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APPLICATION NUMBER:

202497Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	4/10/2012
From	Qin Ryan, M.D., PhD
Subject	Cross-Discipline Team Leader Review
NDA #	202497
Applicant Name	Talon Therapeutic, Inc.
Date of Submission	6/7/2011
PDUFA Goal Date	5/12/2012
Proprietary/Established (USAN) names	Marqibo/Vincristine Sulfate Liposomes Injection, VSLP
Formulation / Strength	Liposomal Solution, Injection
Proposed Dosing regimen	2.25 mg/m^2 intravenously over 60 minutes every 7 days
Proposed Indication(s)	Philadelphia Chromosome-negative (Ph-) Adult Acute Lymphoblastic Leukemia (ALL) patients in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies
Recommended Action:	Accelerated Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Ashkan Emadi, M.D., Ph.D./Qin Ryan, M.D., Ph.D.
Statistical Review	Lan Huang, Ph.D./Mark Rothmann, Ph.D./Rajeshwari Sridhara, Ph.D.
Pharmacology Toxicology Review	M. Stacey Ricci, MEng, ScD; Haleh saber, PhD
CMC Review/OBP Review	Xiao Hong Chen, PhD., Debasis Ghosh, PhD/Janice Brown, PhD /Sarah Pope Miksinski, Ph.D
Microbiology Review	Vinayak Pawar, PhD/ Bryan S. Riley, PhD
Clinical Pharmacology Review	Young Jin Moon, Ph.D./Julie M. Bullock, Pharm.D.
DDMAC	James Dvorsky, Pharm.D
DSI	Anthony Orecia, M.D./Susan Leibenhaut, M.D./Tejashri Purohit-Sheth
ONDQA Biopharmaceutics	John Duan, PhD/Angelica Dorantes, PhD
OSE/DMETS	N/A
OSE/DDRE	N/A
OSE/DSRCS	N/A
Regulatory Project Manager/CPMS	Amy Baird/Janet Jamison

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

1. Introduction

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, relying on the data from Vincristine Sulfate Injection as presented in the label for this drug or on published literature to address certain nonclinical sections of the label. Vincristine, a vinca alkaloid, is an approved drug for treatment of acute leukemia. The current NDA 202497 submission is seeking accelerated approval for Marqibo for the treatment of adult (age $\geq$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/m^2 IV every 7 days as a 60 minute infusion for a 28-day course of treatment.

The NDA was 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. The review high lights of non-comparative clinical efficacy and safety and statistics, clinical pharmacology and biopharmaceutical, CMC, and pharcotoxicology and scientific investigation are included in the CDTL review. In addition, the clinical issues was presented and discussed in the Oncologic Drugs Advisory Committee (ODAC) on March 21, 2012. The insights and recommendations of ODAC regarding the benefit and risk of Marqibo are briefly summarized in this review. It is noteworthy that the decision on regulatory action for this NDA is complicated. The decision of given an accelerated approval to Marqibo for the proposed indication will be contingent on whether applicant will be able to adequately address issues of CMC and clinical postmarket requirement.

2. Background

In the United States, of 5300 new cases of ALL reported annually, approximately 2000 are in adults (age $\geq$18 years). Seventy percent (1400 subjects) of new annual cases of adult ALL are Ph-. Based on published treatment response rates and treatment-related mortality rates, approximately 500 patients per year are in second or greater relapse and require second or greater salvage therapy.

For the first line treatment of ALL in adult patients, vincristine, corticosteroids, anthracyclines and asparaginase continue to be the effective chemotherapy backbone for treatment of ALL. Cyclophosphamide, cytarabine (ara-C), etoposide, teniposide, methotrexate, and 6-mercaptopurine are other chemotherapeutic agents that have been used in treatment of ALL. Postremission therapy is comprised of intensified consolidation and maintenance therapy or HSCT. Approximately 60-70% of patients would relapse after the first-line of therapy or are refractory to it. Remission rates ranging 20-80% have been reported in adults with refractory ALL or after the first relapse of ALL. Remissions after the first salvage therapy, if achieved,

are usually short with median durations ranging from 2 to 7 months. Adults with relapsed Ph-ALL have 5-year survival of approximately 7%.

