient ID	Infusion Number During Cycle 1	Body Surface Area	Dose Received (mg/m^2)	Dose Received (mg)
0026-0394	1	2.42	2.25	5.22
0026-0394	2	2.42	2.25	5.22
0026-0394	3	2.42	2.25	5.22
0026-0394	4	2.42	2.25	5.22
0106-0811	1	2.31	2.25	5.20
0106-0811	2	2.31	2.25	5.20
0106-0811	3	2.31	2.25	5.20
0106-0811	4	2.31	2.25	5.20
0106-0812	1	2.28	2.25	5.13
0106-0812	2	2.28	2.25	5.13
0106-0812	3	2.28	2.25	5.13
0106-0812	4	2.28	2.25	5.13
0106-0814	1	2.45	2.25	5.51
0106-0814	2	2.45	2.25	5.51
0106-0814	3	2.45	2.25	5.51
0106-0814	4	2.45	2.25	5.51
0107-0091	1	2.29	2.25	5.15
0107-0091	2	2.29	2.25	5.15

Source: FDA reviewer's analysis

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Four subjects (394, 811, 812, and 91) received a cumulative dose greater than 20 mg. Subject 814 received three times (weeks 1, 2, 3) 5.51 mg and no dose in week 4. Subjects 394, 811, and 812 each received four doses that exceeded 5 mg. Subject 91 received two doses (on weeks 1 and 2) that exceeded 5 mg. Requirement of preparation of more than one kit may increase the medication error and microbiological contamination.

6.4.7.2 Categorical Cumulative Dose by Treatment Cycle

Table 22 shows the frequency of categorical cumulative dose of Marqibo received by patients within each treatment cycle. These data indicate that majority of the patients did not receive Marqibo beyond cycle 2 and within each cycle several dose adjustments occurred.

Table 23. Frequency of Categorical Cumulative Dose of Marqibo by Treatment Cycle in Study HBS407

N = 65	Cycle 1, n	Cycle 2, n	Cycle 3, n
Cumulative dose (mg)			
0	0	34	55
> 0 - < 6	6	4	3
6 - < 8	3	0	2
8 - < 10	6	2	0
10 - < 12	4	5	2
12 - < 14	8	6	
14 - < 16	9	6	0
16 - < 18	10	3	1
≥ 18	19	5	0
Cumulative dose (mg/m²)			
0	0	34	55
> 0 - < 2.5	6	4	3
2.5 - < 5	8	1	2
5 - < 7	11	10	3
7 - < 9	3	2	1
9	37	14	1

Source: FDA reviewer's analysis

6.4.7.3 Exposure to Marqibo

On a weekly treatment schedule, four weeks per cycle, 74% of patients completed cycle 1, 30% completed cycle 2, and only 5% completed cycle 3, Figure 7 (Source: ISS Tables, Table 1.3). These data indicate that Marqibo administration was not completed for majority of patients beyond the first cycle.

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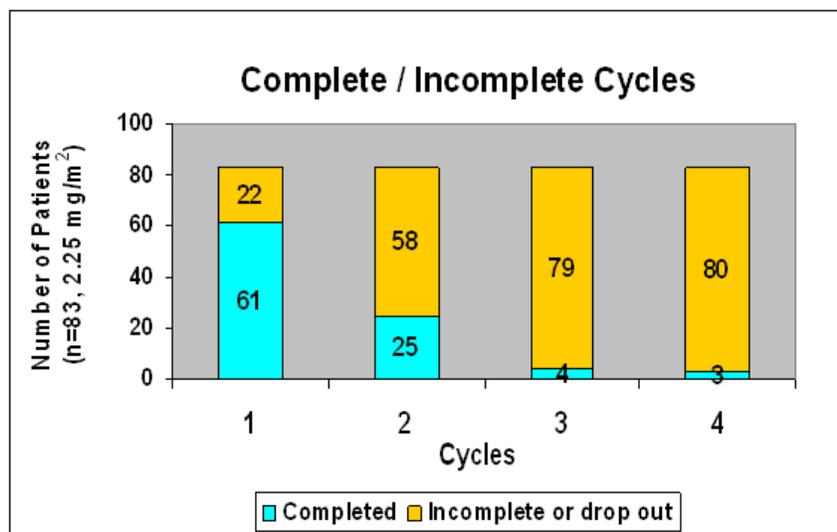
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Figure 7. Treatment Cycles Completion in Treated Population



Source: FDA reviewer's analysis

6.4.8 Patient Disposition

Treatment was ultimately discontinued in all 65 patients (100%) in the ITT Population of Study HBS407. The most common reason for study treatment discontinuation was disease progression (40.0%, 26/65), followed by adverse events (36.9%, 24/65), investigator request (9.2%, 6/65), HSCT (7.7%, 5/65), and patient withdrawn consent (6.2%, 4/65).

6.4.9 Analysis of Primary Endpoint

The primary efficacy endpoint of Study HBS407 was the proportion of patients who achieved CR+CRi, as determined by IRRC and PI using IWG Criteria.²⁰

In Study VSLI-06, VSLI plus dexamethasone was administered as the first, the second, and the third salvage therapy option for adult patients with relapsed and/or refractory ALL. Given the small sample size, multiple dosages used, concomitant use of dexamethasone, no clear individual dose response effect, and assessment only by PI, the study VSLI-06 does not provide adequate support for evaluation of clinical benefit of Marqibo for the proposed indication.

Table 24 summarizes the clinical response assessment reported by the applicant. The applicant reported a total of 13 (20.0%) CR or CRi based on PI determination in the treated population, 11 (20.8%) based on IRRC determination in the IRRC evaluable population, and 11 (16.9%) based on IRRC determination in the treated Population. The PI assessment included two cases of CR+CRi which were bone marrow blast (BMB) responses, which represent CR without recovery of both neutrophil and platelet counts, by IRRC

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assessment. Applicant reported that the 8 CR based on IIRC determination. For comparison with this reviewer's assessment of CR+CRi rate, see Section 6.1.1 and Table 26.

Table 24. Clinical Response Assessment Reported by the Applicant - Study HBS407

Best Response Assessment	IIRC Evaluable (N=53)	Treated by IIRC (N=65)	Treated by PI (N=65)
Overall Remission (CR+CRi) [n (%)] 95% CI	11 (20.8) (10.8 -34.1)	11 (16.9) (8.8 -28.3)	13 (20.0) (11.1 -31.8)
Complete Remission (CR) [n (%)] 95% CI	8 (15.1) (6.7 -27.6)	8 (12.3) (5.5 -22.8)	7 (10.8) (4.4 -20.9)
Complete Remission with Incomplete Blood Count Recovery (CRi) [n (%)] 95% CI	3 (5.7) (1.2 -15.7)	3 (4.6) (1.0 -12.9)	6 (9.2) (3.5 -19.0)
Partial Remission (PR) [n (%)] 95% CI	4 (7.5) (2.1 -18.2)	4 (6.2) (1.7 -15.0)	6 (9.2) (3.5 -19.0)
Bone Marrow Blast (BMB) [n (%)] 95% CI	4 (7.5) (2.1 -18.2)	4 (6.2) (1.7 -15.0)	4 (6.2) (1.7 -15.0)
Stable Disease (SD) [n (%)] 95% CI	13 (24.5) (13.8 -38.3)	13 (20.0) (11.1 -31.8)	12 (18.5) (9.9 -30.0)
Progressive Disease (PD) [n (%)] 95% CI	21 (39.6) (26.5 -54.0)	21 (32.3) (21.2 -45.1)	20 (30.8) (19.9 -43.4)
Not Evaluable: Response Assessment Not Done [n (%)]	0	12 (18.5)	10 (15.4)

CI calculated by Clopper-Pearson method.

Source: Module 5, HBS407 CSR, Table 14.2.1

Of the 13 claimed CR+CRi by PI, two were bone marrow morphologic response without both platelet AND neutrophil recovery. For one patient (0193-0692, Table 8), the report of CR was based on switching the pathology reports on the basis of an inadequate sample with clear evidence of disease progression 4 weeks later and no evidence of CR or CRi in the previous cycles. Hence this reviewer does not consider this patient as CR or CRi.

Of the remaining 10 (15.4%) patients whose disease achieved either confirmed or unconfirmed CR or CRis, 8 (12.3%) were confirmed and two were unconfirmed due to the lack of subsequent confirmatory bone marrow biopsies. Table 25 summarizes the characteristics of the 10 CR+CRis.

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Table 25. Clinical Characteristics of the 10 CR+CRis

ITT Population = 65	Total number (%) of patients in each stratum	Best response assessment for treated population (CR+CRi by the Reviewer) (n) including two unconfirmed CR+CRi		
		CR+CRi	CR	CRi
Age (years)				
(18, 29)	29 (45)	7	2	5
(30, 59)	28 (43)	2	0	2
≥60	8 (12)	1	1	0
Gender				
Female	32 (49)	5	1	4
Male	33 (51)	5	2	3
Extramedullary disease				
Yes	10 (15)	4	1	3
No	55 (85)	6	2	4
ECOG at baseline				
0	17 (26)	4	2	2
1	33 (51)	6	1	5
2	11 (17)	0	0	0
3	4 (6)	0	0	0
Platelet count				
≤50k	39 (60)	2	0	2
>50k	26 (40)	8	3	5
Platelet count				
≤75k	44 (68)		1	2
>75k	21 (32)	7	2	5
Platelet count				
≤100k	48 (74)	5	2	3
>100k	17 (26)	5	1	4
ALL Subtype at Study Entry				
Pre-B ALL	55 (85)	8	2	6
Pre-T ALL	10 (15)	2	1	1
Number of Prior Lines of Therapies				
2	32 (49)	5	1	4
3	24 (37)	4	1	3
4	8 (12)	1	1	0
6	1 (2)	0	0	0
Number of Prior HSCT				
0	34 (52)	4	1	2
1	29 (45)	6	2	5
2	2 (3)	0	0	0
Best Response to Prior Anti-Leukemic				
CR	62 (95)	8	2	6
PD	1 (2)	0	0	0
Not reported	1 (2)	0	0	0
Unknown	1 (2)	0	0	0

Source: NDA 202497 and FDA reviewer's analysis

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The majority (70%) of the responders were younger than 30 years of age. The response was distributed equally among males and females. Interestingly 4 (40%) of the responders had extramedullary disease at baseline, while only 10 (15%) out of the 65 patients had extramedullary ALL. CR or CRi was achieved in 10/50 (20%) of the treated population with ECOG PS of 0 or 1. No patients with an ECOG PS of 2 or 3 achieved a CR or CRi. Thrombocytopenia is generally considered a poor prognostic factor for response to therapy in relapsed or refractory acute leukemia; 80% of responders had a platelet counts greater than $50,000 \times 10^9/L$. The response rates were similar among patients with B- and T-ALL. For the 10 patients whose disease achieved CR or CRi, 6 received prior HSCT, and 2 experienced a third relapse prior to entering the study.

Table 26 includes detail data related to the 11 patients for whom achievement of CR or CRi were claimed. Table 26 was generated by a comprehensive review of the CRFs (See also Efficacy Summary above).

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Table 27 demonstrates the reported CRs or CRi by the applicant and this reviewer. According to the protocol, declaration of CR or CRi needed a confirmatory bone marrow and CBC examination. For example, if a patient's disease achieved CR at the end of cycle 1, CRi at the end of cycle 2 with no subsequent BMBx, according to the protocol the status of response for this patient should be considered CRi, because only CRi was confirmed. The last column in Table 27 provides details about BMBx for each patient, which clarifies the confirmed response status.

Table 27. CR or CRi Status Reported by The Applicant and FDA's Reviewer

Subject	IRRC Assessment	FDA Assessment Based on CRFs	
	Response	Response	FDA Comments
Patients who received Prior Asparaginase Products			
0063-0010	CRi	CRi	BMBx#2 was obtained 7 days after BMBx#1 Received new therapy 16 days after BMBx#2
0063-0004	CR	CR	BMBx#1 - "inadequate and non-diagnostic" BMBx#2 - CR No further BM assessment Off study due to AE/disease progression less than 1.5 months after BMBx#2
0217-0781	CR	CRi	BMBx#1 - CR BMBx#2 - CRi Conditioning chemotherapy for allo-HSCT 3 days after BMBx#2
0022-0031	CR	CR	BMBx#1 - CR BMBx#2 - CR Patient discontinued study due to AEs, and received subsequent chemotherapies 33 days after BMBx#2
0026-0391	CR	CRi	BMBx#1 - CRi BMBx#2 - CRi BMBx#3 - CRi BMBx#4 - CR Conditioning chemotherapy for allo-HSCT 2 days after BMBx#4
0193-0694	CR	CRi	BMBx#1 - CRi BMBx#2 - CRi BMBx#3 - CR BMBx#4 - CRi BMBx#5 - CRi BMBx#6 - CR Patient withdrew consent and went to hospice after the last BMBx.
0107-0093*	CR	CR	Kidney Biopsy#1 - CR Kidney Biopsy#2 - CR Patient discontinued study due to AEs 20 days after kidney Biopsy#2
Patients who did not receive Prior Asparaginase Products			
0063-0003	CRi	CRi	BMBx#1 - CRi Conditioning chemotherapy for allo-HSCT 9 days after BMBx#1
0026-0393	CR	CRi	BMBx#1 - CRi BMBx#2 - CR Conditioning chemotherapy for allo-HSCT 24 days after BMBx#2
0192-0211	CRi	CRi	BMBx#1 - CRi (with radiographic resolution of extramedullary disease) BMBx#2 - CRi allo-HSCT 34 days after BMBx#2

Source: NDA 202497 and FDA reviewer's analysis

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6.4.10 Analysis of Secondary Endpoints(s)

Secondary endpoints, which are analyzed below, include duration of CR or CRi, time to CR or CRi, overall survival, leukemia-free survival, time to peripheral blast clearance, time to bone marrow blast clearance, time to extramedullary disease resolution, number and proportion of patients who received post-VSLI HSCT.

