

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202497Orig1s000

STATISTICAL REVIEW(S)



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL TEAM LEADER REVIEW MEMO

NDA: 202497

Drug Name: VSLI, Marqibo

Indication(s): Treatment of Philadelphia chromosome negative (Ph-) adult acute lymphoblastic leukemia (ALL) in patients in second or greater relapse or whose disease has progressed following two or greater anti-leukemia therapies

Applicant: Talon Therapeutics

Date(s): Submitted date: July 12, 2011
Received date: July 12, 2011
PDUFA date: May 12, 2012

Review Priority: Standard

Biometrics Division: Division of Biometrics V

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Qin Ryan, M.D. (clinical team leader),
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Project Manager: Amy Baird

Keywords: open label, single arm, ALL, response rate, sample size

REVIEW MEMO

This application is for the use of vincristine sulfate liposomes injection (VSLI, Marqibo®, the active ingredient vincristine sulfate) for the treatment of Philadelphia chromosome negative (Ph-) adult acute lymphoblastic leukemia (ALL) in patients in second or greater relapse or whose disease has progressed following two or greater anti-leukemia therapies. Efficacy data are included from two studies (Study VSLI-06 and Study HBS407). See the statistical review of Dr. Lan Huang for further details on the design and results of these studies. I do not have disagreements with Dr. Lan Huang on the issues in this submission.

This memo provides a change in the FDA clinical reviewer's summary of CR/CRi for study HBS407. This change affects Tables 7, 8 and 13 of the Dr. Huang's review. During the course of the review of NDA 202497, based on their evaluation of response, the clinical reviewer changed the response classification of one subject from CR to CRi. Based on this change, the summary for CR/CRi of the FDA clinical reviewer is 3 CRs and 7 CRi's.

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Date:

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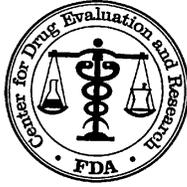
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/s/

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05/02/2012

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05/02/2012



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number: 202-497

Drug Name: VSLI, Marqibo

Indication(s): Treatment of Philadelphia chromosome negative (Ph-) adult acute lymphoblastic leukemia (ALL) in patients in second or greater relapse or whose disease has progressed following two or greater anti-leukemia therapies

Applicant: Talon Therapeutics

Date(s): Submitted date: July 11, 2011
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Biometrics Division: Division of Biometrics V

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1. EXECUTIVE SUMMARY

This application is for vincristine sulfate liposomes injection (VSLI, Marqibo®), the active ingredient vincristine sulfate), intended for the indication, “treatment of Philadelphia chromosome negative (Ph-) adult acute lymphoblastic leukemia (ALL) in patients in second or greater relapse or whose disease has progressed following two or greater anti-leukemia therapies” at a dose of 2.25 mg/m² as an intravenous (IV) infusion over 1 hour every 7 days. This indication targets adult (age ≥ 18 years) patients with advanced, relapsed and/or refractory Ph-ALL for whom there is no approved and standard treatment options.

Efficacy data are included from 2 completed studies (Study VSLI-06 and Study HBS407) that evaluated the efficacy of VSLI in a total of 101 adult subjects with ALL or lymphoblastic lymphoma (100 Ph- and 1 Ph+) who received VSLI doses of 1.5-2.0 mg/m², 2.25 mg/m², or 2.4 mg/m² based on actual body surface area (no dose capping). In Phase I/II Study VSLI-06, VSLI was given in conjunction with pulse dexamethasone. In Phase 2 Study HBS407, VSLI was given as a single-agent.

The focus of the review is on study HBS407. Twelve subjects (possible failure cases) included in Intent-to-Treat (ITT) population (HBS407) were excluded in the Independent Response Review Committee (IRRC) evaluable population. The primary endpoint is the proportion of subjects who achieved complete response (CR) plus CR with incomplete blood count recovery (CRi), as determined by the PI and IRRC using IWG Criteria. According to FDA reviewer, a total of 10 subjects (10/65=15.4%, CI as (7.6%, 15%)) achieved confirmed/unconfirmed CR or CRi based on IRRC determination in the ITT population, and 8 subjects (8/65=12.3%, CI as (5.5%, 22.8%)) achieved confirmed CR or CRi based on IRRC determination in the ITT population. Note that the confirmed/unconfirmed CR or CRi cases were identified by the FDA medical reviewer.

The results for the primary analyses from FDA reviewer are not the same as those provided by the sponsor because the identified CR and CRi cases by FDA medical officer are different with those provided by the sponsor. The duration of the Overall remission (OR) among the subjects with OR (CR plus CRi) is difficult to evaluate as evaluations stopped when subsequent treatments (e.g., HSCT, other drugs, etc) begin. The patient population is heterogeneous and the sample size is small. Some baseline variable may confound estimate treatment effect in the open label, single arm study. Without a control arm, it is difficult to claim that the efficacy observed is due to the test treatment or some baseline variables (e.g., age, prior ALL therapy, disease severity, etc).

The Oncologic Drugs Advisory Committee meeting for Marqibo was held on March 21, 2012. The committee discussed the New Drug Application (NDA) 202497 and the panel members expressed different perspectives in regard to the risk-benefit profile of Marqibo. For the question “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?” Seven 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. Four

members who voted “No” expressed doubt that the evidence was strong enough to suggest a reasonable likelihood of clinical benefit. Two members who abstained from voting cited a lack of comfort with the quality of the data, and a concern over questions that remained unaddressed.

2. INTRODUCTION

2.1. Overview

2.1.1. Indication

The sponsor seeks approval of VSLI for the indication, “treatment of Philadelphia chromosome negative (Ph-) Adult Acute Lymphoblastic Leukemia (ALL) in patients in second or greater relapse or whose disease has progressed following 2 or greater anti-leukemia therapies”.

2.1.2. History of Program Development

Inex Pharmaceuticals, now known as Tekmira Pharmaceuticals, submitted the IND [IND 59,056] for Marqibo to FDA on September 30, 1999. An NDA [NDA 21-600] seeking accelerated approval of the indication, “treatment of patients with aggressive non-Hodgkin’s Lymphoma that is refractory to, or relapsed after two prior combination chemotherapy regimens” was submitted to FDA on September 29, 2003. Inex received a non-approval action notification on January 14, 2005 (INEX January 14, 2005 NDA 21-600 Action Letter).

Hana Biosciences, now known as Talon Therapeutics, acquired development rights to Marqibo from Inex on May 6, 2006. All pending FDA requests for information and responses to questions that were forwarded to Inex following the non-approval action were addressed in various IND submissions filed by Talon in 2010 and 2011. Talon has held five meetings including:

- Talon October 31, 2006 Type B Clinical meeting: Marqibo proposed Phase 2 study design discussed.
- Talon June 27, 2007 Type A Special Protocol Assessment meeting: Agreement that Marqibo qualifies for Fast Track Designation and general agreement with Talon Phase 2 (HBS407) and Phase 3 (HBS404 now known as TTX404) plans.
- Talon March 26, 2009 Type C Clinical meeting: FDA and Talon discussion of DSHNHL 2009-1 lymphoma study as confirmatory trial, agreed with Agency on QT/QTc assessment plan, and that a clinical assessment of mass balance was not required.
- Talon April 20, 2010 Type B Clinical Pre-NDA meeting: Agreement that Study HBS407 data presented at the meeting continue to support existing Fast Track designation, various aspects of the proposed NDA contents and presentation were discussed.
- Talon November 8, 2010 Type B Pre-NDA meeting: Content and format of proposed NDA discussed.

These meetings have been regarding the clinical development program that seeks accelerated approval for the indication, “treatment of Philadelphia chromosome negative (Ph-) Adult Acute Lymphoblastic Leukemia (ALL) in patients in second or greater relapse or whose disease has progressed following 2 or greater anti-leukemia therapies”.