3. CMC/Microbiology/Device/DMEPA

Based on the CMC review by Dr. Chen, Marqibo (vincristine sulfate liposome injection, 5 mg/31 mL, VSLI) is supplied as a 3-vial kit for constitution to prepare liposome encapsulated vincristine at the pharmacy. Prior to administration, the kit's components are mixed in a prescribed manner to load the active ingredient, vincristine, into the sphingomyelin/cholesterol (SM/Chol) liposome. Following constitution, VSLI is a white to off-white, homogenous, translucent suspension, which is diluted with standard diluents (5% Dextrose or 0.9% Sodium Chloride) prior to IV infusion.

Manufacturing of Marqibo consists of the production of each individual component as listed below and packaging of all the components into the kit:

- Vincristine Sulfate Injection USP (5 mg/ 5 mL) (VSI)
- Sphingomyelin/Cholesterol Liposome Injection (103 mg/mL) (SCLI)
- Sodium Phosphate Injection (355 mg/25 mL) (SPI)

Manufacturing of VSI is the same as that of the RLD, Vincristine Sulfate Injection, USP. Manufacturing of SPI and SCLI were developed by INEX, the sponsor of the initial IND 59,056 and previous NDA 21-600. (b) (4) have been used to manufacture the SCLI liposome. The (b) (4) was used to manufacture the liposome used to formulate VSLI for Phase I and IIa clinical trials. The (b) (4) was later developed to facilitate the anticipated scale-up of the commercial production. The SCLI liposome manufactured using the (b) (4) were used in the pivotal Phase II clinical trial.

From a CMC perspective, this application is recommended for a Complete Response action. The following issues need to be completely resolved before this NDA can be recommended for approval. 1) An overall acceptable recommendation from the Office of Compliance; 2) Satisfactorily resolving the CMC deficiencies listed as follows;

1. The requested VSI impurity profile comparison between the applicant's VSI lots and RLD was not provided in the Amendment (SN0009) dated February 13, 2012. Provide full comparative data for the complete impurity profiles of the proposed VSI formulation (at least 3 lots) and the reference listed drug, i.e. list all individual related substances with their RRTs (relative retention time).

2. Regarding the VSI OOS results at the accelerated conditions at 3 and 6 months, although the applicant provided up to 2 months stability data (one month data for 3 lots and two months data for 1 lot) at the accelerated conditions of 25°C/60% RH in the amendment, the applicant did not provide the shipping conditions, such as duration and temperature. Therefore, you did not adequately address the concern regarding two months stability data at 25°C/60% RH being sufficient to support the shipping and handling conditions for both VSI and VSLI.

3. Include the proposed acceptance limit for unspecified degradation products of no more than (b) (4) in the table for SCLI specification.

4. The applicant have stated that vincristine sulfate is a natural product that is one of the over 70- member vinca alkaloid chemical family isolated from the periwinkle plant Catharanthus roseus (Madagascar periwinkle). Provide the source of the raw material, the periwinkle plant, and indicate whether it is grown as a wild plant or cultivated plant. If it is a wild grown plant, you will need to file an Environmental Assessment (EA). If it is cultivated non-wild grown plant, you may claim categorically exclusion under 21 CFR 25.31(a) and/or 21 CFR 25.31 (c). Please refer to the attached FDA document regarding EA Review Requirements for Drugs Derived from Plant Sources.

Based on the Product Quality Microbiology review by Dr. Pawar, Drug Product Marquibo® was submitted under NDA 21-600 by Tekmira Pharmaceuticals. This NDA received a non-approval action in 2005. Talon addressed Quality and other issues from the Agency's enquiry and claims there are no outstanding issues from NDA 21-600 non-approval letter that would prevent submission and acceptance for filing NDA 202497. IQA was filed by CMC on 09/06/2011. On February 9, 2012 an IR was sent to the sponsor to request information on the aseptic handling of the Marquibo kit during reconstitution in a pharmacy setting and to justify the post constitution storage of 12 hours through the absence of microbial growth. The justification for post constitution storage of 12 hours was provided on March 23, 2012. Per Dr. Pawar's review, the deficiencies pertain to the human factor involvement in the aseptic manipulations and preparation of the Marquibo kit and the lack of (b) (4) process validation information from two components of this kit. The microbiology issuea are pending for resolution.