It should be noted that the sample size for analysis of many of these secondary endpoints was small. Overall survival analysis in a single arm study is exploratory and difficult to interpret because the result may be heavily influenced by other non-drug factors such as baseline disease characteristics.

6.4.10.1 CR/CRi Duration

The duration of CR/CRi is summarized in Section 6.1.3, Table 10 and Table 27.

Table 28 demonstrates the duration of CR / CRp / CRi from first documented response to relapse or to death or to administration of the next anti-leukemia therapy. Duration of responses were generally short, because most of the patients went on to receive other therapies. Five out of 10 patients had a duration of response less than 2 months.

Several measures of the duration of survival and/or response have been used as outcomes in the clinical oncology literature over the years, and there have been no standard definitions or nomenclature for these outcomes. The following is IWG's recommendation with respect to duration of remission:

- “In the previous [IWG] guidelines, a 4-week duration of complete response was required to qualify as a CR. However, some patients who fulfilled the other criteria for CR could not be considered CR because of the administration of postremission therapy before full recovery of blood counts within that time period, or because they had evidence of recurrent or persistent disease after more than 4 weeks but no documentation that all response criteria were satisfied for at least 4 weeks. Therefore, no duration of response is required in the current recommendations.”
- “Remission duration is defined only for patients who achieve CR, and is measured from the date of CR by blood count recovery and bone marrow examination (rather than the date of the confirmatory bone marrow), until the date of relapse. However, unlike DFS, it is measured only until the date AML relapse is detected. For patients who die without report of relapse, remission duration is censored on the date of death, regardless of cause. For a patient with no report of relapse by the end of the follow-up data collection, observation is censored on the date of his or her last follow-up examination. Remission duration is subject to the competing risk of death without relapse.”

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Table 28. Duration of CR or CRi from the First Response Date to Death, to Relapse Date or to Date of Post-VSLI Anti-leukemia Therapy Including HSCT

Subject	IRRC Assessment	Duration of CR/CRi by IRRC (days)	FDA assessment based on BMBx and CBC assessments at the end of each cycle	Duration of CR or CRi Until Death, Relapse, or Subsequent Anti-Leukemia Therapy Including HSCT by the Reviewer (days)
0063-0003	CRi	132d	- CRi (cy1d28, ANC<1×10 ⁹ /L, Not confirmed)	9d from cy1d28 to next Tx (conditioning chemo for allo-HSCT)
0063-0010	CRi	42d	- CRi (cy1d28, ANC<1×10 ⁹ /L and PLT<100×10 ⁹ /L) - CRi (BMBx 7 days after cy1d28, PLT<100×10 ⁹ /L)	23d from cy1d28 to next Tx (rituximab)
0063-0004	CR	35d	cy1d28 - non-diagnostic BMBx by local and central pathologists - CR (cy2d28, Not confirmed)	35d from cy2d28 to relapse
0217-0781	CR	463d	CR (cy1d28) CRi (cy2d28, PLT<100×10 ⁹ /L)	39d from cy1d28 to next Tx (conditioning chemo for allo-HSCT)
0026-0393	CR	135d	CRi (cy1d28, PLT<100×10 ⁹ /L) CR (cy2d28)	50d from cy1d28 to next Tx (conditioning chemo for allo-HSCT)
0022-0031	CR	162d	- CR (cy1d28 - inadequate BMBx to be assessed accurately, normal PLT, discordant ANC) - CR (cy2d28)	61d from cy1d28 to next Tx (methotrexate, 6-MP, dexamethasone)
0192-0211	CRi	210d	CRi (cy1d28, PLT<100×10 ⁹ /L)	62d from cy1d28 to next Tx (conditioning chemo for allo-HSCT)
0026-0391	CR	162d	CRi (cy1d28, PLT<100×10 ⁹ /L) CRi (cy2d28, ANC<1×10 ⁹ /L) CRi (cy3d28, ANC<1×10 ⁹ /L)	65d from cy1d28 to next Tx (conditioning chemo for allo-HSCT)
0107-0093	CR	166d	cy1d28 – right and left kidney lesions radiographically CR (cy2d22, negative kidney biopsy) CR (cy3d22, negative kidney biopsy)	146d from cy2d22 to relapse
0193-0694	CR	144d	CRi (cy1d25, ANC<1×10 ⁹ /L) CRi (cy2d28, ANC<1×10 ⁹ /L) CR (cy3d28) CRi (cy4d28, ANC<1×10 ⁹ /L) CRi (cy5d28, PLT<100×10 ⁹ /L) CR (cy6d28)	144d from cy1d25 to relapse

Source: FDA reviewer's analysis

Applicant reported that for the 11 HBS407 patients who achieved CR or CRi, based on IRRC assessment, the median duration of remission was 5.4 months (162 days) with a maximum duration of remission over 1 year (463 days). As mentioned in Section 6.1.3, this reviewer considered three methods to calculate the CR duration.

Based on the above analysis and the data in Table 28, this reviewer disagrees with the applicant analysis of duration of remission. The applicant's reported CR or CRi duration is biased because in a single arm study, it attributes the effects of other drugs including stem cell transplantation to Marqibo.

Nevertheless, because the goal of treatment with any single agent in this heavily pre-treated patients with ALL with unfavorable cytogenetics and several other poor

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prognostic factors cannot be curative intent, but rather transition to stem cell transplantation (if eligible) or clinical trials with novel agents (if available); this reviewer acknowledges that isolated duration of response without considering other factors such as comorbidities and validated quality of life reports might not be a meaningful clinical benefit. Hence, as recommended by IWG, a short duration of CR or CRi might not indicate lack of clinical benefit as long as patients were able to undergo transplantation. This point was discussed in ODAC and agreed upon by some members of the expert panel.

6.4.10.2 Time to CR or CRi

Time to CR or CRi was defined as the time from the start of the first study dose infusion date to the date the patient first achieved CR or CRi. Patients who never achieved CR or CRi were censored at the date of last treatment.

The applicant reported that of the 11 patients who achieved CR or CRi, time to response ranged from 25 to 81 days with 45% (5/11) achieving the remission within 35 days and 91% (10/11) within 57 days. Review of CRFs (Table 26) indicated a 25 to 56 days range in time to response. One patient showed CR or CRi at cycle 1 day 25, five patients (some unconfirmed) at cycle 1 day 28, one patient at day 50, and three patients at cycle 2 day 28 (day 56).

The median time to CR or CRi was not observed in the treatment follow-up period, which indicates that more than 50% of patients did not experience CR or CRi by the time of treatment discontinuation or last on-treatment assessment.

6.4.10.3 Overall Survival

Study HBS407 was a single arm study. Problems with single arm trials include: 1) limitation of efficacy analysis to response rate and response duration, 2) inadequacy of ability to interpret time-to-event endpoints, such as progression-free survival and overall survival, 3) inability to perform a comprehensive safety evaluation due to lack of ability to attribute adverse events, 4) often smaller in size compared to randomized clinical trials.

Overall survival was defined by the applicant in the protocol as the time from the entry onto the trial date (date informed consent signed) to death from any cause. Patients who did not die had their survival times censored on the date of last contact.

The median length of OS for all patients was 139 days (95% CI: 99 – 163, N=65). The median length of OS for patients whose disease achieved CR or CRi was 230 days (95% CI: 71 – 321, N=10) compared to 142 days (95% CI: 110 – 167, N=55) for patients

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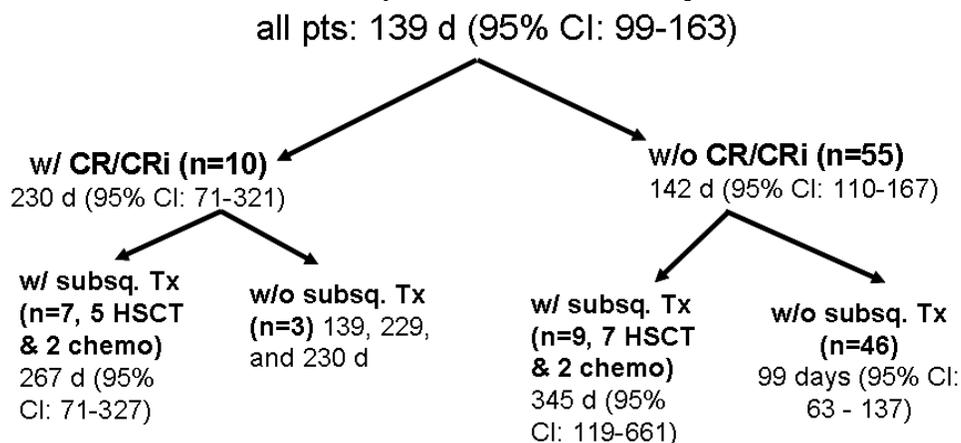
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whose disease did not achieve CR or CRi. Survival times (days) for the 10 patients with CR or CRi were 71, 139, 163, 229, 230, 230, 267, 321, 327, and 699 (censored). Most (70%) of CR+CRi patients survived at least 7 months.

In the 7 of 10 patients whose disease achieved CR or CRi and received subsequent anti-leukemia therapy (5 HSCT and 2 subsequent chemotherapies), the median OS was 267 days (95% CI: 71 – 327), and for the 3 patients who did not receive any subsequent anti-leukemia therapy, the survival times were 139, 229, and 230 days.

For 9 out 55 patients whose disease did not achieve CR or CRi but received subsequent anti-leukemia therapy (including HSCT), the median OS was 345 days (95% CI: 119 - 661). For 46 out 55 patients whose disease did not achieve CR or CRi and did not receive subsequent anti-leukemia therapy (e.g., HSCT), the median OS was 99 days (95% CI: 63 - 137). These data suggest that the median OS for patients whose disease did not achieve CR or CRi but they were able to receive HSCT was longer than patients whose disease achieved CR or CRi and underwent HSCT. Figure 8 summarized the median length of OS.

Figure 8. Median Length of Over Survival in Different Groups of Patients Based on CR or CRi Achievement and post-VSLI HSCT in Study HBS407



Source: FDA reviewer's analysis

The median OS in patients with PS 2 or 3 (N = 15) was 63 (range 17 - 110) days; whereas, the median OS in patients with PS 0 or 1 (N = 50) was 155 days (range 119 - 230).

Figure 9 presents the K-M plots of overall survival for the treated Population. Figure 10 presents the K-M plots of overall survival for the treated Population by response (CR or CRi) versus no-response. Table 29 demonstrates the K-M estimates of overall survival

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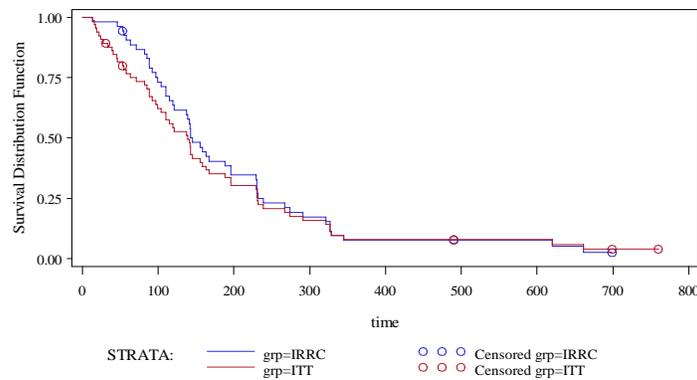
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rates at 180 days and 360 days in the treated population. In a responder analysis, patients who achieved CR or CRi tend to have improved OS (but not statistically significant by log-rank test because of the sample size) within a short period (K-M survival rate of 70% for responders versus 29% for non-responders at half year), but no benefit is observed in long term (K-M survival rate is approximately 7-10% for both responders and non-responders at one year).

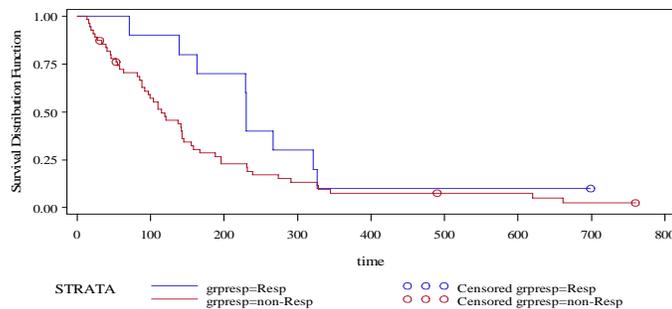
In addition to the known bias associated with responder analysis in single arm studies, heterogeneous baseline conditions and small sample size makes it difficult to draw a valid conclusion that patients had longer survival because of Marqibo. The summary of medical histories for five patients with the longest survival are provided below, which clearly shows lack of evidence that Marqibo was the cause of long survival.