2.1.3. Specific Studies Reviewed

Study HBS407 (the focus of this review) is a Phase 2, international, multicenter, open-label, single-arm study. It was designed to evaluate the performance of VSLI (2.25 mg/m² dose level) in adult subjects with: 1) Ph- ALL or lymphoblastic lymphoma in second or greater relapse; or 2) Ph- ALL or lymphoblastic lymphoma who failed 2 or greater treatment lines of anti-leukemia chemotherapy.

The study was conducted at 22 study sites in Canada, Germany, Israel, and the United States. On average 1 to 5 subjects, with a maximum of 11 subjects, were to be enrolled at each site.

A total of 68 subjects were screened and enrolled into Study HBS407; the ITT population included 65 subjects (95.6%), and the IRRC Evaluable Population included 53 subjects (81.5%) of the ITT population. The 12 subjects not included in the IRRC Evaluable Analysis Set lacked protocol specified assessment of disease response to VSLI. The most common reason for this lack of assessment was death secondary to infection prior to the first scheduled assessment. Thus, neither disease response nor disease progression could be confirmed.

Study VSLI-06 is a Phase I/II, multicenter, open-label, dose escalation study. It was designed to (1) determine the maximum tolerated dose (MTD) of VSLI given with pulse dexamethasone and 2) determine the efficacy of VSLI given with Pulse dexamethasone. The study was conducted at 3 study sites in the United States.

The primary efficacy endpoint was the proportion of subjects who achieved an overall response (OR), defined as complete response (CR) or partial response (PR) [CR+PR] as determined by the principal investigator (PI). A total of 36 subjects were enrolled in the study and received at least 1 dose of VSLI plus dexamethasone.

For study VSLI-06, the sample sizes for the subgroups with doses from 1.5mg/m² to 2.4 mg/m² are very small. Therefore, the 95% CI for the CR is very large for the subgroups. The sponsor did not provide enough information on the performance of the subgroups and dose selection. Therefore, we do not extensively evaluate VSLI-06 study. More details are included in Appendix **Phase I/II study VSLI-06 design**.

2.2 Data Sources

All materials reviewed including the applicant study reports, data sets and literature referenced are provided electronically, and the full electronic path of the document is [\\Cdsesub1\evsprod\NDA202497\](\\Cdsesub1\evsprod\NDA202497).

The application study reports reviewed include Clinical overview, Summary of Clinical Efficacy, Summary of Clinical Safety in M2.

Data sets analyzed for study **VSLI-06** (with data definition document) were located in M5 <\\Cdsesub1\evsprod\NDA202497\0000\m5\datasets\vsli-06\analysis\datasets>

Data sets analyzed for study **HBS407** (with data definition document) were located in M5 <\\Cdsesub1\evsprod\NDA202497\0000\m5\datasets\hbs-407\analysis\datasets>

The datasets analyzed include ADSL (demographics and disposition), ADAE (adverse events), AL (ALL disease history).

3. STATISTICAL EVALUATION

3.1. Data and Analysis Quality

Corrections shown in the following were made to the data for the primary and secondary analyses.

- According to IRRC determination, the sponsor identified 11 responses (8 CR plus 3 CRi). However, FDA medical reviewer identified 10 responses (4 CR plus 6 CRi), out of which there are 8 confirmed responses (2 CR plus 6 CRi).
- According to FDA medical reviewer, subjects with id number 407-0107-0095 (with stable disease) and 407-0186-0481 (with progressed disease) did not have subsequent HSCT or subsequent chemotherapy after treatment with Marqibo. In the sponsor's records, both patients had subsequent chemotherapy.
- The sponsor defined duration of response as the time from the occurrence of response to relapse. However, FDA medical reviewer defined the duration of response as the time before the introduction of any concomitant treatment (HSCT, chemotherapy, etc).
- According to variable PRALT4 (prior anti-L treatment in line 4), subject HBS407-0063-0004 did not have prior anti-Leukemia treatment in line 4, but has been coded with PRALTN=4 (has 4 lines of prior anti-Leukemia treatment) by the sponsor. Similarly, subject HBS407-0193-0693 has PRALTN=3, but without any treatment included in variable PRALT3 (prior anti-L treatment in line 3).
- Some numbers in the ISS safety tables can not be obtained from the data provided by the sponsor (for example, NDA 202497, ISS Tables, Table 1.3; NDA 202497, ISS tables, Table 3.2.6).

3.2. Evaluation of Efficacy

3.2.1. Study Design and Endpoints

In this section, the reviewer's comments for the design, endpoints are in italics.

Phase I/II study VSLI-06

Study VSLI-06 is a Phase I/II, multicenter, open-label, dose escalation study. It was designed to (1) determine the maximum tolerated dose (MTD) of VSLI given with pulse dexamethasone and 2) determine the efficacy of VSLI given with Pulse dexamethasone.

The primary efficacy endpoint was the proportion of subjects who achieved an overall response (OR), defined as complete response (CR) or partial response (PR) [CR+PR] as determined by the principal investigator (PI).

A total of 36 subjects were enrolled in the study and received at least 1 dose of VSLI plus dexamethasone.

This regimen was active at a spectrum of uncapped dose levels ranging from 1.5 to 2.4 mg/m². There was no clear individual dose response effect because of the small sample size in the subgroups. According to the sponsor, because of DLTs at the 2.4 mg/m² dose level, the 2.25 mg/m² dose administered weekly was declared the MTD, and the MTD dose was recommended for further evaluation in Phase 2.

In the following, we present information on Study HBS407 only. More details are included in Appendix **Phase I/II study VSLI-06 design**.

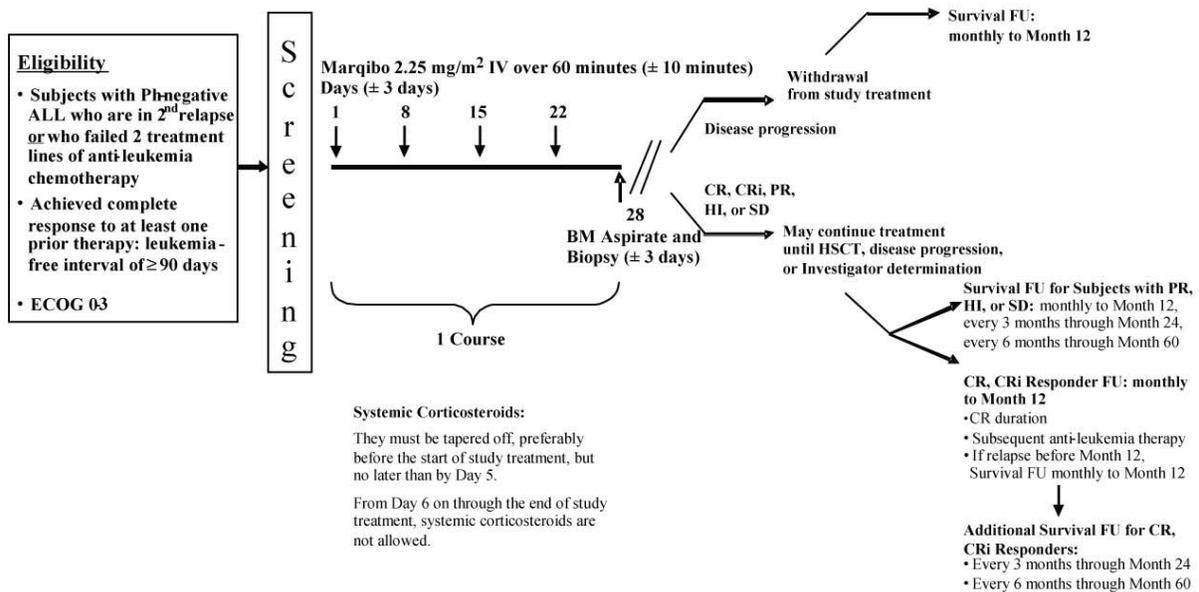
Phase II study HBS 407:

HBS407 was a Phase 2, international, multicenter, open-label, single-arm trial evaluating VSLI in adult subjects with: 1) Ph- ALL or lymphoblastic lymphoma in second or greater relapse; or 2) Ph- ALL or lymphoblastic lymphoma who failed 2 or greater treatment lines of anti-leukemia chemotherapy (**Figure 1**). Eligible subjects 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. Previous HSCT was considered a treatment line of anti-leukemia chemotherapy. *Note that poor baseline diagnosis (not treatment) may lead to worse survival.*

Eligible subjects received single-agent VSLI at 2.25 mg/m², based on actual body surface area, IV via peripheral or central venous access over 60 minutes (± 10 minutes). Dosing was administered every 7 days (± 3 days) on Days 1, 8, 15, and 22 with no less than 4 days between dosing. Dosing was administered in an inpatient or outpatient setting at the discretion of the PI. Dose calculations were based on body surface area using the subject's height (from Screening) and actual weight for each course. Four weekly doses of VSLI constituted 1 course of study treatment. The weekly 2.25 mg/m² dose was the MTD in Study VSLI-06. Pulse dexamethasone was not included as part of this study.