Based on DMEPA consult review, the design of Marqibo introduces opportunities for the occurrence of medication errors in many steps of the medication use process. The most serious concerned is the packaging configuration and the complexity of the preparation of the product:

- The product preparation includes (b) (4) steps, which provides for multiple opportunities for errors.

- Three separate vials are required to achieve the final product. In addition, the vials must be combined in a specific order and heated at a specified temperature (65ºC) and for a specific length of time (10 minutes).

- There are a number of required equipments/tools for the proposed product preparation. If the required materials are not supplied in the kit (i.e., water bath, calibrated thermometer, calibrated electronic timer, sterile syringes, sterile venting filter needles), this may lead to pharmacy personnel using alternative means to prepare the product that may lead to confusion, error, and the possibility that the product is not properly prepared for patient administration.

4. Nonclinical Pharmacology/Toxicology

The Pharmacotoxicology reviews were conducted by Drs. Rocci and Saber. They point out that, in general, liposomal formulation of a drug may result in reduced Cmax-related toxicities and increased AUC-related toxicities. The Applicant suggests that the encapsulated formulation will reduce vincristine-related neurotoxicities.

The original NDA application for Marqibo was submitted to the FDA in 2003, under NDA # 21600. The nonclinical studies were reviewed by Dr. Doo Y Lee Ham. No nonclinical approvability issues were identified by the reviewer; the review was archived on 3/15/2004. According to the review, the liposomal vincristine (VSLI) had a better anticancer activity in the murine tumor models when compared to the free vincristine (VCR). However, repeat-dose toxicology studies in rodents suggest increased neurotoxicity associated with VSLI when compared to VCR. In a 6-cycle repeat-dose toxicology study in Sprague-Dawley rats, VSLI or VCR was administered to animals intravenously once per week. Clinical signs of toxicity suggestive of neurotoxicity were more evident with VSLI than with VCR at equal doses of 2 mg/m2/week and included uncoordinated movements, weakness/ reduced muscle tone, and limited usage of the limbs. Neurological testing using a standard Functional Observation Battery after six cycles of VSLI or VCR at 2 mg/ m2/week indicated that both VSLI and VCR induced peripheral neurotoxicity. Based on the histopathology examination after 6 cycles of VSLI or VCR dosing, VSLI induced greater peripheral neurotoxicity (nerve fiber degeneration) and secondary skeletal muscle atrophy than the equal dose of VCR. In a separate tissue distribution study in rats, 2 mg/m2 of VSLI or VCR was administered to animals. Significantly greater (2 to 3-fold) accumulation of vincristine was observed in sciatic and tibial nerves of the animals after administration of VSLI. Based on the findings in animals, the increased anticancer activity of the liposomal vincristine was accompanied by increased peripheral neuropathy.

5. Clinical Pharmacology/Biopharmaceutics

According to the clinical pharmacology reviewer, Dr. Habtemariam, the plasma pharmacokinetics of Marqibo was investigated in 13 adult patients with relapsed acute lymphoblastic leukemia (ALL) who received a Marqibo dose of 2.25 mg/m^2 administered as a 1 hour infusion. Additional pharmacokinetic studies in patients with solid tumors demonstrated that released vincristine is undetectable at most timepoints in all patients for whom this was evaluated. Therefore, the total vincristine measured in plasma reflects liposomally encapsulated drug that may not be immediately bioavailable and may not be directly comparable to plasma levels of vincristine after administration of standard vincristine, which is in an immediately bioavailable form.

The calculated pharmacokinetic parameters for total plasma vincristine are given in Table 7 of his review.

Table 7: PK Parameters from ALL Patients Dosed with 2.25 mg/m^2 Marqibo[a]

Variable	N	Mean	SD	SE	Median	Range
AUC_∞ (h•ng/mL)	13	14566	6368	1766	13680	7036-26074
CL (mL/h/m^2)	12	345	177	100	302	148-783
C_{max} (ng/mL)	13	1220	229	64	1230	919-1720

a. Dose was administered as a 1-hour infusion.
Source: Dr. Habtemariam's clinical pharmacology review.