Figure 9. Kaplan-Meier Plot of Overall Survival



Source: FDA statistics reviewer's analysis

Figure 10. Kaplan-Meier Plot of Overall Survival by Response (CR or CRi) versus No-response



Source: FDA statistics reviewer's analysis

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Table 29. K-M Estimates of OS Rates at 180 days and 360 days for Treated Population

Group	Sample size	Estimated OS (std) (%)		Logrank test of equality over strata
		180 days	360 days	Chi-square (p-value)
Treated population	65	35.1 (6.0)	8.0 (3.4)	0.36 (0.5478)
Treated responders	10	70 (14.5)	10 (9.5)	2.8(0.0933)
Treated non responders	55	28.6 (6.2)	7.6 (3.7)	

Source: FDA statistics reviewer's analysis

6.4.10.3.1 Patients with No Report of Death at Data Cut-off

Out of 65 patients who were enrolled in Study HSB407, 60 died with documented death dates. For 5 patients, death dates were not reported at the time of data cut-off. Only one out of these 5 patient (0217-0781) achieved CRi after Marqibo and underwent allogeneic HSCT. Four out of these 5 patients did not respond to Marqibo. These patients include:

- 0194-0062: 83 year-old female with pre-B-ALL, no response to Marqibo, withdrew consent after two cycles, last contact (b) (6)
- 0034-0121: 42 year-old female with pre-B-ALL, no response to Marqibo, discontinued study after two cycles due to lack of response and peripheral neuropathy in her fingers, received matched related allogeneic HSCT, alive at least 12 months after HSCT, last contact (b) (6)
- 0026-0398: 23 year-old female with pre-B-ALL, no response to Marqibo, withdrew consent only after one dose of Marqibo, no more Marqibo administered due to gum bleed and generalized weakness, no documented survival follow-up.
- 0193-0691: 28 year-old female with pre-B-ALL, due to receiving steroid was taken off the study after one dose of Marqibo, received matched unrelated HSCT five months after the first and only dose of Marqibo, the chemotherapy before transplant was not reported, patient was alive at 24 months survival follow-up, last contact (b) (6)

6.4.10.3.2 Long-term survivors

Four patients had overall survival in excess of 1 year and were considered by applicant as "potential long-term survivors as a result of VSLI" (page 73 summary of clinical efficacy). An additional patient, not evaluable according to the IRRC, was a long-term survivor making a total 5 long-term survivors in study HBS407. Figure 11 (provided by applicant) depicts the OS for each patient in the treated population. It demonstrates the existence of 5 (7.7%) long-term (greater than 1 year) survivors following VSLI salvage therapy. The medical histories of these five patients were reviewed, extracted from CRFs and summarized below. This reviewer disagrees with the applicant about the conclusion that the long term survivorship was a result of Marqibo.

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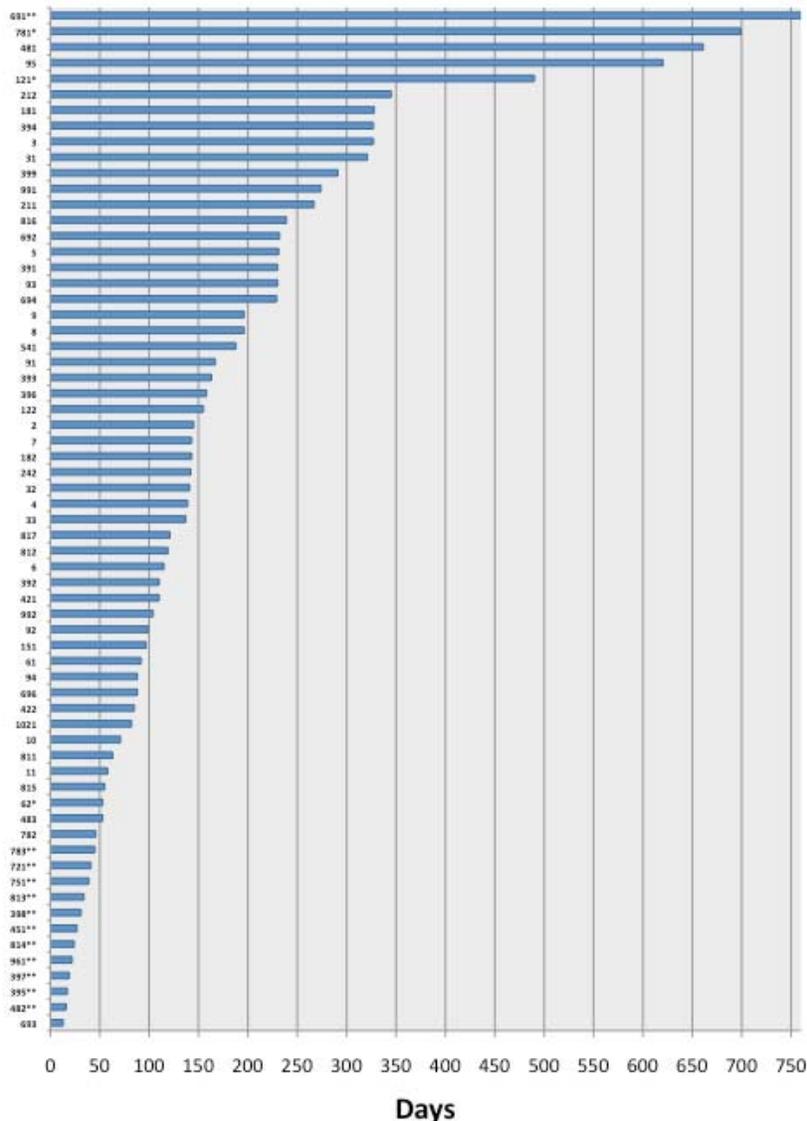
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In ODAC, applicant reported that 2 out of 65 patients were alive by March 21, 2012. According to the applicant, one of the two patients responded to Marqibo, underwent HSCT, relapsed several months after HSCT and currently receives Marqibo on a compassionate use. The applicant did not provide details about the other live patient, who might be one of the two patients whose disease did not achieve CR or CRi, nevertheless underwent HSCT (Table 13)

Figure 11. Individual Patient Overall Survival in the Treated Population



(Source: Module 5, HBS407 CSR, Listing 16.2.3.7.1)

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According to the following brief reviews of clinical histories of CRFs of these five patients, the isolated effect of Marqibo on these overall survival rates is unclear and unconfirmed. Indeed, by labeling these patients as “long-term survivors as a result of VSLI”, the applicants underscores the weakness of evaluating survival in such single arm study and furthermore questions the value of achievement of CR or CRi as only one patient (#781) out of these five patients achieved CRi.

Applicant reported that response assessments were lacking for two patients (#481, #95). CRF review revealed that patient 95 had >25% blast in bone marrow after 4 doses of Marqibo and discontinued due to severe neuropathy after 3 more doses of Marqibo and refused to have more bone marrow biopsy exam. This patient was followed by his local oncologist and received methotrexate, L-asparaginase and transfusion support and lived approximately 19 months after the last dose of Marqibo. To this reviewer, the contribution of Marqibo to this patient survival is minimal at the best.

One patient (#691) only received a single dose of Marqibo with dexamethasone and was withdrawn from the study due to receipt of concomitant dexamethasone and underwent the second allogeneic HSCT. One patient (#212) showed only stable disease after receiving Marqibo. For this patient, the initial diagnosis of ALL was not clear, patient received autologous transplant after first relapse, bone marrow at staging showed 0% blast and biopsy of paraspinal mass resulted in diagnosis of precursor T-cell leukemia. This patient had persistent extramedullary disease after enrollment, discontinued study HBS407 due to Grade 3 neuropathy, and subsequently received more anti-leukemia therapies as well as allogeneic HSCT.

- 1) **Patient 691** was a 28 year-old white woman with Ph- ALL. She achieved an initial remission in response to first-line therapy that included 10 different chemotherapy drugs including standard VCR. Following a first relapse, she received first salvage therapy consisting of 5 drugs including standard VCR. She underwent a HSCT in second remission following myeloablative therapy with busulfan and cyclophosphamide. Following a second relapse after HSCT, she was enrolled in study HBS407 and received a single 4 mg dose of VSLI as second salvage therapy. *She was withdrawn from the study due to receipt of concomitant dexamethasone and prior to protocol specified disease assessment.* Shortly after study withdrawal, she underwent her second HSCT with resultant long-term survival.
- 2) **Patient 781** (last patient in Table 26) was a 22 year-old white woman with Ph- ALL. She achieved an initial remission in response to first-line therapy that included 6 different chemotherapy drugs including standard VCR and asparaginase. Following a first relapse after approximately 28 months of remission, she received first salvage therapy consisting of 8 drugs including standard VCR. Following a second relapse, she received second salvage therapy consisting of 3 drugs including a non-VCR vinca alkaloid but was refractory to response. She was enrolled in study HBS407 and received 7 doses of VSLI totaling 25.2 mg as third salvage therapy. She achieved a CR and a confirmed CRi that was followed by a HSCT with resultant long-term survival.

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- 3) **Patient 481** was a 75 year-old white woman with Pre-B Ph- ALL. Her past medical history is notable for non-Hodgkin's lymphoma treated with 2 lines of therapy prior to the diagnosis of ALL. She achieved an initial remission for her ALL following 2 lines of therapy each consisting of 3 different chemotherapy drugs (first line: cyclophosphamide, chlorambucil, and prednisone, second line: cytarabine, methotrexate and purinethol). Following the first ALL relapse after being approximately in remission for one year, she received second salvage therapy consisting of 9 chemotherapeutic agents including standard VCR. Following the second ALL relapse after being approximately 9 years in remission, she received third salvage therapy consisting of 8 drugs including standard VCR. Following the third ALL relapse, she was enrolled in study HBS407 and received 2 doses of VSLI totaling 8.24 mg as fourth salvage. Patient discontinued the study due to hyponatremia (Na = 119) secondary to syndrome of inappropriate antidiuretic hormone (SIADH) and continued to complain of worsening peripheral neuropathy in the subsequent 12 months follow up. Applicant reported that "response assessment was lacking"; however, review of the CRF revealed the result of the bone marrow biopsy at the end of the study visit read by both local and central pathologists as persistent M3 marrow with approximately 90% blasts. This result clearly indicate the lack of response to Marqibo. Applicant also reported that "she was a long-term survivor without report of any post-VSLI therapy"; however, in the CRF (page 202, the row before the last), it is written "Did patient receive any subsequent therapy? Yes, Cortisone from (b) (6) and Chemotherapy from 30". This patient died approximately 21 months after the last dose of Marqibo during which time she received supportive care and other available anti-leukemia therapies.
- 4) **Patient 95** was a 27 year-old Hispanic man with Pre-B Ph- ALL. He achieved an initial remission in response to first-line therapy that included 7 different chemotherapy drugs including standard VCR. Following a first relapse after being approximately 5 years in remission, he received first salvage therapy consisting of 8 drugs including standard VCR. He underwent an autologous HSCT in second remission following myeloablative therapy with total body irradiation, etoposide and cyclophosphamide. Following a second relapse after being approximately 2 years in remission, he was enrolled in study HBS407 and received 7 doses of VSLI totaling 34.3 mg as second salvage therapy. Patient received several pRBC and platelet transfusions during the study. Patient discontinued the study due to weakness and slow gate secondary to neuropathy. Response assessment is lacking; cycle 1 day 28 bone marrow biopsy showed >25% marrow and patient refused to undergo another bone marrow biopsy after three more doses of VSLI and before discontinuation of the study. The applicant reported that "the patient was a long-term survivor without report of any post-VSLI therapy"; however, in the CRF it is reported that for the 12 months following treatment with Marqibo, "patient has stable disease not CR/CRp. Followed monthly by local physician and receiving blood support, methotrexate, L-asparaginase; No stem cell transplant". This patient died approximately 83 weeks after the last dose of Marqibo during which time he received supportive care and other available anti-leukemia therapies.
- 5) **Patient 212** was a 34 year-old black man with T-cell lymphoma as the reported initial diagnosis in CRF and later clarification of diagnosis to Ph- ALL. However, "remote auto stem cell transplant" reported as medical history and presence of only extramedullary disease at study entry are more consistent with diagnosis of relapsed lymphoma than leukemia. He achieved an initial remission in response to first-line therapy that included 6 different chemotherapy drugs including standard VCR. Following a first relapse, he received first salvage therapy consisting of one cycle of 4 drugs (carmustine, etoposide, cytarabine and melphalan) as preparatory regimen for peripheral blood autologous

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HSCT. Following a second relapse, he was enrolled in study HBS407 with protocol exemption due to extramedullary ALL with a paraspinal, a midpole renal, a left side medial renal and a right renal masses (bone marrow was negative for ALL and CT guided biopsy of para-spinal mass showed precursor T-lymphoblastic leukemia). Patient received 11 doses of VSLI totaling 49 mg as second salvage therapy. Patient's paraspinal and midpole renal lesions persisted (i.e. no CR) in radiographic evaluations. Residual T-ALL from fine needle aspiration of paraspinal mass was also documented after 8 doses of VSLI. Patient discontinued the study due to Grade 3 neuropathy. This patient's best response was documented as stable disease. Approximately 2 months after the end of therapy visit, patient received cytarabine, mitoxantrone, etoposide and prednisone. The patient underwent allogeneic HSCT with matched unrelated donor four months later and died two months after HSCT due to transplant-related causes.