Those subjects who had a CR, CR with incomplete hematologic recovery (CRi), bone marrow blast (BMB) response (i.e., morphologic remission without blood platelet count and neutrophil recovery), PR, hematologic improvement (HI) or stable disease (SD, e.g., no significant hematological and extramedullary change from baseline) 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.

Figure 1: HBS407 ----treatment schema (from sponsor's summary of clinical efficacy 2.7.3)



Note: ALL = acute lymphoblastic leukemia; BM = bone marrow; CR = complete remission; CRi = complete remission with incomplete blood count recovery; FU = Follow-up; HI = hematologic improvement; PR = partial remission; HSCT = Hematopoietic stem cell transplantation; SD = stable disease

Two analysis datasets were utilized for the analysis of efficacy:

- Intent-to-Treat (ITT) Analysis Set which included all subjects who received at least 1 dose of study drug and had histologically and molecularly proven Ph- ALL that was confirmed by a central hematopathologist.
- IRRC Evaluable Analysis Set that included ITT Analysis Set subjects who had reviewable data to assess and determine response or lack of response as determined by the IRRC.

Primary endpoints:

The primary efficacy endpoint is the proportion of subjects who achieved CR or CRi, as determined by the PI and IRRC using IWG Criteria

Secondary endpoints:

The secondary efficacy endpoints, based on IWG Criteria when applicable, included:

- Best response categories CR, CRi, BMB response, PR, SD and PD
- CR+CRi duration based on first response dates and relapse dates or dates of post-VSLI anti-leukemia therapy including HSCT
- Time to CR or CRi
- Overall survival
- Leukemia-free survival

- The time to peripheral blast clearance
- The time to bone marrow blast clearance
- Time to extramedullary disease resolution
- Number and proportion of subjects who received post-VSLI HSCT.

Complete remission (CR) requires “<5% blast in BM” and “>1000 ANC” and “>100 10⁹/L Platelet”.

CRi is “Complete Remission with Incomplete Blood Count”, and CRp is “Complete Remission without Full Platelet Recovery”.

Overall remission (OR) only include CR and CRi. The analysis on OR is the primary efficacy analysis.

3.2.2. Patient Disposition, Demographic and Baseline Characteristics

As shown in Table 1, there are 65 subjects in ITT population. All ITT subjects discontinued with different reasons.

The 12 subjects not included in the IRRC evaluable analysis set lacked protocol specified assessment of disease response to VSLI. The most common reason for this lack of assessment was death secondary to infection prior to the first scheduled assessment. Thus, neither disease response nor disease progression could be confirmed.

For the 12 subjects without disease response confirmation are treated as non-response in the ITT analysis. IRRC evaluable population does not include the 12 subjects, which is not proper.

Table 1: Patient disposition (HBS407)

Total screened and enrolled subjects	68
ITT	65
Discontinued with disease progression	26/65=40%
Discontinued followed by adverse events	24/65=37%
Discontinued by investigator request	6/65=9%
Discontinued with planned HSCT (stem cell transplantation)	5/65=8%
Discontinued with subject withdrawn consent	4/65=6%
IRRC evaluable population	53

The distributions of the demographic variables are shown in table 2. Most of the patients are White. There are more non-hispanic and young patients in the study. The numbers of subjects with intermediate or unfavorable Cytogenetics are similar (Shown in Table 3).

Table 2: Demographic characteristics (HBS407)

Variable at baseline	HBS407 (ITT) N=65	HBS407 (IRRC evaluable) N=53
Gender [n(%)]		
Female	32 (49.2)	26 (49.1)
Male	33 (50.8)	27 (50.9)
Race [n(%)]		
White	56(86.2)	45(84.9)
Black or African American	4(6.2)	4(7.5)
Asian	2(3.1)	1(1.9)
Other	3(4.6)	3(5.7)
Ethnicity [n(%)]		
Hispanic or Latino	17(26.2)	14(26.4)
Not Hispanic or Latino	48(73.8)	39(73.6)
Age at consent (years)		
Mean(std)	36.4 (16.4)	37.4 (17.1)
Median	31.0	32.0
Min, max	19, 83	19, 83
Age group [n(%)]		
18-29 years	29 (44.6)	22 (41.5)
30-59 years	28 (43.1)	24 (45.3)
>=60 years	8 (12.3)	7 (13.2)

Table 3: Baseline Cytogenetics (HBS407)

Findings	HBS407 (ITT) N=65	HBS407 (IRRC evaluable) N=53)
Intermediate Cyto		
Normal	20(30.8)	19(35.9)
Del	2(3.1)	1(1.9)
Del-Y	1(1.5)	1(1.9)
Cyto unfavorable		
Complex karyotypes	18(27.7)	18(34.0)
+8	1(1.5)	1(1.9)
-7/del(7q)	2(3.1)	2(3.8)
-7/del(7q)+8	1	
-7/del(7q) complex	1	
Abnl 11q	2	1
Abnl 17q	1	
Abnl 21q	2	
Abnl 21q and 17q	1	1
Abnl 21q and 9q	1	
Abnl 9q	2	2
Del (5q)/-5q	1(1.5)	
Missing	9(13.9)	7(13.2)

As shown in Table 4, there are more patients with precursor B-lymphoblastic leukemia, without extramedullary disease, lower ECOG scores (better health condition at baseline), PLATELET count less than $50 \times 10^9/L$. The baseline characteristics are very heterogeneous for the 65 ITT population. The prior anti-ALL treatment is also heterogeneous (shown in Table 5). Patients have different # of treatment lines and # of transplantation.

Table 4: Baseline characteristics (HBS407)

Baseline parameter	HBS407 (ITT) N=65	HBS407 (IRRC evaluable) N=53
Type of ALL [n(%)]		
Precursor B-lymphoblastic leukemia	55(84.6)	45(84.9)
Precursor T-lymphoblastic leukemia	10(15.4)	8(15.1)
Time since diagnosis of ALL (yr)		
Mean (std)	2.7(2.8)	2.7(2.55)
Median	1.8	1.8
Min, max	<1, 15	1, 12
Extramedullary disease [n(%)]		
Yes	10(15.4)	9(17.0)
No	55(84.6)	44(83.0)
ECOG performance status [n(%)]		
0	17(26.2)	16(30.2)
1	33(50.8)	26(49.1)
2	11(16.9)	9(17.0)
3	4(6.2)	2(3.8)
Platelet count 10 ⁹ /L		
<=50	39(60.0)	29(54.7)
>50	26(40.0)	24(45.3)
<=75	44(67.7)	34(64.2)
>75	21(32.3)	19(35.9)
<=100	48(73.9)	37(69.8)
>100	17(26.2)	16(30.2)

Table 5: HBS407---Prior anti-leukemia therapy

Therapy type	ITT (N=65)	IRRC evaluable (N=53)
# prior lines of anti-Leukemia trt (max per subject)		
2	33(50.8)	32(60.4)
3	24(36.9)	14(26.4)
4	7(10.8)	7(13.2)
6	1(1.5)	
Best response to trt line 1 [n(%)]		
Complete Response (CR)	62(95.4)	51(96)
Progressive Disease (PD)	1(1.5)	1(2)
No Response (NR)	1(1.5)	0
Unknown (NR)	1(1.5)	1(2)
# Prior HSCT [n(%)]		
0	34(52.3)	31(58)
1	29(44.6)	21(40)
2	2(3.1)	1(2)

From the above tables, the subjects in the IRRC evaluable population have less prior anti-leukemia therapy compared with those in ITT population. In the following, ITT analyses will be the focus of the study.