The plasma clearance (CL) of Marqibo is slow, 345 mL/h/m^2, at a dose of 2.25 mg/m^2. This is in comparison to the rapid clearance of conventional vincristine at 189 mL/min/m^2 (11,340 mL/h/m^2). The slow clearance of Marqibo contributes to a much higher AUC for Marqibo relative to conventional vincristine. However, the total plasma concentration of vincristine following administration of Marqibo represents liposome-encapsulated drug and may not be immediately available.

Following IV administration of Marqibo, urinary excretion was a minor route of elimination for vincristine and a metabolite. Less than 8% of the administered dose was eliminated in urine over the 96-hour observation period. Urinary excretion of the parent drug vincristine accounted for approximately 7% and a metabolite accounted for 0.8% of the administered dose. The maximum rate of excretion occurred during the 24-48 hour postdose collection interval. Similarly, vincristine urinary excretion levels were previously observed to be approximately 12% of a radiolabeled dose was recovered in the urine over 72 hours, with 6.5% excreted during the first 3 hours.

Pharmacokinetic data were available from seven patients with moderate (n=6) and severe (n=1) hepatic impairment, which were compared to the PK of patients with normal hepatic function who took part in a separate study. The PK of VSLI was evaluated in metastatic melanoma subjects with moderate hepatic dysfunction secondary to liver metastases. The dose adjusted C_{max} and AUC of VSLI in subjects with moderate hepatic impairment was comparable to the C_{max} and AUC of patients with ALL who had otherwise normal hepatic function.

The biopharmaceutical reviewer Dr. Duan evaluated acceptability of the proposed in vitro release assay (IVR) and acceptance criteria. Dr. Duan stated that the IVR method below is acceptable.

Dr. Duan's Table: IVR Method for Marqibo Liposomes Injection

Apparatus	Shaker-waterbath
Media	1-Butanol in PBS 2.75%
Volume	10^5mL
Pre incubation time	1 h
Agitation speed	70 rpm
Temperature	37±0.1 °C
Analytical Method	HPLC Analysis with UV at 297nm for vincristine sulfate

Source: Dr. Duan's review.

With respect to the proposed acceptance criteria for the IVR test, Dr. Duan indicated that there were several communications between FDA and the Applicant (3/19/12 IR Letter, 3/14/12 Applicant's response, and 3/26/12 IR Letter). In a submission dated 4/10/12 (SN #0012), the Applicant accepted FDA's recommendation and the final acceptance criteria for the IVR test of Marqibo are listed in the summary Table from Dr. Duan's review.

Dr. Duan's Table: Acceptance criteria

Test	Analytical Procedure	Acceptance Criteria
Vincristine Sulfate Content Total Free	NT 100-1553	(b) (4)
In Vitro Release 0.5 hours 6 hours 24 hours 96 hours	NT 100-1552 (HPLC)	

Source: Dr. Duan's review and communication.

6. Scientific Investigation of Clinical Trial Conduct

In the Scientific Investigation summary, Dr. Orencia stated that three clinical investigator sites, two for Protocol HSB-07 and one for Protocol VSLI-06, were inspected. Based on review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication.

7. Clinical/Statistical Review on Efficacy

Based on Dr. Emadi's Clinical review and Dr. Huang's statistical review, Marqibo® was studied in an open-label, single-arm trial, HBS407. Eligible patients were 18 years of age or older with Philadelphia chromosome negative ALL in second or greater relapse or whose disease progressed after two or greater treatment lines of anti-leukemia therapy. Patients had to have achieved a complete remission (CR) from one of prior anti-leukemia chemotherapies, defined by a leukemia-free interval of equal or more than 90 days. Patients were not eligible for immediate hematopoietic stem cell transplantation (HSCT) at the time of screening and enrollment.

Patients received intravenous Marqibo® at 2.25 mg/m^2. Dosing was administered every 7 days. Concomitant corticosteroids were not permitted beyond Day 5.

The treated population included 65 patients who received at least one dose of Marqibo®. All of the treated patients received prior vincristine sulfate. Among treated patients, 51% were male, 86% were white, 45% were under 30 years of age and 11% were age 65 or older. Disease characteristics were 85% - B-cell ALL, and 15% - T-cell ALL. In addition, 22 out of 65 (34%) treated patients did not receive asparaginase products prior to enrollment. Efficacy results are shown in the Table 3 of Dr. Emadi's review.