6.4.10.4 Leukemia-free Survival

Because of small sample size this endpoint was not analyzed.

6.4.10.5 Time to Peripheral Blast Clearance

Because of small sample size for the time to peripheral blast clearance, this endpoint was not analyzed.

6.4.10.6 Time to Bone Marrow Blast Clearance

Because of small sample size for the time to bone marrow blast clearance, this endpoint was not analyzed.

6.4.10.7 Time to Extramedullary Disease Resolution

Because of small sample size for the time to extramedullary disease resolution, this endpoint was not analyzed.

6.4.10.8 Number and Proportion of Patients Who Received post-VSLI HSCT

Twelve patients (18%), in Study HBS407, underwent HSCT after receiving Marqibo (Table 30). Five out of these 12 (8% of all) patients achieved CR/CRi after Marqibo administration and prior to HSCT. The rest of 7 patients who received HSCT, their disease did not achieve CR or CRi to Marqibo.

Among patients who did not respond to VSLI but underwent HSCT, post-transplant survival ranged from 5.7 to 19.3 weeks. The post-transplant survival was longer in the patient population who underwent HSCT after their disease achieved CR or CRi to VSLI (19.8 - 41.3 weeks). Again, it should be noted that the sample size was very small and this type of responder analysis in a single arm study is prone to a significant bias. The ALL in two of the three recipients of HSCT for whom death dates were not reported at the time of last survival follow-up did not achieve CR or CRi in response to Marqibo.

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Based on these data, this reviewer concludes that response to Marqibo neither correlates with nor predicts the rate of subsequent HSCT in this patient population. “bridge to transplant” cannot be claimed as a valid clinical endpoint on the basis of study HBS407 data because several patients underwent HSCT irrespective of their response status to Marqibo.

However, the data provided in this NDA submission may suggest the positive correlation between the outcome of HSCT (i.e. prolonged survival) and response to Marqibo.

The observation that 8% of these heavily pre-treated patients received Marqibo as a single agent in an out-patient setting and their disease achieved CR or CRi and they were able to be eligible and undergo HSCT is considered by some leukemia specialists, including a few of ODAC members, as a meaningful clinical benefit.

Table 30. Post-VSLI HSCT in Study HBS407 and Duration of Survival after Transplant (days)

Patient ID	Response to Marqibo before HSCT	Duration of Survival after Transplant (days)
0026-0393	CRi	79 d (~ 2.5 mo)
0026-0391	CRi	118 d (~ 4 mo)
0192-0211	CRp	175 d (~6 mo)
0063-0003	CRi (unconfirmed)	279 d (~9 mo)
0217-0781	CRi	No report of date of death
0063-0008	No response	40 d (~1 mo)
0106-0812	No response	42 (~ 1.5 mo)
0192-0212	No response	64 d (~ 2 mo)
0063-0009	No response	128 d (~4 mo)
0026-0399	No response	135 d (~ 4.5 mo)
0193-0691	No response	No report of date of death
0034-0121	No response	No report of date of death

Source: FDA statistics reviewer’s analysis

6.4.11 Other Endpoints: Response Based on The Prior Lines of Treatment

The most used chemotherapy agents for the first and the second treatment lines in both responders and non-responders were vincristine, cyclophosphamide, doxorubicin, methotrexate and cytarabine. There was no statistically significant difference between responders and non-responders with respect to the prior anti-leukemia agents.

There was also no significant difference in the rate of CR/CRi achievement in patients who received asparaginase products in prior lines of therapy compared with the ones who did not. It seems that the history of use of asparaginase or lack of it was mainly

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driven by the institution and treating physician than patients' age or disease characteristics.

It appears that patients being treated previously on pediatric ALL protocols or not did not have positive or negative impact on the rates of CR/CRi achievement.

6.4.12 Subpopulations

The applicant reported that adult patients were screened for enrollment into study HBS407 based on a lack of available, standard therapies for Ph- ALL in second or greater relapse or that has progressed following 2 or greater lines of anti-leukemia therapy. However several patients regardless of response or lack of response to Marqibo received subsequent anti-leukemia therapies such as L-asparaginase, methotrexate, corticosteroids and multi-agent chemotherapy regimens pre-transplant (See Table 12 and Section 6.4.10.3.2).

6.4.13 Analysis of Clinical Information Relevant to Dosing Recommendations

Patients in the treated population received a median of 4 doses of VSLI (range 1-18) with median individual absolute dose size of 4.12 mg (range 3.14 - 5.51 mg). The median dose size per kg was 0.06 mg/kg (range 0.04 - 0.08 mg/kg). The median dose density was 2.25 mg/m²/week (range 0.94-2.29 mg/m²/week).

Sixty-five of 358 (18.2%) infused doses of VSLI were dose reduced. See also Section 6.4.7.

6.4.14 Discussion of Persistence of Efficacy and/or Tolerance Effects

See Sections 6.1 and 6.4.9.

6.4.15 Additional Efficacy Issues/Analyses

The applicant indicated that the efficacy response rate (CR+CRi) induced by VSLI in adults with advanced, relapsed and/or refractory Ph- ALL is comparable to those for clofarabine in pediatric ALL and nelarabine in adult T-cell ALL (Table 31).

Clofarabine was given accelerated approval in 2004 for the treatment of pediatric relapsed or refractory ALL after at least 2 prior regimens. CR+CRp rate was approximately 20%. Responses were seen in both pre-B and T-cell immunophenotypes of ALL.

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Nelarabine was given accelerated approval in 2005 for the treatment of patients with T-cell ALL and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. The rate of CR+CR* (which was defined as CR without complete hematologic recovery) was approximately 21%. Nelarabine was approved for both adult and pediatric patients with T-cell ALL.

Table 31. Agents with Accelerated Approval for Relapsed and/or Refractory ALL

Clofarabine (Clolar) - 2004	Nelarabine (Arranon) - 2005
Pediatric relapsed or refractory B- and T-Cell ALL after at least 2 prior regimens	T-cell ALL and T-cell lymphoblastic lymphoma refractory to or relapsed after greater than or equal to 2 chemotherapy regimens
CR+CRp in 10/49 (20.4%) - CR 6/49 (12.2%) - CRp 4/49 (8.2%)	CR+CR* in 6/28 (21.4%) - CR 5/28 (17.9%) - CR* 1/28 (3.6%)

Source: Clolar package insert (Genzyme Clolar PI 2008); Arranon package insert (GlaxoSmithKline Arranon PI 2009); and NDA 202497 Module 5, HBS407 CSR, Tables 14.2.1 through 14.2.2 and Table 14.2.5.3.

7 Review of Safety

7.1 Safety Summary

The nature and pattern of AEs in subjects treated with VSLI were similar to those known to be associated with VCR administration. No new or unexpected AEs were observed with VSLI. The overall frequency and severity of these AEs did not appear to be superior to vincristine. The majority of patients (56.4%) reported AEs prior to receiving the first dose of VSLI. Overall, the most frequently reported pretreatment AEs were under the Blood and Lymphatic System Disorders (17.8%) and Metabolism and Nutrition Disorders (16.8%) SOCs. The most frequently reported pretreatment AEs were fatigue (12.9%), thrombocytopenia (10.9%), anemia (7.9%), hypokalemia (5.9%), and hypomagnesemia (5.9%). Other pretreatment AEs of note included constipation (3.0%) and neutropenia (3.0%).

A total of 83 patients from two single arm ALL trials received Marqibo at a dose of 2.25 mg/m². Approximately 96% of patients had an adverse event of Grade 3 or higher, 76% of patients reported serious AEs, 29% of patients had AEs with outcome of death and 28% had AEs leading to discontinuation.

Vincristine's major toxicity is neuropathy. The applicant is suggesting that Marqibo is better tolerated than vincristine with relation to AEs. However, again, due to lack of a randomized trial, it is difficult to support any advantage in safety. Marqibo's neuropathy

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safety profile from the two single arm ALL trials showed that 87% of patients reported neuropathy of any grade, 33% reported neuropathy related AEs of grade 3 or higher, 13% suffered of serious adverse events of neuropathy, and 10% discontinued study treatment due to peripheral neuropathy.

The tolerability of Marqibo can be questioned by the number of dose adjustments, which include missed dose in 21% of patients, dose reduction and dose delay in 22% and 6% of patients, respectively.

Patient entered into study HBS407 were heavily pretreated and had poor prognosis. Nevertheless, 23% of patients died during the treatment period. The single arm trial precludes any ascertainment of cause of death.

7.2 Standard Vincristine Dosing and Toxicity

The long-standing clinical experience with standard vincristine describes a safety profile most notable for neuropathy and myelosuppression. Sensory, motor and autonomic neuropathy are common, and are cumulative. Symptoms of neuropathy include hypoesthesia, hyperesthesia, paresthesia, hyporeflexia, areflexia, neuralgia, jaw pain, decreased vibratory sense, cranial neuropathy, ileus, burning sensation, arthralgia, myalgia, muscle spasm or weakness, both before and during treatment. Orthostatic hypotension may occur. Vincristine-related neuropathies are reversible in 25-80% of events after discontinuation depending on event severity, with diminishment of symptoms typically over several months to years although low-level residual symptoms may persist.²¹

Dosing of vincristine (VCR) has changed since its initial approval. In a study by Carbone and colleagues²², patients were treated with weekly IV infusions of VCR. At individual doses below 0.03 mg/kg (2.1 mg for a 70 kg human) toxicity was occasionally observed, but increased in frequency and severity linearly as the dose was increased. At the 0.075 mg/kg dose level, an estimated dose of approximately 5 mg for a 70 kg human, the majority of subjects experienced Grade 2-3 toxicity. These moderate and severe toxicities included alopecia, paresthesias, motor weakness, and myalgia.

In the publications by DeVita and colleagues, describing a National Cancer Institute (NCI) clinical study investigating combination therapy for Hodgkin's lymphoma^{23, 24}, the dose of standard VCR was not capped. Responses were clinically significant and cures were reported. However, the development of sensory and motor neuropathy suggested the need for decreased doses of VCR. Lower doses of VCR were associated with a reduction in tumor response but equally, a reduction in neurotoxicity including debilitating motor neurotoxicity.²⁵ The link between efficacy and toxicity had been established and the narrow therapeutic index of VCR had been appreciated. Lower

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grade neurotoxicity tended to improve and resolve more quickly than higher-grade toxicity.

The first published report of dose capping at 2 mg came from Moore and colleagues at Stanford in 1973.²⁶ While attempting to replicate DeVita's NCI experience in Hodgkin's lymphoma, these investigators noted the severe neurotoxicity that developed with VCR at 1.4 mg/m² administered on days 1 and 8 of a 28-day cycle. The authors described the loss of deep tendon reflexes and foot drop in all study patients. In the study by Haim and colleagues²⁷, designed specifically to investigate the neurotoxicity of uncapped VCR (mean dose of 2.55 mg in men and 2.29 mg in women), neuropathy was occurred in 92% of patients. This rate of neuropathy was attributable to two key factors, the high dose of VCR (greater than 2 mg per dose in 90% of patients) and the prospective nature of the study. It was believed that the emphasis on careful and complete neuropathy data collection impacted the reported incidence. Table 32²⁷ summarizes the spectrum of neurotoxicity symptoms found in this population of lymphoma patients. Approximately 30% of patients who made it to cycle 8 received a VCR dose greater than 2 mg. Grade 3 or 4 constipation was observed in 10% patients and after a single dose in 7%.

Table 32. Symptoms of Neurotoxicity Associated with Full Dose Vincristine in 104 Lymphoma Patients

Symptom	Number of Subjects (%)
Paresthesia/ dysesthesia	81 (78)
Motor weakness	
Overall	40 (38)
Upper extremities	32 (31)
Lower extremities	26 (25)
Muscle cramps	47 (45)
Muscle/ bone pain	24 (23)
Autonomic	
Constipation (± abdominal pain)	61 (59)
Urinary dysfunction	3 (3)
Erection/ ejaculation dysfunction	9/59 (15)
Symptoms of postural hypotension	15 (14)
Cranial nerves	
Jaw pain	25 (24)
Disturbance of taste	9 (9)
Hoarseness and unilateral cord paresis	1 (1)
96 subjects (92%) reported at least one symptom	

Source: NDA 202497

Though no group or committee recommended or authorized vincristine dosing guidelines, at that time, a community-wide practice emerged of capping the adult dose of vincristine at 2 mg per infusion. The 2 mg dose cap remains today and is espoused in

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practice guidelines and employed in major ALL, NHL, and Hodgkin's lymphoma clinical studies. Sixteen of the 23 major studies published between 1993 and 2005 employed either a fixed 2 mg VCR dose or applied a 2 mg per dose cap (Table 3).