The exact treatment used in each treatment lines (at baseline) is shown in Table 6. In the first line of treatment for ITT patients in this study, the most used drugs are VINCRISTINE (98% patients used), CYCLOPHOSPHAMIDE (88%), CYTARABINE (74%), METHOTREXATE (71%), ETOPOSIDE (60%), and ASPARAGINASE (55%). In the 2nd line of treatment, the most used ones are CYTARABINE (60%), CYCLOPHOSPHAMIDE (46%), VINCRISTINE (42%), ANDMETHOTREXATE (31%). In the 3rd line of treatment, the most used ones are CYCLOPHOSPHAMIDE (22%), CYTARABINE (18%), and METHOTREXATE (12%). Very few drugs are used for the 4th, 5th, and 6th line of treatment for patients at baseline. The treatment choices are very different for patients at baseline.

Table 6: # Prior line treatment (all)

Obs	Trtname	Freq 1	per1	Freq 2	per2	freq3	per3	freq4	per4	freq5	per5	freq6
1	6-MERCAPTOPYRINE	30	46.15	5	7.69	3	4.62	1	1.54	.	.	.
2	6-THIOGUANINE	5	7.69	1	1.54	1	1.54
3	ACTINOMYCIN – D	1	1.54
4	ANTITHYMOCYTE GLOBULIN	.	.	2	3.08	2	3.08	1	1.54	.	.	.
5	ASPARAGINASE	36	55.38	16	24.62	1	1.54
6	BUSULFAN	.	.	2	3.08	5	7.69	1	1.54	.	.	.
7	CAMPATH	1	1.54
8	CARMUSTINE	2	3.08	1	1.54
9	CHLORAMBUCIL	1	1.54
10	CISPLATIN	.	.	1	1.54
11	CLOFARABINE	.	.	4	6.15	1	1.54	2	3.08	.	.	.
12	CYCLOPHOSPHAMIDE	57	87.69	30	46.15	14	21.54	1	1.54	.	.	.
13	CYTARABINE	48	73.85	37	56.92	12	18.46	2	3.08	.	.	.
14	DAUNOMYCIN	28	43.08	7	10.77	1	1.54
15	DEXAMETHASONE	34	52.31	14	21.54	7	10.77	1	1.54	.	.	.
16	DOXORUBICIN	39	60.00	11	16.92	4	6.15
17	ETOPOSIDE	10	15.38	12	18.46	6	9.23
18	FLUDARABINE	1	1.54	7	10.77	6	9.23	4	6.15	.	.	.
19	HYDROCORTISONE	4	6.15	.	.	1	1.54
20	HYDROXYUREA	3	4.62	1	1.54	2	3.08
21	IDARUBICIN	3	4.62	1	1.54	2	3.08	2	3.08	.	.	.
22	IFOSFAMIDE	3	4.62	4	6.15	2	3.08
23	LIPOSOMAL ANNAMYCIN	.	.	1	1.54
24	MELPHALAN	.	.	2	3.08	2	3.08	1	1.54	.	.	.
25	METHOTREXATE	46	70.77	20	30.77	8	12.31	1	1.54	.	.	.
26	METHYL PREDNISOLONE	6	9.23	3	4.62	1	1.54
27	MITOXANTRONE	8	12.31	7	10.77	2	3.08
28	NELARABINE	.	.	2	3.08	.	.	1	1.54	.	.	1
29	PREDNISONE	33	50.77	10	15.38	2	3.08
30	RITUXIMAB	7	10.77	2	3.08	2	3.08
31	SOLAMBUSOL	1	1.54

Obs	Trtname	Freq 1	per1	Freq 2	per2	freq3	per3	freq4	per4	freq5	per5	freq6
32	TENIPOSIDE	3	4.62	1	1.54	.	.	.
33	THIOTEPA	1	1.54
34	VINBLASTINE	.	.	1	1.54
35	VINCRISTINE	64	98.46	27	41.54	5	7.69	1	1.54	.	.	.
36	VINDESINE	2	3.08
37	VINORELBINE	1	1.54
38	_Unknown	.	.	1	1.54	1	1.54	.	.	1	1.54	.

Note: Table includes #subjects in each treatment drugs in line 1, 2, 3, 4, 5, and 6. One subject can take several drugs at each line (per=freq/65*100%). The table by response is included in appendix.

3.2.3. Statistical Methodologies

In this section, the reviewer's comments and alternative methods are in italics. If there is no comment, the methods proposed by the sponsor were used by the reviewer.

Study HBS407:

The primary efficacy endpoint was summarized as the proportion of subjects who achieved CR or CRi (designated as CR+CRi). An exact 2-sided 95% CI was constructed around the estimated CR+CRi proportion. Separate summaries were provided for PI determined CR+CRi responses and IRRC determined CR+CRi responses. The ITT population and IRRC Evaluable Population analysis sets were used for the summary of efficacy.

The secondary analyses include the following (by sponsor).

The individual response assessments (CR, CRi, PR, BMB, SD, PD, and Not Evaluable) were summarized similarly to the primary efficacy variable, CR+CRi. Separate summaries were presented for the IRRC determined responses using the ITT and IRRC determined evaluable analysis sets.

CR+CRi duration was calculated from the date the subject first met the definition of CR or CRi until the date of relapse. The duration of CR+CRi was derived using only the IRRC determined response dates of CR+CRi.

One definition of response duration used by the FDA in the review of this submission was time of CR or CRi until the date of adding other treatment (drugs or HSCT) or relapse. This definition is used in this review.

Overall survival was defined as the time from the entry onto the trial date (date informed consent signed) to death from any cause. Subjects who did not die had their survival times censored on

the date of last contact. The K-M method was used to estimate the distribution of overall survival.

Time to CR or CRi was defined as the time from the start of the first study dose infusion date to the date the subject first achieved CR or CRi. Time to CR or CRi was derived using only the IRRC determined response dates of CR+CRi. Subjects who never achieved CR+CRi were censored at the date of last On-treatment PI response assessment date or death. The K-M product limit method was used to estimate the median event time using the IRRC determined evaluable data sets.

Additional time to event secondary analyses include

- Post-treatment HSCT (number and proportion)
- Time to Peripheral blood blast clearance (K-M analysis)
- Time to Bone marrow blast clearance (K-M analysis)
- Time to extramedullary disease clearance (K-M analysis)

Time to event endpoints in a single arm study are not interpretable. These analyses are considered exploratory description. In this review, because of the small sample size for the subjects with a particular type of response (e.g., Bone marrow clearance, and others), the survival analyses will only be conducted for the overall survival. Time to CR or CRi will be summarized in tables instead of K-M analysis.

Additional analyses were conducted to explore the response rates by different definitions (sponsor, FDA medical officer (with confirmed information), and FDA medical officer (without confirmed information), the number of treatment used in the prior line of treatment for all patients in the ITT population and by responders (10 responders with/without confirm defined by FDA medical officer), the pattern of duration of response.

The response rates with/without confirmed information for ITT population (defined by FDA medical officer) are treated as primary results.

All safety analyses were performed on the Safety Population. In general, summaries were presented by course and day. Additional 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.

3.2.4. Results and Conclusions

Brief summary of the applicant's results and conclusion from VSLI-06 and HBS407

In Study VSLI-06, VSLI plus pulse dexamethasone was an effective first, second, and third salvage therapy option for adult patients with relapsed and/or refractory ALL. The overall response rate of 22.2% and CR rate of 19.4%, in the ITT population based on PI assessment.

In summary, Study VSLI-06 met the pre-defined study objectives and therapeutic goals. The VSLI dose was significantly intensified, a maximum tolerable dose (MTD) was declared, compelling responses were observed at more than one dose level, and the safety profile at the MTD and lower dose levels was predictable and manageable.