Table 3: Efficacy results of Trial HBS 407

RESPONSE	Trial HSB 407 (N=65)
Complete remission (CR), n (%)	3 (4.6)
CR with incomplete blood count recovery (CRi), n (%)	7 (10.8)
CR + CRi, n (%) (95% CI[a])	10 (15.4) (7.6 – 26.5)
MEDIAN DURATION of CR or CRi (days), (95% CI)	
Based on the first date of CR or CRi to the date of the last available assessment of the same response (n=8)	28 (7, 36)
Based on the first date of CR or CRi to date of documented relapse, death or subsequent chemotherapies including HSCT (n=10)	56 (9, 65)

a CI = Confidence interval (Clopper-Pearson)
Source: Reviews of Drs. Emadi and Huang.

Twelve patients received allogeneic HSCT after receiving Marqibo. Of these 12 patients, 5 achieved CR or CRi with Marqibo® treatment and underwent transplantation. Seven of 12 patients' disease did not achieve CR or CRi following Marqibo. Nevertheless, Six of these 7 patients whose disease did not achieve CR or CRi with Marqibo® received multi-agent chemotherapy pre-transplant and underwent subsequent allogeneic HSCT.

8. Safety

Marqibo, at a dose of 2.25 mg/m^2 weekly, was studied in 83 patients in two trials: study HBS407 and study VSLI-06. Dose reduction, delay or omission occurred in 53% of patients during the treatment. Adverse reactions were observed in 100% of patients and adverse reactions $\geq$ Grade 3 were seen in 96% of patients. The most common adverse reactions (>30%), regardless causality, were constipation (57%), nausea (52%), pyrexia (43%), fatigue (41%), peripheral neuropathy (39%), febrile neutropenia (38%), diarrhea (37%), anemia (34%), decreased appetite (33%), and insomnia (32%). The adverse reaction $\geq$ Grade 3 in $\geq$5% of patients are summarized in Table 34 of Dr. Emadi's review.

Table 34: Most Commonly Reported (> 5%) Grade 3 or Higher Adverse Reactions

Adverse Events Grade ≥3	Study 1 and 2 (N=83) n (%)
Blood and Lymphatic System Disorders	47 (56.6)
Febrile Neutropenia	26 (31.3)
Neutropenia	15 (18.1)
Anemia	14 (16.9)
Thrombocytopenia	14 (16.9)
Infections	33 (39.8)
Pneumonia	7 (8.4)
Septic Shock	5 (6.0)
Staphylococcal Bacteremia	5 (6.0)
Neuropathy*	27 (32.5)
Peripheral Sensory and Motor Neuropathy	14 (16.7%)
Constipation	4 (4.8)
Ileus, Colonic Pseudo-Obstruction	5 (6.0)
Asthenia	4 (4.8)
Muscular Weakness	1 (1.2)
Respiratory Thoracic and Mediastinal Disorders	17 (20.5)
Respiratory Distress	5 (6.0)
Respiratory Failure	4 (4.8)
General Disorders and Administration Site Condition	31 (37.3)
Pyrexia	12 (14.5)
Fatigue	10 (12.0)
Pain	7 (8.4)
Gastrointestinal Disorders	21 (25.3)
Abdominal Pain	7 (8.4)
Investigations	20 (24.1)
Aspartate Aminotransferase Increased	6 (7.2)
Vascular Disorders	8 (9.6)
Hypotension	5 (6.0)
Psychiatric Disorders	9 (10.8)
Mental Status Changes	3 (3.6)
Cardiac Disorders	9 (10.8)
Cardiac Arrest	5 (6.0)
Renal and Urinary Disorders	6 (7.2)
Musculoskeletal and Connective Tissue Disorders	7 (8.4)

* Including neuropathy-associated adverse reactions.
Source: Dr. Emadi's review.