While VCR is widely known to be associated with alopecia and skin necrosis (in the event of extravasation during infusion), neurotoxicity is the dose-limiting side effect. Vincristine-induced neurotoxicity manifests as a peripheral, symmetric mixed sensory, motor, and autonomic polyneuropathy.^{28, 29} CNS effects are rare. In the study by Gidding and colleagues, 57% of patients developed decreased or absent deep tendon reflexes, 40% developed constipation, 26% developed ileus, and 23-26% developed foot and/or wrist drop. A general predisposition for developing neuropathy has been observed in nerves previously affected by diabetes mellitus, alcohol, inherited neuropathy, and presumably neurotoxic chemotherapy.³⁰

7.3 Methods

For evaluation of safety profile of VSLI and factor it in risk-benefit analysis, it is important to consider the following factors:

1. A comprehensive safety evaluation is not possible in a single arm trial because it does not allow for attribution of adverse events.
2. Both studies HBS407 and VSLI-06 involved heavily pre-treated patients with ALL, all of whom received prior vincristine and approximately 80% of them had a history of neuropathy.

Additional AE summaries were derived as the minimum or maximum for all on-treatment assessments and presented similarly to the other time points at the end of the displayed summary tables. This allowed an assessment of either the best or worst value assessed throughout the on-treatment period. The maximum and minimum calculations used all post-baseline data, including any unscheduled assessments.

7.3.1 Studies/Clinical Trials Used to Evaluate Safety

Applicant reported that by the time of NDA 202497 submission, VSLI had been infused in 774 patients in 17 clinical studies (1 study [HBS408] ongoing) and 2 compassionate use programs (1 program ongoing). Malignancies represented in these studies include ALL, metastatic melanoma, NHL, Hodgkin's lymphoma, and lung cancer. Both adults and children have been studied.

The review of Marqibo safety profile for NDA 202497 includes the safety data from the 101 patients in Phase 1/2 Study VSLI-06 and Phase 2 Study HBS407, with particular focus on the 83 (65 in HBS407 and 18 in VSLI-06) patients who were treated with weekly VSLI at a dose of 2.25 mg/m².

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In addition to the safety data from studies VSLI-06 and HBS407, only relevant safety data was included from the metastatic melanoma supportive studies (Phase 2 Study HBS408) and Phase 1/2 Study VSLI-12. Safety data from the 13 legacy Studies are available in the respective clinical study reports (CSRs, Module 5.3 of the NDA 202497). Of the 13 legacy studies, 1 study (Study DM97-162) included 16 patients with a diagnosis of ALL who were treated with VSLI 2.0 mg/m² bi-weekly. Data from the ALL subgroup in Study DM97-162 are not included in the pooled safety analysis in this application (the initial pre-NDA meeting on April 20, 2010).

The applicant submitted a 120-day safety update report, which included data from 2 ongoing trials, as well as SAE reports received from an ongoing compassionate use. The two ongoing single arm studies include

- HBS408: A phase 2 open-label study of Marqibo in patients with metastatic uveal melanoma. There were two cohorts in this study: cohort 1 subjects received VSLI 2.25 mg/m² IV every 14 days, where 1 dose of VSLI in a 14-day period constituted 1 cycle of study treatment; cohort 2 subjects had to be metastatic disease treatment naïve and received VSLI 2.25 mg/m² every 7 days, where 2 doses of VSLI in a 14-day period constituted 1 cycle of study treatment.

-  (b) (4)

The results from neither of these two studies were relevant to this NDA proposed treatment population and therefore were not the focus of this safety review.

7.3.2 Categorization of Adverse Events

Adverse event data for studies HBS407 and VSLI-06 were reported by System Organ Class (SOC) and MedDRA Preferred Term.

7.3.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

See section 7.2.

7.4 Adequacy of Safety Assessments

7.4.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 83 patients with relapsed and/or refractory ALL received VSLI 2.25 mg/m² in study HSB407. Eighteen additional ALL patients received doses other than 2.25 mg/m² in study VSLI-06.

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Among the 83 patients who received at least one dose of VSLI 2.25 mg/m², the mean and median duration of VSLI therapy was 6.1 and 4.0 weeks, respectively (range: 1 to 23 weeks), and the mean number of VSLI infusions was 5.3 (median: 4.0), with the number of infusions ranging from 1 to 18 (Source: ISS Tables, Table 3.1.1).

For overall exposure to VSLI, see Section 6.4.7.1, 6.4.7.2, and 6.4.7.3.

Demographic characteristics, time since diagnosis of ALL, presence/absence of extramedullary disease, ECOG performance status, and percentage bone marrow blasts of the safety population were similar to such characteristics for efficacy population and were generally consistent across studies and no important trends were noted by dose of VSLI. Study VSLI-06 primarily enrolled patients with ALL with no designated lineage (ALL alone); whereas Study HBS407 enrolled patients designated as precursor B- and T-lymphoblastic leukemia, exclusively.

The dose and schedule of Marqibo in the two single arm solid tumor trials (n=53) submitted in safety update report were ranged from 1.75 mg/m² to 2.25 mg/m². The overall exposure was limited. The disease and patient population of neither of these two studies were germane to the proposed treatment population of this NDA.

7.4.2 Explorations for Dose Response

In Study HBS407, the median dose by body weight was 0.057 mg/kg (range: 0.042 mg/kg to 0.078 mg/kg) and the median dose density was 2.25 mg/m²/week (0.94 to 2.29 mg/m²/week). The median cumulative exposure to VSLI in Study HBS407 was 18.84 mg (range: 3.5 mg to 70.12 mg) (Source: ISS Tables, Table 3.1.1 and Table 3.1.3). See also Section 6.4.7.2.

7.4.3 Special Animal and/or In Vitro Testing

See Non-Clinical Pharmacology / Toxicology review.

7.4.4 Routine Clinical Testing

Routine clinical testing including pre-treatment, and on-treatment history and physical exams, as well laboratory testing including CBC and comprehensive metabolic panel were adequate.

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Evaluation of Neuropathy:

Pre-treatment (i.e., pre-VSLI) neuropathy events in studies HBS407 and VSLI-06 were analyzed using data collected from several different CRFs and divided into three categories:

- Category 1: Prior neuropathy history based on an evaluation excluding the protocol specific pre-study neurological exam (history and physical exam) data
- Category 2: Prior neuropathy history based on an evaluation including the protocol specific pre-study neurological exam data
- Category 3: Prior neuropathy history based on an evaluation including the protocol specific pre-study neurological exam data whether or not ongoing at study start

Category 1 reflects the pre-VSLI ongoing neuropathy that would have been detected without the use of a specific detailed examination intended to optimize neuropathy detection. The difference between category 2 and category 1 results reflects pre-VSLI neuropathy signs and symptoms exclusively detected by the detailed neuropathy-oriented exam. Category 3 adds the neuropathy signs and symptoms that were not ongoing at study start.

Applicant reported that in order to provide a complete basis for the evaluation of neuropathy in the study subjects, neuropathy was evaluated in 3 methods:

1. Neuropathic medical conditions by medical history,
2. Targeted neurological assessment at baseline and regular intervals (ideally before each weekly infusion) during study treatment
3. Treatment-emergent neuropathy-associated adverse events.

7.4.5 Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology review.

7.4.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See section 7.2 for a review of vincristine dose and toxicity. Other vinca alkaloids such as vinblastine and vinorelbine share similar toxicity profile. No studies in healthy human volunteers have been conducted.

7.5 Major Safety Results

As displayed in Table 33, all patients (100%) in studies HBS407 and VSLI-06 reported AEs. Overall, 80 out of 83 (96.4%) patients who received 2.25 mg/m² Marqibo reported AEs of Grade ≥3 and 75.9% (63/83) of patients reported serious AEs. A total of 89 (88.1%) patients reported at least one AEs that was considered by the investigator to be related to study treatment.

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Table 33. Overall Summary of Adverse Events

Adverse Event Category	2.25 mg/m ²			Overall Total (N=101) n (%)
	VSLI-06 (N=18) n (%)	HBS407 (N=65) n (%)	Total (N=83) n (%)	
Any Adverse Event	18 (100)	65 (100)	83 (100)	101 (100)
Any Grade ≥ 3 Adverse Event	18 (100)	62 (95.4)	80 (96.4)	98 (97.0)
Any Serious Adverse Event (SAE)	17 (94.4)	46 (70.8)	63 (75.9)	79 (78.2)
Any Adverse Event with Outcome of Death	3 (16.7)	21 (32.3)	24 (28.9)	24 (23.8)
Any Adverse Event Leading to Discontinuation	1 (5.6)	22 (33.8)	23 (27.7)	28 (27.7)

Source: ISS Tables, Table 3.2.2

AEs experienced by ≥10% of patients (overall) included constipation (57.4%), nausea (51.5%), pyrexia (42.6%), fatigue (40.6%), peripheral neuropathy (38.6%), febrile neutropenia (37.6%), diarrhea (36.6%), anemia (33.7%), decreased appetite (32.7%), and insomnia (31.7%).

7.5.1 Adverse Events Grade ≥3

Table 34 summarizes any adverse events Grade ≥3 in ≥5% of patients who received 2.25 mg/m² Marqibo in Studies HBS407 and VSLI-06 by System Organ Class. Neuropathy-related AEs are reported in Table 38 in further detail.

Table 34. Adverse Events Grade ≥3 in ≥5% of Patients Received 2.25 mg/m² Marqibo in Studies HBS407 and VSLI-06

Adverse Events Grade ≥3	VSLI-06 (N=18) n (%)	HBS407 (N=65) n (%)	Total (N=83) n (%)
Blood and Lymphatic System Disorders	12 (66.7)	35 (53.8)	47 (56.6)
Febrile Neutropenia	5 (27.8)	21 (32.3)	26 (31.3)
Neutropenia	4 (22.2)	11 (16.9)	15 (18.1)
Anemia	6 (33.3)	8 (12.3)	14 (16.9)
Thrombocytopenia	3 (16.7)	11 (16.9)	14 (16.9)
Infections	10 (55.6)	23 (35.4)	33 (39.8)
Pneumonia	0	7 (10.8)	7 (8.4)
Septic Shock	1 (5.6)	4 (6.2)	5 (6.0)
Staphylococcal Bacteremia	4 (22.2)	1 (1.5)	5 (6.0)
Neuropathy-Related AEs	3 (16.7)	24 (36.9)	27 (32.5)
Peripheral Sensory and Motor Neuropathy	1 (5.6)	13 (20.0)	14 (16.7%)
Constipation	2 (11.1)	2 (3.1)	4 (4.8)
Ileus and Colonic Pseudo-Obstruction	0	5 (7.7)	5 (6.0)
Asthenia	0	4 (6.2)	4 (4.8)
Muscular Weakness	1 (5.6)	0	1 (1.2)
Respiratory Thoracic and Mediastinal Disorders	5 (27.8)	12 (18.5)	17 (20.5)
Respiratory Distress	2 (11.1)	3 (4.6)	5 (6.0)
Respiratory Failure	1 (5.6)	3 (4.6)	4 (4.8)
General Disorders and Administration Site Condition	8 (44.4)	23 (35.4)	31 (37.3)
Pyrexia	5 (27.8)	7 (10.8)	12 (14.5)

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Adverse Events Grade ≥3	VSLI-06 (N=18) n (%)	HBS407 (N=65) n (%)	Total (N=83) n (%)
Fatigue	3 (16.7)	6 (9.2)	9 (10.8)
Pain	1 (5.6)	6 (9.2)	7 (8.4)
Gastrointestinal Disorders	8 (44.4)	13 (20.0)	21 (25.3)
Abdominal Pain	4 (22.2)	3 (4.6)	7 (8.4)
Investigations	6 (33.3)	14 (21.5)	20 (24.1)
Aspartate Aminotransferase Increased	2 (11.1)	4 (6.2)	6 (7.2)
Vascular Disorders	3 (16.7)	5 (7.7)	8 (9.6)
Hypotension	3 (16.7)	2 (3.1)	5 (6.0)
Psychiatric Disorders	4 (22.2)	5 (7.7)	9 (10.8)
Mental Status Changes	1 (5.6)	2 (3.1)	3 (3.6)
Cardiac Disorders	3 (16.7)	6 (9.2)	9 (10.8)
Cardiac Arrest	2 (11.1)	3 (4.6)	5 (6.0)
Renal and Urinary Disorders	1 (5.6)	5 (7.7)	6 (7.2)
Musculoskeletal and Connective Tissue Disorders	1 (5.6)	6 (9.2)	7 (8.4)

Source: NDA 202497, Integrated Summary of Safety Tables, Table 3.2.6

The most common treatment-related AEs judged by investigators included constipation (40.6%), peripheral neuropathy (36.6%), nausea (22.8%), hypoesthesia (19.8%), paraesthesia (18.8%), neutropenia (17.8%), fatigue (16.8%), anemia (12.9%), thrombocytopenia (10.9%), and abdominal pain (11.9%). The incidences of these events were similar across dose groups.

Safety update report was submitted based on the results from two single arm studies in patients with metastatic uveal melanoma and pediatric population with advanced cancer. The disease and patient population of neither of these two studies were germane to the proposed treatment population of this NDA.