In Study HBS407, VSLI, dosed as a single agent at 2.25 mg/m² (MTD determined in VSLI 06), was an effective first, second, and third salvage therapy option for adult patients with advanced, relapsed and/or refractory Ph- ALL regardless of lineage (B or T). Based on the ITT population and response assessments performed by the expert leukemia physicians who served as study PIs, 35.4% of subjects achieved a response (CR+CRi+PR+BMB) and 20% achieved a morphologic CR with or without complete peripheral blood count recovery (CR+CRi) as reported by the sponsor. There were 2 fewer CR+CRi based on IRRC assessment. The OR and CR+CRi rates were comparable in the ITT and IRRC Evaluable Populations and exceeded the CR+CRi success threshold of 16% set prior to Study HBS407 commencement. Based on this very encouraging single-agent salvage rate in the context of such a sick population and modest (12%) 30-day mortality rate, the results of HBS407 are likely to predict for clinical benefit in Ph- ALL.

Of the 11 subjects who achieved CR+CRi (by IRRC evaluation), time to response ranged from 25 to 81 days with 45.0% (5/11) achieving the remission within 35 days and 91% (10/11) within 57 days. The median CR+CRi response duration was 162 days (95% CI: 35, 210). The median response duration until subsequent anti-leukemia therapy (including HSCT) was 144 days (95% CI: 144, 166). The median length of leukemia-free survival was 144 days (95% CI: 42, 166). The median length of OS was 139 days (95% CI: 104, 163). All 11 CR+CRi subjects had an OS of at least 2 months, most (8/11=72.7%) survived at least 7 months, and 9.1% (1/11) reached OS duration of 21 months.

The nature and pattern of AEs in subjects treated with VSLI are qualitatively similar to those known to be associated with standard VCR administration. No new or unexpected Aes were observed with VSLI.

Results on efficacy from the reviewer

The results by the reviewer on VSLI-06 are consistent with those provided by the sponsor. However, because of the issues on the sample size, multiple doses, additional treatment, and the

PI assessment, the study VSLI-06 can not provide support for the drug approval. In the following, only HBS 407 study is explored in detail and the results for HBS 407 are presented.

In summary, a total of 10 subjects (15.4%, CI as (7.6%, 15%)) achieved confirmed/unconfirmed CR or CRi based on IRRC determination in the ITT population, and 8 subjects (12.3%, CI as (5.5%, 22.8%)) achieved confirmed CR or CRi based on IRRC determination in the ITT population. Subjects with OR tend to have improved overall survival within a short period (K-M survival rate of 79% (14.5%) for responders vs. 29% (6.2%) for non-responders at half year), but no benefit is observed in long term (K-M survival rate is about 10%-7% for both responders and non-responders at one year). It is difficult to conclude that patients have higher OR rate or longer survival with the treatment of Marqibo, due to lack of small sample size, no controlled arm, confounded treatments, and heterogeneous baseline conditions.

More details are discussed in the following sections. If not stated, the results are for HBS407 study.

Efficacy analyses on response (primary and secondary)

According to FDA medical reviewer, there are only 10 subjects with CR or CRi. Only 8 CR and CRi cases are confirmed. The results with 8 CR and CRi cases are similar to those with 10 CR and CRi analyses. In the following, major focus will be the analyses with the 10 CR and CRi cases.

A total of 10 subjects (15.4%) achieved unconfirmed CR or CRi based on IRRC determination in the ITT population (shown in Table 7).

With PI determination, there are 13 subjects (20%) achieved CR or CRi in the ITT population, which is more than those obtained by IRRC determination.

Table 7: Efficacy evaluation based on response to test treatment

Best response assessment	Assessment population		
	IRRC (IRRC evaluable) N=53	IRRC (ITT) N=65	PI (ITT) N=65
Sponsor's definition of CR and CRi			
Overall Remission (CR+Cri) [n(%)] Exact 95% CI in %	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(%)] Exact 95% CI in %	8 (15.1) (6.7, 27.6)	8 (12.3) (5.5, 22.8)	7 (10.8) (4.4, 20.9)
1CRi (including CRp) [n(%)] Exact 95% CI in %	3(5.7) (1.2, 15.7)	3 (4.6) (1.0, 12.9)	6 (9.2) 93.5, 19.0)
FDA medical officer's definition with confirmed			
Overall Remission (CR+Cri) [n(%)] Exact 95% CI in %		8 (12.3) (5.5, 22.8)	
Complete Remission (CR) [n(%)] Exact 95% CI in %		2 (3.1) (0.4, 10.7)	
CRi (including CRp) [n(%)] Exact 95% CI in %		6(9.2) (3.5, 19.0)	
FDA medical officer's definition without confirmed			
Overall Remission (CR+Cri) [n(%)] Exact 95% CI in %		10 (15.4) (7.6, 26.5)	
Complete Remission (CR) [n(%)] Exact 95% CI in %		4 (6.2) (1.7, 15.0)	
CRi (including CRp) [n(%)] Exact 95% CI in %		6 (9.2) (3.5, 19.0)	

Secondary analysis: # Prior line treatment (all and by response)

This analysis is done according to the FDA medical reviewer's request, for understanding if the common drugs for ALL patients were used in prior line treatments for the patients included in this study.

The results on prior drugs used in the different treatment lines by response are provided in the appendix. The most used drugs for responders are VINCRISTINE (98%), CYCLOPHOSPHAMIDE (89%), CYTARABINE (80%), METHOTREXATE (73%) for the first treatment line, and the same four drugs with lower percent of subjects (about half of the percent for the 1st line) using the drugs for the 2nd treatment line.

For non-responders, the most used drugs are VINCRISTINE (100%), CYCLOPHOSPHAMIDE (80%), DOXORUBICIN (70%), and METHOTREXATE (60%) for the 1st line of treatment; and the same four drugs with lower percent of subjects (about half of the percent for the 1st line except CYCLOPHOSPHAMIDE)) using the drugs for the 2nd treatment line. CYCLOPHOSPHAMIDE is used in 70% percent of subjects in the 2nd treatment line.

DOXORUBICIN is used by 58% of patients in the 1st treatment line, and 15% in the 2nd treatment line among the non-responders.

Secondary analysis: Summary of Time to OR (data from medical reviewer)

Patients with CR or CRi are 10:

- 25 days - 1 patient
- 28 days - 5 patients
- 50 days - 1 patient
- 56 days - 3 patients.

For the 10 subjects, the mean time to OR is 38 days with std 14 days. Median is 28 days.

Secondary analysis: Duration of Response

The duration of response used by the sponsor is the duration of CR and CRi after taking Marqibo and before relapse. By FDA medical reviewer, the duration of response should be the duration of CR and CRi after taking Marqibo and before any other treatment action (e.g., HSCT and other treatments) or relapse (used in the review). The duration is slightly longer in CR subjects than that in CRi subjects.

Table 8: Summary of the duration (days) of response (defined by the medical reviewer).

	N	mean	std	median	Min	Max
All	10	61.2	47.2	47	9	151
CR	4	65.0	49.0	45	33	137
CRi	6	58.7	50.5	52	9	151

Secondary analysis: Number and proportion of post-treatment HSCT

Twelve patients (18.5% with CI as (9.9%, 30%)) out of 65 in the ITT population underwent HSCT after receiving Marqibo (information about after treatment HSCT obtained from the FDA medical reviewer). Five subjects out of the 12 (42% with CI as (15.2%, 72.3%)) subjects achieved OR (CR or CRi) after Marqibo administration and prior to HSCT. More than 50% subjects underwent HSCT without OR.

Two out of three HSCT recipients who were alive at the time of last survival follow-up did not achieve CR or CRi or PR in response to Marqibo.

Secondary analysis: overall survival for all subjects and by response

In a single arm study, OS is not interpretable. Therefore, results are not presented here.

3.3. Evaluation of Safety

The safety population is the same as the ITT population in the HBS407 study (65 subjects). As shown in Table 10, most of the patients discontinued the study because of adverse events and disease progression.