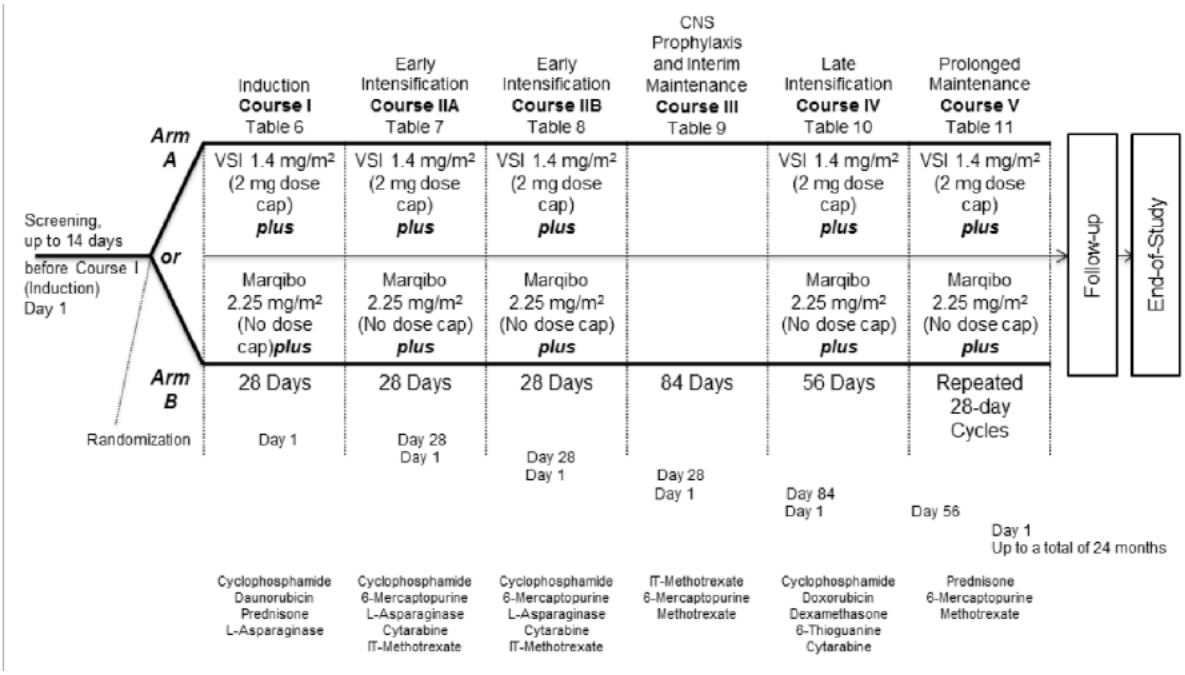
Twenty-eight percent of patients experienced adverse reactions leading to treatment discontinuation. The leading adverse reactions that caused treatment discontinuation were peripheral neuropathy (10%), leukemia-related (7%), and tumor lysis syndrome (2%).

Adverse reactions related to neuropathy leading to treatment discontinuation and reported each in one patient included decreased vibratory sense, facial palsy, hyporeflexia, constipation, asthenia, fatigue, and musculoskeletal pain.

Twenty-three percent deaths were reported in study HBS407. The non-ALL related causes of deaths were 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).

9. The Applicant Proposed Randomized Trial

As described in Dr. Emadi's review, 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 who are ≥ 60 years old and newly diagnosed acute lymphoblastic leukemia (ALL). The primary endpoint of the study is OS with HR = 0.70. The proposed sample size is 348. First patient enrolled on March 22, 2012.



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

- (b) (4)
- (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:

- (b) (4)

(b) (4) and is in an ongoing discussion between the applicant and the FDA.

10. 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. Based on the 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.

Several ODAC 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 might 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.

In additionally, ODAC members discussed the design of the proposed randomized trial. Many 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 randomized 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 might be appropriate, but with the expectation that this approval would be withdrawn if the postmarketing trial failed to confirm clinical benefit.

Finally, the ODAC members voted on whether 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, and resulted on 7 yes, 4 no, and 2 abstain.

11. Conclusions and Recommendations

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, in lacking of randomized study to compare Marqibo to vincristine, it is difficult to support any advantage in safety of Marqibo without a direct comparison to vincristine.

However, based on insights of multidiscipline reviews of CMC/mcriobiology, product safety pharmacotoxicology, pharmacology, study conduct clinical and statistical data, as well as the ODAC recommendation, I feel that the existing clinical result, although it is limited, suggests the benefits of Marqibo overweigh its risks. However, the regulatory decision on this application is depending on the resolution of CMC, product quality/microbiology and medication error prevention issues. Furthermore, if accelerate approval is to be considered, an adequate postmarketing trial or trials should be in place before the regulatory action.

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/s/

QIN C RYAN
04/25/2012
CDTL review