7.5.2 Deaths

All patients in Study HBS407 were to be followed for survival, while no long-term follow-up was conducted for Study VSLI-06, hence the number of deaths in Study VSLI-06 is underreported. Sixty out of 65 patients in study HBS407 died during the follow up period. In study HBS407, 15 (23.1%) patients died during the treatment period (i.e. deaths that occurred after the first dose infusion date through last dose date plus 30 days), Table 35.

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Table 35. Overall Summary of Deaths

Time of Death	2.25 mg/m ²		
	VSLI-06 (N=18) n (%)	HBS407 (N=65) n (%)	Total (N=83) n (%)
Deaths During Treatment Period	4 (22.2)	15 (23.1)	19 (22.9)
Deaths During Follow-up	2 (11.1)	45 (69.2)	47 (56.6)

Source: NDA 202497, Integrated Summary of Safety, Tables 3.2.21.1 and 3.2.21.2

As mentioned above, single arm studies preclude the causal attribution of death. Nevertheless, the most common reported cause of death in all patients was ALL (42, 64.6%). Three (3, 4.6%) additional patients died due to complications of HSCT. The remaining 15 deaths were reported to be caused by a brain infarct (1), intracerebral hemorrhage (2), liver failure (1), multi system organ failure (2), pneumonia and septic shock (3), respiratory failure (4), pulmonary hemorrhage (1), and sudden cardiac death (1) (Source: ISS Tables, Table 3.2.21.1).

A total of 24 (23.8%) patients from the pooled ALL studies reported an AE that resulted in death (Note: Four patients died during the follow-up period as a result of an AE with an onset date during the treatment period). The most common AEs resulting in death included ALL (7.9%, 8 patients), septic shock (3.0%, 3 patients), cardiac arrest (3.0%, 3 patients), and respiratory distress (3.0%, 3 patients). Neutropenia was reported as an AE with an outcome of death in 2 patients (2.0%) (Source: ISS Tables, Table 3.2.11).

7.5.3 Nonfatal Serious Adverse Events

A total of 63 of 83 patients (75.9%) who received 2.25 mg/m² VSLI reported at least one AE that was classified as serious (SAEs). In this population, the most frequently reported SAEs included febrile neutropenia (17, 20.5%), pyrexia (11, 13.3%), respiratory distress and respiratory failure (9, 10.8%), pneumonia (7, 8.4%), hypotension (6, 7.2%), peripheral sensory and motor neuropathy (6, 7.2%), cardiac arrest (5, 6%), and sepsis and septic shock (5, 6%), Table 36. It is important to note that infectious complications are common among patients with leukemia after administration of cytotoxic chemotherapies. Infectious-related SAEs were reported under several different MedDRA preferred terms, for example 2 enterococcal bacteremia, 2 staphylococcal bacteremia, one alpha hemolytic streptococcal infection, one cellulitis, one Escherichia sepsis, one infection, one klebsiella Sepsis, and one neutropenic sepsis were reported.

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Table 36. The Most Frequent (≥5%) Serious Adverse Events in The Safety Population

SAE by Preferred Term	VSLI-06 (N=18) n (%)	HBS407 (N=65) n (%)	Total (N=83) n (%)
Febrile Neutropenia	5 (27.8)	12 (18.5)	17 (20.5)
Pyrexia	7 (38.9)	4 (6.2)	11 (13.3)
Respiratory Distress & Respiratory Failure	3 (16.7)	6 (9.2)	9 (10.8)
Hypotension	4 (22.2)	2 (3.1)	6 (7.2)
Pneumonia and Fungal Pneumonia	2 (11.1)	5 (7.7)	7 (8.4)
Cardiac Arrest	2 (11.1)	3 (4.6)	5 (6.0)
Septic Shock and Sepsis	1 (5.6)	4 (6.2)	5 (6.0)
Peripheral Sensory and Motor Neuropathy	0	6 (7.7)	6 (7.2)

Source: ISS Tables, Tables 3.2.14 and 3.2.15

The most frequently reported SAEs *overall* included febrile neutropenia (23.8%), pyrexia (13.9%), and bacteremia (9.9%). Peripheral neuropathy (5.9%), abdominal pain (3.0%), constipation (3.0%) and tumor lysis syndrome (3.0%) were also reported as SAEs (Source: ISS Tables, Tables 3.2.14 and 3.2.15).

7.5.4 Dropouts and/or Discontinuations

Treatment was discontinued in all 101 patients (100%) who received VSLI in the ALL studies. Table 37 summarizes the reasons for dispositions of patients or treatment / study discontinuation. In the 83 patients who received the 2.25 mg/m² dose of VSLI in the safety population, 39.8% discontinued treatment due to disease progression, 30.1% discontinued because of AEs, 7.2% discontinued at the request of the investigator, 6.0% discontinued because of planned HSCT, and 6.0% withdrew their consent.

Table 37. Patients Dispositions in The Safety and The Overall ALL Population

Variable	2.25 mg/m ²			Overall Total, (N=101) n (%)
	VSLI-06, (N=18) n (%)	HBS407, (N=65) n (%)	Total, (N=83) n (%)	
Treatment/Study Discontinued	18 (100)	65 (100)	83 (100)	101 (100)
Response Achieved	1 (5.6)	0	1 (1.2)	2 (2.0)
Disease Progression	7 (38.9)	26 (40.0)	33 (39.8)	42 (41.6)
Adverse Event	1 (5.6)	24 (36.9)	25 (30.1)	29 (28.7)
HSCT	0	5 (7.7)	5 (6.0)	5 (5.0)
Subject Withdrew Consent	1 (5.6)	4 (6.2)	5 (6.0)	6 (5.9)
Subject Eligible for Other Treatment	4 (22.2)	0	4 (4.8)	7 (6.9)
Death	3 (16.7)	0	3 (3.6)	3 (3.0)
Investigator request	0	6 (9.2)	6 (7.2)	6 (5.9)
Other	1 (5.6)	0	1 (1.2)	1 (1.0)

Source: ISS Tables, Tables 3.2.16 and 3.2.17

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7.5.5 AEs Leading to Dose Discontinuation or Dose Modification

The most frequently reported AEs leading to study drug discontinuation in 83 patients who received 2.25 mg/m² Marqibo in studies HBS407 and VSLI-06 were peripheral neuropathy in 8 (9.6%), leukemia-related in 6 (7.2%), and tumor lysis syndrome in 2 (2.4%). AEs potentially related to neuropathy and reported each in one patient included decreased vibratory sense, facial palsy, hyporeflexia, constipation, asthenia, fatigue, and musculoskeletal pain.

Approximately one-half of the 83 patients (53%) who began treatment with 2.25 mg/m² VSLI actually received the intended prescribed dose and dosing schedule. Of the remaining patients, 17 (20.5%) missed doses, 18 (21.7%) had reduced doses, and 5 (6.0%) had delayed doses (Source: ISS Section 3.8. Adverse Events Leading to Dose Modification & ISS Tables, Tables 3.2.17, Listing 5.5 and Listing 5.8). The majority of missed doses occurred in the presence of a new AE.

More than one third of patients (6 of 17 patients, 35%) missed doses due to AEs associated with neuropathy including peripheral neuropathy, pain in extremities, facial neuralgia, and ileus. Neuropathies are the most notable adverse events associated with vincristine. The number of patients who required neuropathy-related dose reduction, dose delay and missed doses do not suggest a better toxicity profile for Marqibo than vincristine. Other AEs related to missed doses included diarrhea, thrombocytopenia, increased hepatic enzymes, and decreased weight. Four doses were missed due to patients not able to make their clinic visit, and 2 missed doses were attributed to study site decisions to wait on dosing (1 waiting for biopsy results, 1 protocol misunderstanding).

Among 18 patient who had dose reductions, the majority of AEs causing dose reductions (19 [65.5%] of 29 AEs) were associated with neuropathy including peripheral neuropathy, constipation, facial neuralgia, ileus, and decreased vibratory sense. Other AEs leading to dose reductions included increased hepatic enzymes (3 patients), decreased weight (2 patients), diarrhea, abdominal pain, Staphylococcal bacteremia, cellulitis, febrile neutropenia, hyponatremia, and fatigue (Source: ISS Tables, Table 3.2.18).

All delayed doses were associated with AEs: abdominal pain, bacteremia, altered mental status and constipation, and two events of constipation. The altered mental status was not considered study drug related; however, the other events were considered by the study investigator to be due to study medication.

7.5.6 Significant Adverse Events

As reported in Table 37, 29 of 101 (28.7%) patients discontinued treatment secondary to AEs. According to ISS Table 3.2.16, 13 of 83 (15.7%) patients who received VSLI at

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2.25 mg/m² experienced neuropathy-related AEs, which led to study drug discontinuation. In study HSB407, 10 of the 24 (41.7%) AEs given as a reason for treatment discontinuation were related to neuropathy.

The most common AEs of Grade \geq 3 were febrile neutropenia (31.7%), neutropenia (22.8%), anemia (21.8%), thrombocytopenia (21.8%), pyrexia (14.9%), and peripheral neuropathy (i.e., MedDRA preferred term neuropathy peripheral) (10.9%) (Source: ISS Tables, Table 3.2.6).

7.5.7 Submission Specific Primary Safety Concerns - Neurotoxicity

Due to the inherent mechanism of action of vincristine, neurotoxicity is experienced whether the patient receives a capped or uncapped dose. However, frequency, severity, and reversibility are affected by dose. In a study in Hodgkin's lymphoma or NHL, 114 patients were enrolled and received either a high or low dose of vincristine. The high dose group (N=67) received 4 mg of VCR at 3-week intervals and the low dose group (N=47) received 2 mg of VCR at 3-week intervals.³¹ In the low dose group, paresthesias developed in 34%, numbness in 43%, and pain in 14% of the patients. Paresthesias and numbness were mild to moderate in severity. In the high dose group, paresthesias developed in 60% (10% severe), numbness in 70% (4% severe), and pain in 62% (16% severe).

All of the patients with ALL had received prior VCR. Prior neuropathy whether or not ongoing at the time of study entry was reported by a total of 79.5% patients prior to receipt of VSLI 2.25 mg/m². Pain (32.5%), asthenia (27.7%), areflexia (24.1%), hypoesthesia (24.1%), hyporeflexia (24.1%), and paresthesia (20.5%) were the most common previous neuropathies (Source: ISS Tables, Table 1.7.1). Constipation was reported with an overall incidence of 19.3% at baseline.

The applicant utilized the descriptions of neuropathy in the prescribing information for marketed VCR products (Oncovin) to create a list of neuropathy-associated terms. In addition, the VSLI safety data were reviewed in an attempt to identify any potential neuropathy events, which may differ from those terms reported in the VCR prescribing information. It should be noted that at the time of final data production for the HBS407 and VSLI-06 CSRs, after the neuropathy term list had been finalized, additional VCR-associated neuropathy terms were recognized, which had not been included in the list. Bladder (urinary) retention (2 patients), incontinence of urine (4 patients) and erectile dysfunction (2 patients) were among additional terms.

Table 38 presents all nervous system disorders by MedRA preferred terms for all (N=101) patients with ALL (Source: ISS Tables, Table 3.2.9). In total 66 (65.3%) patients developed nervous system related AEs, of which 17 (16.8%) were \geq Grade 3 by CTCAE criteria. The most frequently reported (\geq 5%) treatment-related nervous system AEs were peripheral neuropathy 37 (36.6%), hypoesthesia 20 (19.8%), paresthesia 19

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(18.8%), areflexia 7 (6.9%), peripheral sensory neuropathy 7 (6.9%), hyporeflexia 6 (5.9%), and peripheral motor neuropathy 5 (5.0%).

Table 38. Nervous System Disorders AEs by Preferred Term, and Maximum CTCAE Grade

System Organ Class Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
NERVOUS SYSTEM	25 (24.8)	24 (23.8)	14 (13.9)	3 (3.0)	0	66 (65.3)
Neuropathy Peripheral	13 (12.9)	13 (12.9)	10 (9.9)	1	0	37 (36.6)
Hypoesthesia	12 (11.9)	7 (6.9)	1	0	0	20 (19.8)
Paraesthesia	14 (13.9)	4 (4.0)	1	0	0	19 (18.8)
Areflexia	2 (2.0)	4 (4.0)	1	0	0	7 (6.9)
Peripheral Sensory Neuropathy	2 (2.0)	4 (4.0)	0	1	0	7 (6.9)
Hyporeflexia	5 (5.0)	1	0	0	0	6 (5.9)
Peripheral Motor Neuropathy	1	0	4 (4.0)	0	0	5 (5.0)
Decreased Vibratory Sense	1	0	1	0	0	2 (2.0)
Dizziness	2 (2.0)	0	0	0	0	2 (2.0)
Headache	1	1	0	0	0	2 (2.0)
Peroneal Nerve Palsy	1	1	0	0	0	2 (2.0)
Cranial Neuropathy	0	1	0	0	0	1
Ataxia	1	0	0	0	0	1
Dysgeusia	1	0	0	0	0	1
Encephalopathy	1	0	0	0	0	1
Facial Neuralgia	0	1	0	0	0	1
Facial Palsy	0	1	0	0	0	1
Grand Mal Convulsion	0	0	0	1	0	1
Neuralgia	0	1	0	0	0	1
Burning Sensation	1	0	0	0	0	1

Source: ISS Tables, Table 3.2.9

A total of 72 (86.7%) of the 83 patients on 2.25 mg/m² VSLI reported a neuropathy-associated AE during the treatment period. The most common neuropathy-associated AEs for this patient population were constipation (56.6%), peripheral neuropathy (37.3%), paresthesia (22.9%), hypoesthesia (22.9%), asthenia (19.3%), arthralgia (18.1%), and myalgia (14.5%). Table 38 presents neuropathy-related AEs of Grade ≥3 severity and any neuropathy-related SAEs for patients being treated with Marqibo 2.25 mg/m². Each patient might have reported more than one AE.