Table 9: Reason for treatment discontinuation (ITT HBS407)

Reason for trt disc	All (N=65)		Responders (N=10)		Non-responders (N=55)	
	Freq	Per (%)	Freq	Per (%)	Freq	Per (%)
Adverse events	24	36.92	5	50.00	19	34.55
Disease progression	26	40.00	0		26	47.27
Investigator request	6	9.23	0		6	10.91
Planned stem cell Transplantation (HSCT)	5	7.69	4	40.00	1	1.82
Subject withdraw consent	4	6.15	1	10.00	3	5.45

In the following tables (11, 12, 13), 28 subjects out of 65 (43.1%) in the ITT population have neuropathy-related AEs listed in the table. One subject could have one time AE occurrence or up to 9 times AE occurrence after treatment of Marqibo. One subject could have all AEs, actions and all levels of the severity.

Most of the neuropathy-related AE cases are NEUROPATHY PERIPHERAL. Most of the time, there is no action taken after the AEs.

Table 10: Summary of after treatment (Marqibo) neuropathy (ITT population and Safety population have the same results)

	# AE		# subjects with AE	
	Freq (count)	Percent (req/84)	freq	Percent (freq/65)
CRANIAL NEUROPATHY	6	7.1	4	6.2
NEUROPATHY PERIPHERAL	67	79.8	24	36.9
PERIPHERAL MOTOR NEUROPATHY	4	4.8	3	4.6
PERIPHERAL SENSORY NEUROPATHY	6	7.1	3	4.6
POLYNEUROPATHY	1	1.2	1	1.5%

Note: No prior treatment (Marqibo) information on this AE provided by the sponsor.

Table 11: Summary of after treatment (Marqibo) dose delayed, dose reduced, discontinued (ITT population) associated with neuropathy

	# AE		# subjects with AE	
	Freq (count)	Percent (req/84)	freq	Percent (freq/65)
Dose delayed	6	7.1	5	7.7
Dose reduced	2	2.4	2	3.1
Dose delayed and reduced	1	1.2	1	1.5
Study drug discontinued	13	15.5	9	13.8
No action taken	50	59.5	21	32.3
Missing	12	14.3		

Table 12: Summary of after treatment (Marqibo) AE severity (ITT population) associated with neuropathy (1 for mild, 2 for moderate, 3 for severe, 4 for life threatening/disabling)

	# AE		# subjects with AE	
	Freq (count)	Percent (req/84)	freq	Percent (freq/65)
1	31	36.9	19	29.2
2	23	27.4	14	21.5
3	17	20.2	13	20
4	1	1.2	1	1.5
Missing	12	14.3		

In addition, according to the sponsor, from the combined VSLI-06 and HBS407 data, the most common AEs occurring with the proposed dose level of 2.25 mg/m² in adults with advanced, relapsed and/or refractory ALL (Target Indicated Dose Group) were constipation (56.6%), nausea (51.8%), pyrexia (42.2%), fatigue (34.9%), peripheral neuropathy (37.3%), decreased appetite (36.1%), febrile neutropenia (36.1%), diarrhea (34.9%) and anemia (30.1%). Many of the constitutional symptoms may reflect progression of the underlying disease process while other events, such as peripheral neuropathy, likely represent a study drug-related effect.

4. FINDINGS IN SPECIFAL/SUBGROUP POPUATLIONS

Efficacy by baseline variable varied (shown in Table 14). Younger subjects have higher OR rates than older ones. Females and males have similar OR rates. Non-hispanic subjects have higher OR rates than Hispanic. Subjects with extramedullary disease have higher OR rates than others. Subjects with less prior lines of treatment have higher OR rates than others. Subjects with more PLATELET count have higher OR rates than others. The changing threshold among 50, 75, and 100 for PLATELET count do not affect the results a lot.

Table 13: Response (OR) and non-response by baseline variables

		Best response assessment (IRRC) for ITT population (un-confirmed and confirmed CR and CRi defined by FDA medical officer) [n (%)]			
	N in each strata	OR (CR+CRi)	CR	CRi	Non-Resp
Age					
[18, 29)	29	7 (24.1)	3(10.3)	4(13.8)	22(75.9)
[30, 59)	28	2 (7.1)	0	2	26(92.9)
>=60	8	1 (12.5)	1(12.5)	0	7(87.5)
Gender					
Female	32	5(15.6)	1(3.1)	4(12.5)	27(84.4)
Male	33	5(15.2)	3(9.1)	2(6.1)	28(84.9)

Race					
White	56	7(12.5)	3(5.4)	4(4.1)	49(87.5)
Black	4	2(50)	1(25)	1	2
Asian	2	1(50)	0	1	1
Other	3	0(0)	0	0	3
Ethnicity					
Non-hispanic	48	9(18.8)	4(8.3)	5(10.4)	39(81.3)
Hispanic	17	1(5.9)	0	1	16(94.1)
Extramedullary disease					
Yes	10	4(40)	1(10)	3(30)	6
No	55	6(10.9)	3(5.5)	3(5.5)	49(89.1)
ECOG at baseline					
0	17	4(23.5)	2(11.8)	2	13(76.5)
1	33	6(18.2)	2(6.1)	4(12.1)	27(81.8)
2	11	0	0	0	11
3	4	0	0	0	4
Platelet count 10 ⁹ /L					
<=50	39	2 (5.1)	1(2.6)	1(2.6)	37(94.9)
>50	26	8(30.8)	3(11.5)	5(19.2)	18(69.2)
<=75	44	3(6.8)	2(4.6)	1(2.3)	41(93.2)
>75	21	7(33.3)	2(9.5)	5(23.8)	14(66.7)
<=100	48	5(10.4)	2(4.2)	3(6.3)	43(89.6)
>100	17	5(29.4)	2(11.8)	3(17.7)	12(70.6)
Alterm					
B-L Leuk	55	8(14.6)	3(5.5)	5(9.1)	47(85.5)
T-L Leuk	10	2(20)	1	1	8
# prior line trt					
2	33	5(15.2)	2(6.1)	3(9.1)	28(84.8)
3	24	5(20.8)	2(8.3)	3(12.5)	19(79.2)
4	7	0	0	0	7(100)
6	1	0	0	0	1

# prior HSCT					
0	34	3(8.8)	2(5.9)	1(2.9)	31(91.2)
1	29	7(17.2)	2(6.9)	5(17.2)	22(75.9)
2	2	0	0	0	2
	N in each strata	OR (CR+CRi)	CR	CRi	Non-Resp
Intermediate Cytogenetics					
Normal	20	3(15.0)	1(5)	2(10)	17(85.0)
Del	2	0	0	0	2(100)
Del-Y	1	1	1	0	0
	N in each strata	OR (CR+CRi)	CR	CRi	Non-Resp
Cyto unfavorable					
Complex karyotypes	18	2(11.1)	0	2	16(88.9)
Other types	15	2(13.3)	1(6.7)	1	13(86.7)
missing	9	2(22.2)	1 (11.1)	1	7(77.8)

The baseline difference of the responders and non-responders are also shown in Table A.3 in Appendix.

Age, Extramedullary disease, ECOG at baseline, Platelet count, # prior line trt, # prior HSCT are distributed differently in responders and non-responders. Responders tend to have more younger subjects, more subjects with extramedullary disease, more ECOG 0 and 1 subjects, more subjects with Platelet count $>50 \times 10^9/L$, slightly less prior # of treatment lines.

As for unfavorable Cytogene, non-responders have more complex karyotypes (29% vs. 20%). As for intermediate Cytogene, responders and non-responder have similar normal subjects.

Gender and ALL type are distributed similarly in responders and non-responders.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For study VSLI-06, the sample sizes for the subgroups with doses from 1.5mg/m² to 2.4 mg/m² are very small. Therefore, the 95% CI for the CR is very large for the subgroups. The sponsor did not provide enough information on the performance of the subgroups and dose selection.