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Table 39. Neuropathy-related AEs of Grade ≥3 Severity and Any Neuropathy-related SAEs for Patients Who Received Marqibo 2.25 mg/m² in Studies HBS407 and VSL-06

Neuropathy-Related Adverse Events	VSLI-06 (N=18), n (%)	HBS407 (N=65), n (%)	Total (N=83), n (%)
Any Grade ≥3 Neuropathy-Related AEs	3 (16.7)	24 (36.9)	27 (32.5)
Peripheral Sensory and Motor Neuropathy	1 (5.6)	13 (20.0)	14 (16.7%)
Paraesthesia and Hypoaesthesia	0	2 (3.1)	2 (2.4)
Decreased Vibratory Sense	0	1 (1.5)	1 (1.2)
Constipation	2 (11.1)	2 (3.1)	4 (4.8)
Ileus, Colonic Pseudo-Obstruction, Subileus	0	5 (7.7)	5 (6.0)
Asthenia	0	4 (6.2)	4 (4.8)
Gait Disturbance	0	1 (1.5)	1 (1.2)
Pain In Extremity	0	2 (3.1)	2 (2.4)
Areflexia	0	1 (1.5)	1 (1.2)
Arthralgia	0	1 (1.5)	1 (1.2)
Muscular Weakness	1 (5.6)	0	1 (1.2)
Any Neuropathy-Related SAEs	1 (5.6)	10 (15.4)	11 (13.3)
Peripheral Sensory and Motor Neuropathy	0	6 (9.2)	6 (7.2)
Constipation	1 (5.6)	2 (3.1)	3 (3.6)
Ileus and Subileus	0	2 (3.1)	2 (2.4)
Gait Disturbance	0	1 (1.5)	1 (1.2)
Facial Palsy	0	1 (1.5)	1 (1.2)

Source: NDA 202497, Integrated Summary of Safety, Table 3.2.20.1.8 and Table 3.2.20.1.9

7.6 Supportive Safety Results

7.6.1 Common Adverse Events

AEs experienced by ≥10% of all patients (N=101) included constipation (57.4%), nausea (51.5%), pyrexia (42.6%), fatigue (40.6%), peripheral neuropathy (38.6%), febrile neutropenia (37.6%), diarrhea (36.6%), anemia (33.7%), decreased appetite (32.7%), and insomnia (31.7%) (Source: ISS Tables, Table 3.2.4.1).

The most common treatment-related AEs included constipation (40.6%), peripheral neuropathy (36.6%), nausea (22.8%), hypoaesthesia (19.8%), paraesthesia (18.8%), neutropenia (17.8%), fatigue (16.8%), anemia (12.9%), thrombocytopenia (10.9%), and abdominal pain (11.9%). The incidences of these events were similar across dose groups. AE relationships to the treatment in a single arm study are speculative.

Treatment-related AEs with a CTCAE Grade ≥ 3 were reported in 63.4% of patients. The most frequently (≥5%) reported treatment-related AEs with a CTCAE Grade ≥ 3 were neutropenia 15 (14.9%), thrombocytopenia 8 (7.9%), anemia 6 (5.9%), febrile neutropenia 6 (5.9%), peripheral neuropathy 11 (10.9%), thrombocytopenia (7.9%), and abdominal pain 5 (5.0%), and fatigue 5 (5.0%). Again, AE relationships to the treatment in a single arm study are speculative.

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7.6.2 Laboratory Findings

Laboratory findings related to myelosuppression such as neutropenia, anemia and thrombocytopenia are expected after administration of most cytotoxic anti-leukemia therapies. In this population of relapsed and/or refractory ALL patients, the mean ANC at baseline was below the lower limit of the normal reference range. Upon initiation of VSLI therapy, mean ANC levels tended to decrease further from baseline during the course of treatment. Among ALL patients in the safety population (N=83) treated with VSLI 2.25 mg/m², the proportion of patients with Grade 0, 1, 2 or 3 ANC at baseline who progressed to Grade 2, 3 or 4 was 71.6% (53/74, 9 subjects with missing data).

Table 40 presents the data for all (N=101) patients for the shifts of non-hematologic laboratory results to worst post-baseline CTCAE toxicity grade experienced by patients during treatment. To cover all potential liver, kidney and electrolyte-related toxicities of Marqibo, Table 40 includes all patients from both studies HBS407 and VSLI-06 irrespective of dose and concomitant steroid use. The table only shows the laboratory values that had shifts from baseline to the more severe CTCAE Grade 3 or CTCAE Grade 4. The denominator for each analysis reflects subjects with at least 1 post-baseline result for that particular value. The laboratory values with the highest frequencies of laboratory shifts ≥ 1 grade were: hyponatremia with 35 of 63 (55.5%), ALT with 51 of 97 (52.6%), and hypocalcemia with 45 of 97 (46.4%). Severe toxicity that were experienced included hypocalcemia (10 of 97, 10.3%), ALT (9 of 95, 9.5%), AST (5 of 61, 8.2%), hyponatremia (5 of 63, 7.9%), hypokalemia (4 of 63, 6.3%), alkaline phosphatase (3 of 94, 3.2%), bilirubin (3 of 95, 3.2%), and creatinine 1 of 99 (1.0%).

Grade 4 toxicity was experienced by 3 subjects: decreased calcium (2 subjects) and elevated bilirubin (1 subject). No clinical AEs of Grade 4 hypocalcemia were reported. The Grade 4 hyperbilirubinemia occurred in a 24-year-old male subject who had a history of elevated bilirubin and hepatic transaminases. On study Day 29 he was found to have elevated bilirubin (25.65 $\mu\text{mol/L}$) and AST (679 U/L) and multi-organ failure. Although the AST level declined (158 U/L) by study Day 36, the bilirubin level increased further to 167.58 $\mu\text{mol/L}$ on study Day 37. Blood cultures were positive for coagulase negative *Staphylococcus* and *Candida guilliermondii*. The subject died of multi-organ failure on study Day 70.

Serious adverse renal events were reported in 3 subjects (3.0%): hemorrhagic cystitis, urinary retention, and renal failure. The subject with "renal failure" had a Grade 2 BUN elevation 2 days prior to initiation of study drug and was reported with renal insufficiency on study Day 3.

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Table 40. Chemistry Laboratory Shifts by Worst Post-Baseline CTCAE Toxicity Grade – Shifts to Grade 3 or 4 (All ALL Population, N=101)

Laboratory Value	Baseline CTCAE Toxicity Grade	Worst Post-Baseline CTCAE Toxicity Grade - Overall Population (N=101)					Total n (%)
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	
Alkaline Phosphatase	0	38 (60.3)	20 (31.7)	4 (6.3)	1 (1.6)	0	63
	1	3 (12.5)	18 (75.0)	2 (8.3)	1 (4.2)	0	24
	2	0	1	3 (60.0)	1	0	5
	3	0	0	2 (100.0)	0	0	2
	4	0	0	0	0	0	0
	Missing	0	2	0	0	0	2
ALT	0	27 (40.3)	26 (38.8)	10 (14.9)	4 (6.0)	0	67
	1	3 (13.6)	11 (50.0)	6 (27.3)	2 (9.1)	0	22
	2	0	0	2 (40.0)	3 (60.0)	0	5
	3	0	0	0	1	0	1
	4	0	0	0	0	0	0
	Missing	0	2	0	0	0	2
AST	0	15 (38.5)	20 (51.3)	2 (5.1)	2 (5.1)	0	39
	1	1 (5.9)	11 (64.7)	3 (17.6)	2 (11.8)	0	17
	2	1 (20.0)	2 (40.0)	1	1	0	5
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Bilirubin	0	62 (73.8)	14 (16.7)	6 (7.1)	2 (2.4)	0	84
	1	1 (16.7)	2 (33.3)	2 (33.3)	0	1	6
	2	0	3 (75.0)	1	0	0	4
	3	0	0	0	1	0	1
	4	0	0	0	0	0	0
	Missing	2 (100.0)	0	0	0	0	2
Calcium	0	37 (47.4)	17 (21.8)	16 (20.5)	6 (7.7)	2 (2.6)	78
	1	3 (30.0)	5 (50.0)	2 (20.0)	0	0 (0.0)	10
	2	1	1	3 (42.9)	2 (28.6)	0	7
	3	0	0	0	1	0	1
	4	1	0	0	0	0	1
	Missing	1	0	1	0	0	2
Creatinine	0	81 (88.0)	8 (8.7)	2 (2.2)	1	0	92
	1	1	3 (60.0)	1	0	0	5
	2	0	0	0	0	0	0
	3	0	0	1	1	0	2
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Potassium	0	32 (56.1)	22 (38.6)	0	3 (5.3)	0	57
	1	2	1	0	1	0	4
	2	0	0	0	0	0	0
	3	0	0	0	2 (100.0)	0	2
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
Sodium	0	26 (49.1)	22 (41.5)	0	5 (9.4)	0	53
	1	1	8 (88.9)	0	0	0	9
	2	0	0	0	0	0	0
	3	1	0	0	0	0	1
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0

Source: ISS Table 3.4.5

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In the clinical experience with VSLI, 4 subjects (4.0%) were identified with ALT/AST, bilirubin, and alkaline phosphatase levels that were consistent with Hy's Law criteria. A review of each of these cases identifies potentially confounding factors, such as prior or concomitant administration of potentially hepatotoxic drugs, the comorbidities of sepsis/hypotension/metabolic acidosis in 1 subject and the potential for leukemic infiltration of the liver in all these subjects.

7.6.3 Vital Signs

Table 41 demonstrates that, a total of 30 patients (36.1%) experienced a ≥ 30 bpm increase from baseline in heart rate while 11 patients (13.3%) experienced a ≥ 30 bpm decrease from baseline. A total of 16 patients (19.3%) experienced systolic BP > 150 mmHg or diastolic BP > 100 mmHg. Severe hypotension (i.e. systolic BP < 90 mmHg or diastolic BP < 60 mmHg) occurred in 26 patients (31.3%). A total of 37 patients (44.6%) experienced a decrease in body weight of $\geq 5\%$ from baseline.

Table 41. Abnormal Vital Sign Results Observed Any Time During On-Treatment Period (N=83)

	2.25 mg/m ²		
	VSLI-06 (N=18), n (%)	HBS407 (N=65), n (%)	Total (N=83), n (%)
Heart Rate			
< 50 bpm	1 (5.6)	0	1 (1.2)
> 120 bpm	7 (38.9)	25 (38.5)	32 (38.6)
≥ 30 bpm increase from baseline	8 (44.4)	22 (33.8)	30 (36.1)
≥ 30 bpm decrease from baseline	3 (16.7)	8 (12.3)	11 (13.3)
Blood Pressure			
SBP > 150 mmHg or DBP > 100 mmHg	3 (16.7)	13 (20.0)	16 (19.3)
SBP > 200 mmHg or DBP > 110 mmHg	0	1 (1.5)	1 (1.2)
SBP < 90 mmHg or DBP < 60 mmHg	6 (33.3)	20 (30.8)	26 (31.3)
Respiration Rate			
< 8 breaths/min	0	0	0
> 40 breaths/min	0	0	0
Temperature			
> 38.3°C	1 (5.6)	12 (18.5)	13 (15.7)
Change in Weight			
$\geq 5\%$ increase from baseline	0	1 (1.5)	1 (1.2)
$\geq 5\%$ decrease from baseline	9 (50.0)	28 (43.1)	37 (44.6)

Source: ISS Table 3.5

7.6.4 Electrocardiograms (ECGs)

In study HBS407, electrocardiograms were analyzed from patients who had undergone up to 3 courses of therapy with VSLI. The variables (time intervals) measured were heart rate, PR interval, QRS duration, QT interval, and QTcF (Corrected QT Interval

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using Fridericia's formula) duration. ECGs were reviewed by a cardiologist. The primary focus of the analysis was the change from baseline (Course 1, Day 1, pre-dose) in the QTcF. Electrocardiograms were evaluated at the following time points; Screening, pre-dose and 2 to 4 hours on Course 1, Days 1, 7, 15 and 22, pre-dose and 2 to 4 hours on Course 2, Days 1, 7, 15 and 22, pre-dose and 2 to 4 hours on Course 3, Day 1, and End of Therapy.

A total of 171 ECGs from 20 patients included in the NDA report. There was no apparent trend toward EKG changes or QT prolongation as evidenced by 12-lead ECGs (Source: Module 5, HBS407 CSR, Appendix 16.1.12 [central ecg report]). The change from the mean pre-dose QTcF duration on Course 1, Day 1 to the 2-4 hour post-dose QTcF duration was 4.3 msec. Two male subjects had a QTcF value greater than 450 msec. One subject (0814) had a baseline QTcF of 445 msec and a QTcF of 476 msec on Course 1, Day 8, pre-dose. The second subject (0816) had a baseline QTcF of 404 msec and a QTcF of 454 msec on Course 2, Day 22, pre-dose.

7.6.5 Special Safety Studies/Clinical Trials

See section 7.5.7.

7.6.6 Immunogenicity

See the non-clinical reviews.

7.7 Other Safety Explorations

7.7.1 Dose Dependency for Adverse Events

Because of small sample size, any attempt to compare relative AE frequencies across dose groups would not be accurate as the lower (1.5-2.0 mg/m²) and upper (2.4 mg/m²) dose levels were only given to 11 and 7 patients, respectively, in study VSLI-06.

However, three patients experienced DLT at a dose of 2.4 mg/m², which suggest either a very steep dose-response curve with respect to toxicity (i.e. narrow therapeutic index) or an inadequate characterization of dose dependency for adverse events.

7.7.2 Time Dependency for Adverse Events

See Section 7.7.3 below.

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7.7.3 Drug-Demographic Interactions

Doses of VSLI have ranged from 0.5 mg/m² (Study IDP93-C01) to 2.8 mg/m² (Study IDP93-C01) and dose regimens ranged from single doses to dosing every 3 weeks, every 2 weeks (biweekly), and every 7 days (weekly). The incidence of selected AEs reported for all VSLI studies is provided in the ISS Comparative AE Table of all VSLI Studies (Source: Module 5, Section 5.3.5.3, pages 3634 -3652).

Comparison of AEs across studies of VSLI is difficult, due to the variety of dose ranges and dosing schedules used in the different studies with diverse underlying disease characteristics. The indications for use varied widely between studies, and included (in addition to ALL) NHL, Hodgkin's lymphoma, relapsed small cell lung cancer, pancreatic cancer, metastatic colon cancer, and malignant melanoma. Comparison is further complicated by the study of pediatric age patients, young adults, and elderly adults. In some studies VSLI was used as a single agent, and in others it was part of a multi-drug regimen.

Because all of the studies have been single arm trials, it is difficult to support any advantage in safety of Marqibo without a direct comparison to vincristine. Nevertheless, in general, the type and incidence of AEs reported in all clinical studies were consistent with the rate of AEs reported in the ALL studies HBS407 and VSLI-06.

7.7.4 Drug-Disease Interactions

See Section 7.5.3. above.

7.7.5 Drug-Drug Interactions

No clinically significant drug-drug interaction was noted in the study HBS407 and VSLI-06. For detailed review of potential drug-drug interactions, see clinical pharmacology review.

7.8 Additional Safety Evaluations

7.8.1 Human Carcinogenicity

VSLI is a cytotoxic chemotherapy with similar carcinogenicity profile to other chemotherapeutic agents. For further information for human and animal carcinogenicity, see vincristine label and non-clinical pharmacology toxicology review.

7.8.2 Human Reproduction and Pregnancy Data

There is limited or no data on human reproduction and pregnancy related to VSLI. See non-clinical pharmacology toxicology review.

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7.8.3 Pediatrics and Assessment of Effects on Growth

There is limited or no data on assessment of effects of VSLI on growth. Vincristine is a common component of multi-drug chemotherapeutic regimens for childhood ALL.

7.8.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

This category is not relevant to this drug, disease setting and patient population.

7.9 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Marqibo is not an approved drug. There is no postmarketing experience related to Marqibo.

9 Proposed Confirmatory Study

The proposed confirmatory study (TTX404) is a phase 3, multicenter, randomized study to evaluate the substitution of Marqibo for standard vincristine sulfate injection in the induction, intensification, and maintenance phases of combination chemotherapy in the treatment of patients ≥ 60 years old with newly diagnosed acute lymphoblastic leukemia (ALL). The primary endpoint of the study is OS with HR = 0.70. The proposed sample size is 348. (b) (4)



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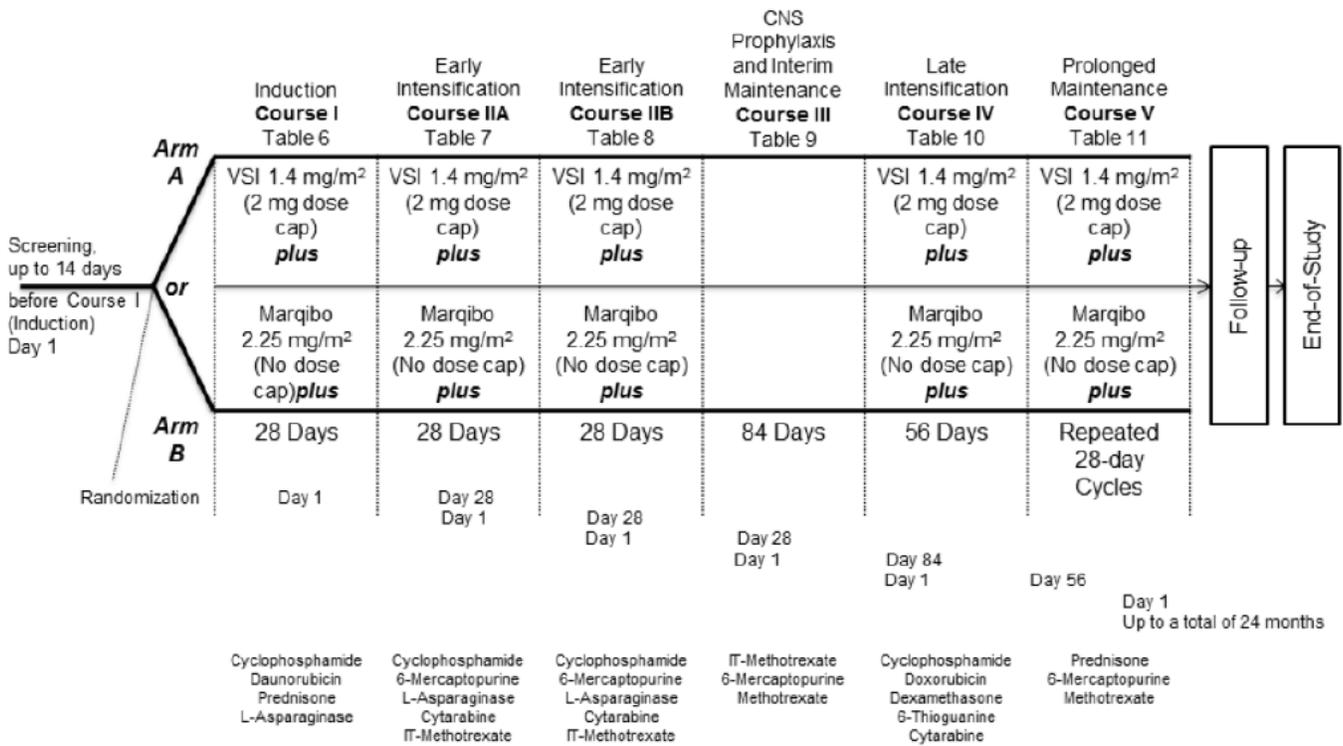
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Figure 12. Design of Study TTX404



Source: Applicant ODAC Presentation

The applicant proposed the following timelines with the regard to study TTX404:

- [Redacted] (b) (4)
- [Redacted] (b) (4)

In response to Agency’s and ODAC member serious concerns about the feasibility of study TTX404, applicant provided the following potential strategies to enhance TTX404 enrollment rate:

- [Redacted] (b) (4)
- [Redacted]
- [Redacted]
- [Redacted]

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10 Appendices

10.1 Advisory Committee Meeting

An ODAC meeting was held on March 21, 2012 and the members discussed the risk / benefit profile of Marqibo based on a single arm study HBS407.

Questions to the Committee:

Given the following risk/benefit profile of Marqibo:

- a 5% Complete Response (CR) rate; a 15% CR+CRi (CR with incomplete blood count recovery) rate
- a safety profile, including 33% neuropathy adverse events (AEs) of Grade 3 or higher and 10% discontinuation due to peripheral neuropathy.

VOTE: Has Marqibo demonstrated a favorable risk-benefit for the treatment of adult patients with Philadelphia chromosome negative acute lymphoblastic leukemia in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy?

YES: 7

NO: 4

ABSTAIN: 2

Panel members expressed several different perspectives in regard to the risk-benefit profile of Marqibo. Several members discussed a lack of treatment options for the patient population which was studied, and stated that these patients will often receive only palliative therapies. In this context, some members stated that the relatively small response rate may be in line with existing therapies, and likely with fewer associated toxicities. Some members concurred that successfully bridging a patient to transplant did represent a real clinical benefit to those patients. Others on the panel expressed a feeling that the data from the trial did not conclusively demonstrate a clinical benefit to patients.

Members also discussed the liposomal formulation of the product and its possible impact on the effectiveness of the drug. One member expressed skepticism that the formulation would make a significant improvement on the activity of the parent drug, vincristine. Because the biologically active drug is identical between the products, some members stated that Marqibo may simply be an alternate mechanism to deliver vincristine to the patient. As a counter to this perspective, some members cited examples of other liposomal formulations which significantly affected activity of a drug.

Members who voted “yes” cited a feeling that the response rate in the trial was similar to the limited options that could otherwise be used in these patients, but with less toxicity. Some of these members expressed that this, combined with a subset of patients being successfully bridged to transplant, represented a clinical benefit. Another member

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mentioned a possible benefit to patients in receiving a single agent rather than the multi-drug regimen that would otherwise be used. One member stated that the “yes” vote was more an indictment of the lack of other options than enthusiasm about Marqibo.

Members who voted “no” expressed doubt that the evidence was strong enough to suggest a reasonable likelihood of clinical benefit. One member cited skepticism of the pharmacology of the agent and its superiority to vincristine, which is already available.

Members who abstained from voting cited a lack of comfort with the quality of the data, and a concern over questions that remained unaddressed.

Additionally, members discussed the design of the proposed Phase 3 randomized trial. Many of those on the panel expressed skepticism regarding the feasibility of the trial, citing potential issues with accrual, investigator enthusiasm, and likelihood of meeting the endpoints. Members consistently stated that the phase 3 trial was critical in assessing the benefit of Marqibo. Some members indicated that the trial should be completed before approval, while several indicated that accelerated approval may be appropriate, but with the expectation that this approval would be withdrawn if the phase 3 trial failed to confirm clinical benefit.

10.2 Labeling Recommendations

See Final Label.

10.3 Literature Review/References

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/s/

ASHKAN EMADI
04/17/2012

QIN C RYAN
04/17/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202497

Applicant: Talon Therapeutics

Stamp Date: 07/12/2011

Drug Name: Vincristine Sulfate
Liposomes Injection (Marqibo)

NDA Type: Priority

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?		X		Section 1.14. The Label is not in the FDA recommended format.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Section 5.3.5.3 iss
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Section 5.3.5.3 ise
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? -- Study Number: VSLI-06 -- Study Title: Phase 1-2 Study of Liposomal Vincristine (VSLI) and Dexamethasone in Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL) -- Sample Size: 36 (single arm dose-escalation study) -- Arms: 1.5-2.0 mg/m ² (11 pts), 2.25 mg/m ² (18 pts), 2.4 mg/m ² (7 pts) -- recommended dose is 2.25 mg/m ² , which was used as a single agent in 65 subjects in study HBS-407 for relapsed / refractory ALL	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Location in submission: 5.3.5.2.				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? -- Pivotal Study #1: Study HBS-407; A Phase 2 Study to Evaluate the Safety and Efficacy of Weekly Doses of Marqibo (vincristine sulfate liposomes injection) in Adult Patients with Philadelphia Chromosome-negative Acute Lymphoblastic Leukemia (ALL) in Second Relapse or Adult Patients with Philadelphia Chromosome-negative ALL Who Failed Two Treatment Lines of Anti-leukemia Chemotherapy Location in submission: 5.3.5.2. Pivotal Study #2: n/a	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			The pivotal study is a single arm study with 65 ITT population in heavily pretreated ALL patients. The approvability of this application is going to be a review issue.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.		X		There were not previous Agency agreements regarding primary endpoint of CR+CRi. However, given the patient population, the application appears to be reviewable.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			HBS408 is an ongoing Phase 2 study of VSLI in 47 subjects with metastatic uveal melanoma. One secondary objective of this study is to determine whether or not ECG variables change as a result of VSLI administration.
20.	Has the applicant presented a safety assessment based on all	X			Summary in section 2.7.4

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	Oncology indication for life threatening disease
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	Oncology indication for life threatening disease
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			Section 5.3.5.2.25.3.3.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Myelosuppression and Neuropathy
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Section 1.9.2.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	Format not discussed with Division.
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Section 5.3.5.2.24 for both studies HSB-407 and VSLI-06
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			annotated CRF in section 5.3.5.2.25.4
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			Section 1.3.4
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ashkan Emadi, MD, PhD 9/01/2011

 Reviewing Medical Officer Date

Qin Ryan, MD, PhD 9/01/2011

 Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ASHKAN EMADI
09/12/2011

QIN C RYAN
09/12/2011