For study HBS407, the results for the primary analyses are not the same as those provided by the sponsor because the identified CR and CRi cases by FDA medical officer are different with those provided by the sponsor.

The duration of the Overall remission (OR) among the subjects with OR (CR plus CRi) is difficult to evaluate in a single arm study due to subsequent treatments (e.g., HSCT, other drugs, etc).

Results are not conclusive because of the heterogeneous patient population, small sample size, and lack of a control arm.

5.2 Conclusions and Recommendations

Study VSLI-06 is just a dose selection study with several dose levels and very few subjects within each dose level. Can not provide support on the efficacy of Marqibo in terms of OR rates and survival of the patients.

From HBS407, a total of 10 subjects (15.4% with 95% exact CI as (7.6%, 26.5%)) achieved unconfirmed CR or CRi based on IRRC determination in the ITT population, and 8 subjects (12.3% with 95% exact CI as (5.5%, 22.8%)) achieved confirmed CR or CRi based on IRRC determination in the ITT population. The statistical results do not provide adequate evidence to support the claims proposed in the NDA that Marqibo provides “treatment of Philadelphia chromosome negative (Ph-) Adult Acute Lymphoblastic Leukemia (ALL) in patients in second or greater relapse or whose disease has progressed following 2 or greater anti-leukemia therapies”.

The patient population is very heterogeneous in terms of demographics, baseline characteristics, and baseline treatment. The sample size is small (65 in ITT population) and subgroup analyses can not provide enough evidence of efficacy because there is no control arm in this study for comparison.

We recommend conducting a well controlled, double blind study to provide evidence that patients benefit from Marqibo.

Primary Statistical Reviewer:

Lan Huang, Ph.D.

Date:

April 5, 2012

Concurring Reviewer(s):

Statistical Team Leader:

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Appendix:

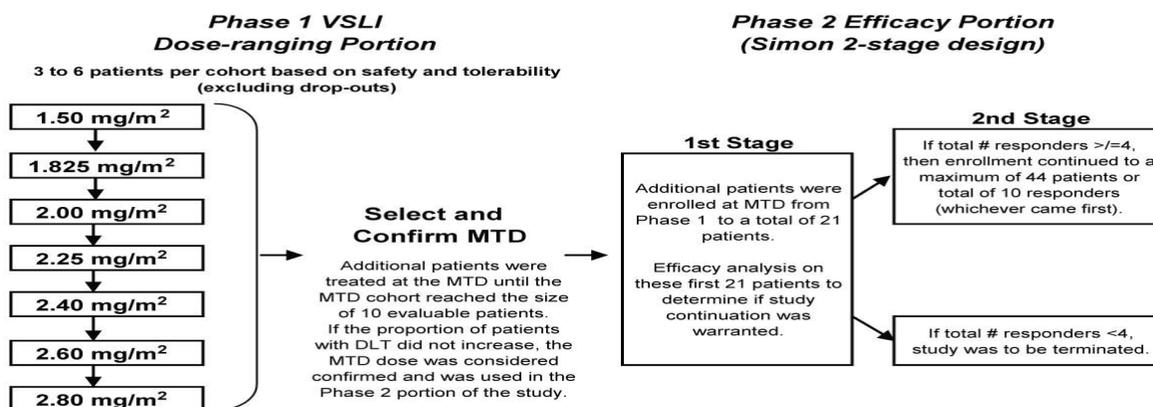
Phase I/II study VSLI-06 design

Study VSLI-06 was a Phase 1/2, multicenter, open-label, dose escalation study of VSLI combined with pulse dexamethasone. Subjects were required to have relapsed or refractory ALL (including lymphoblastic lymphoma or Burkitt's leukemia/lymphoma-like subtypes) and to have measurable disease. VSLI was combined with dexamethasone in this study

Study VSLI-06 was designed to be conducted in 2 phases. The Phase 1 portion of the study was designed to define the maximum tolerated dose (MTD) of VSLI. Up to 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 subjects 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 determine the efficacy of the VSLI MTD in a larger cohort of subjects. Subjects from the first phase could be included in the second phase analysis.

The study design is represented in **Figure A.1**. In order to be included in the MTD evaluation, subjects 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. Subjects who received fewer than four infusions were replaced for the MTD evaluation. To define the MTD and DLT more precisely, 8 to 10 additional subjects were added to the MTD cohort. Subjects completed screening procedures no more than 30 days prior to the first treatment. Each subject received VSLI intravenously (IV) over 60 minutes 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. Subjects with stable disease or a response were allowed to receive up to three courses (12 doses total) of study therapy. Subjects were followed for safety for 30 days following the last dose of study drug. Subjects with a CR at the end-of-treatment visit were followed periodically until relapse or death.

Figure A.1: VSLI-06 study design



Note: DLT = dose-limiting toxicity; MTD = maximum tolerated dose; VSLI = vincristine sulfate liposomes injection

The primary efficacy endpoint was the proportion of subjects who achieved an overall response (OR), defined as complete response (CR) or partial response (PR) [CR+PR] as determined by the principal investigator (PI). In addition to the PI assessment of response, a post hoc adjudication of CRs by the HBS407 Independent Response Review Committee (IRRC) was performed.

A total of 36 subjects were enrolled in the study and received at least 1 dose of VSLI plus dexamethasone. Of the 36 subjects enrolled, 26 subjects (72.2%) were included in the MTD Evaluable Population. Thirty-four (94.4%) subjects were evaluable for leukemia response by the PI.

Because of the following issues in the VSLI-06 study, it will not be the focus of the review.

- *Sponsor included PR in OR rate calculation. However, according to FDA medical reviewer, pre-specified IRRC determined response (CR plus CRi) should be used for primary assessment on OR.*
- *The subjects received 7 different doses, and the sample size is very small for each dose group. The results can not provide any valid information for the response performance within each dose group.*
- *VSLI were used together with dexamethasone in this study. The two drugs are confounded.*

Appendix

Table A.1: Number of prior line treatment (by response)---#subjects in each treatment drugs in line 1, 2, 3, 4, 5, and 6. One subject can take several drugs at each line (per=freq/55 for non-responders, and per=freq/10 for responders).

Obs	IRRCresp2	trtname	freq1	per1	freq2	per2	Freq 3	per3	freq4	per4	freq5	per5	freq6	per6
1	Non-resp	6-MERCAPTOPYRINE	26	47.27	3	5.45	3	5.45	1	1.82
2	Non-resp	6-THIOGUANINE	5	9.09	1	1.82	1	1.82
3	Non-resp	ACTINOMYCIN - D	1	1.82
4	Non-resp	ANTITHYMOCYTE GLOBULIN	.	.	2	3.64	2	3.64	1	1.82
5	Non-resp	ASPARAGINASE	32	58.18	11	20.00	1	1.82
6	Non-resp	BUSULFAN	.	.	2	3.64	3	5.45	1	1.82
7	Non-resp	CAMPATH	1	1.82
8	Non-resp	CARMUSTINE	2	3.64	1	1.82
9	Non-resp	CHLORAMBUCIL	1	1.82
10	Non-resp	CISPLATIN	.	.	1	1.82
11	Non-resp	CLOFARABINE	.	.	4	7.27	1	1.82	2	3.64
12	Non-resp	CYCLOPHOSPHAMIDE	49	89.09	23	41.82	14	25.45	1	1.82
13	Non-resp	CYTARABINE	44	80.00	32	58.18	11	20.00	2	3.64
14	Non-resp	DAUNOMYCIN	25	45.45	6	10.91	1	1.82
15	Non-resp	DEXAMETHASONE	29	52.73	12	21.82	7	12.73	1	1.82
16	Non-resp	DOXORUBICIN	32	58.18	8	14.55	4	7.27
17	Non-resp	ETOPOSIDE	10	18.18	11	20.00	5	9.09
18	Non-resp	FLUDARABINE	1	1.82	7	12.73	6	10.91	4	7.27
19	Non-resp	HYDROCORTISONE	4	7.27	.	.	1	1.82
20	Non-resp	HYDROXYUREA	3	5.45	1	1.82	2	3.64
21	Non-resp	IDARUBICIN	2	3.64	1	1.82	2	3.64	2	3.64
22	Non-resp	IFOSFAMIDE	3	5.45	3	5.45	2	3.64
23	Non-resp	MELPHALAN	.	.	2	3.64	.	.	1	1.82
24	Non-resp	METHOTREXATE	40	72.73	17	30.91	8	14.55	1	1.82
25	Non-resp	METHYL PREDNISOLONE	6	10.91	3	5.45	1	1.82

Obs	IRRCresp2	trtname	freq1	per1	freq2	per2	Freq 3	per3	freq4	per4	freq5	per5	freq6	per6
26	Non-resp	MITOXANTRONE	8	14.55	7	12.73	1	1.82
27	Non-resp	NELARABINE	.	.	2	3.64	.	.	1	1.82	.	.	1	1.82
28	Non-resp	PREDNISONONE	28	50.91	9	16.36	2	3.64
29	Non-resp	RITUXIMAB	7	12.73	2	3.64	2	3.64
30	Non-resp	SOLAMBUSOL	1	1.82
31	Non-resp	TENIPOSIDE	3	5.45	1	1.82
32	Non-resp	THIOTEPA	1	1.82
33	Non-resp	VINCRISTINE	54	98.18	22	40.00	5	9.09	1	1.82
34	Non-resp	VINDESINE	2	3.64
35	Non-resp	_Unknown	1	1.82	.	.
36	OR(CR+CRi)	6-MERCAPTOPYRINE	4	40.00	2	20.00
37	OR(CR+CRi)	ASPARAGINASE	4	40.00	5	50.00
38	OR(CR+CRi)	BUSULFAN	2	20.00
39	OR(CR+CRi)	CYCLOPHOSPHAMIDE	8	80.00	7	70.00
40	OR(CR+CRi)	CYTARABINE	4	40.00	5	50.00	1	10.00
41	OR(CR+CRi)	DAUNOMYCIN	3	30.00	1	10.00
42	OR(CR+CRi)	DEXAMETHASONE	5	50.00	2	20.00
43	OR(CR+CRi)	DOXORUBICIN	7	70.00	3	30.00
44	OR(CR+CRi)	ETOPOSIDE	.	.	1	10.00	1	10.00
45	OR(CR+CRi)	IDARUBICIN	1	10.00
46	OR(CR+CRi)	IFOSFAMIDE	.	.	1	10.00
47	OR(CR+CRi)	LIPOSOMAL ANNAMYCIN	.	.	1	10.00
48	OR(CR+CRi)	MELPHALAN	2	20.00
49	OR(CR+CRi)	METHOTREXATE	6	60.00	3	30.00
50	OR(CR+CRi)	MITOXANTRONE	1	10.00
51	OR(CR+CRi)	PREDNISONONE	5	50.00	1	10.00
52	OR(CR+CRi)	VINBLASTINE	.	.	1	10.00
53	OR(CR+CRi)	VINCRISTINE	10	100.00	5	50.00
54	OR(CR+CRi)	VINOURELBINE	1	10.00
55	OR(CR+CRi)	_Unknown	.	.	1	10.00	1	10.00

Table A.2: Reason of death (ITT HSB407)

Primary cause of death	All (N=65)		Responders (N=10)		Non-responders (N=55)	
	freq	Per (%)	freq	Per (%)	Freq	Per (%)
ALL	42	64.62	6	60.00	36	65.45
OTHER, CORTICO-INFARCT, BRAIN	1	1.54	0		1	1.82
OTHER, INTRACEREBRAL HEMORRHAGE DUE TO CNS LEUKEMIA	1	1.54	1	10.00	1	1.82
OTHER, LARGE CEREBELLAR HEMORRHAGE	1	1.54	0		0	0
OTHER, LIVER FAILURE	1	1.54	0		1	1.82
OTHER, MULTI SYSTEM ORGAN FAILURE	1	1.54	0		1	1.82
OTHER, PNEUMONIA	1	1.54	0		1	1.82
OTHER, PULMONARY HEMORRHAGE	1	1.54	0		1	1.82
OTHER, RESPIRATORY FAILURE	2	3.08	0		2	3.64
OTHER, RESPIRATORY FAILURE SECONDARY TO ALL	1	1.54	0		1	1.82
OTHER, SEPSIS AND RESPIRATORY FAILURE.	1	1.54	0		1	1.82
OTHER, SEPTIC SHOCK, SECONDARY TO NEUTROPENIA, - CAUSED BY ALL. (PSEUDOMONAS SEPSIS)	1	1.54	0		1	1.82
OTHER, STREP MITUS LEADING TO MULTI-ORGAN FAILURE	1	1.54	0		1	1.82
OTHER: AE#25 PNEUMONIA & AE#34 SEPTIC SHOCK SECONDARY TO ALL	1	1.54	0		1	1.82
SUDDEN CARDIAC ARREST	1	1.54	0		1	1.82
TRANSPLANT-RELATED MORTALITY	3	4.62	2	20.00	1	1.82
Missing	5	7.69	1	10.00	4	7.27

As shown in Table A.2, for both responders and non-responders, about 60%-65% subjects died because of ALL. There are more other reasons of death in the non-responder group.

Table A.3: Baseline variable distribution by response [n(column %)]

	OR (CR+CRi) N=10	Non- Resp N=55
Age		
[18, 29)	7 (70)	22(40)
[30, 59)	2 (20)	26(47.3)
>=60	1 (10)	7(12.7)
Gender		
Female	5(50)	27(49.1)
Male	5(50)	28(50.9)
Extramedullary disease		
Yes	4(40)	6(10.9)
No	6(60)	49(89.1)
ECOG at baseline		
0	4(40)	13(23.6)
1	6(60)	27(49.1)
2	0	11(20)
3	0	4(7.3)
Platelet count 10 ⁹ /L		
<=50	2 (20)	37(67.3)
>50	8(80)	18(32.7)
Alterm		
B-L Leuk	8(80)	47(85.5)
T-L Leuk	2(20)	8(14.5)
# prior line trt		
2	5(50)	28(50.9)
3	5(50)	19(34.5)
4	0	7(12.7)
6	0	1(1.8)
# prior HSCT		
0	3(30)	31(56.4)

1	7(70)	22(40)
2	0	2(3.6)
	OR (CR+CRi)	Non- Resp
Intermediate Cytogenetics		
Normal	3(30)	17(30.9)
Del	0	2(3.6)
Del-Y	1	0
Cyto unfavorable		
Complex karyotypes	2(20)	16(29.1)
Other types	2 (20)	13 (23.6)
Missing	2 (20)	7 (12.7)

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/s/

MARK D ROTHMANN

04/05/2012

Signing for Dr. Lan Huang and signing as the Statistical Team Leader; I concur

RAJESHWARI SRIDHARA

04/09/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202497

Applicant: Talon Therapeutics

Stamp Date: July 2011

Drug Name: Marqibo

NDA/BLA Type: NDA

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	Yes			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	Yes			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	Yes			Gender, age, and ALL type. All whites
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	Yes			Have data and programs for the two major studies HBS407 and VSLI-06

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? yes

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	Y			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Y			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			NA	No interim analysis
Appropriate references for novel statistical methodology (if present) are included.			NA	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	Y			

File name: 5_Statistics Filing Checklist for a New NDA 202497

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			NA	ITT vs. Evaluable IRRC, and missing → unfavorable , or impute using the most conservative definition
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STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
HBS407	Phase II, international, multicenter, open-label, single-arm	1 arm/65	Rate of complete response (CR) plus CR with incomplete blood count recovery (Cri)/exact test	Effective
VSLI-06	Phase I/II, multicenter, open-label, dose escalation study	1arm/36	CR+PR/exact test	Effective

Note: all the studies in this submission are open-label single arm studies without control arm.

Lan huang 8/30/2011

Reviewing Statistician Date

Mark Rothman 9/1/2011

Supervisor/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/

LAN HUANG
09/08/2011

MARK D ROTHMANN
09/08/2011