Oncologic Drugs Advisory Committee
Briefing Document

FDA Review

NDA 21-600

Marqibo® (Vincristine Sulfate Liposomes Injection)

Indication: Treatment of Patients with Aggressive Non-Hodgkin's Lymphoma Previously Treated with at Least Two Combination Chemotherapy Regimens

Oncology Drug Advisory Committee Meeting
December 1, 2004

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1 SUMMARY:

Inex Pharmaceuticals has submitted a New Drug Application (NDA) for Marqibo, Vincristine Sulfate Liposomes Injection (VSLI) for accelerated approval based primarily on results from an international, multicenter, single arm study in patients with relapsed, aggressive Non-Hodgkin's Lymphoma (NHL). Inex seeks the following indication: Marqibo is indicated for the treatment of patients with aggressive Non-Hodgkin's Lymphoma previously treated with at least two combination chemotherapy regimens.

Several regulatory and scientific issues are pertinent for this ODAC meeting concerning VSLI. The regulatory issues for this application include: Accelerated Approval, Available Therapy, Confirmatory Trial and requirement for adequate and well-controlled trials. The scientific issues to consider for this application include: whether partial responses are reasonably likely to predict for clinical benefit in relapsed, aggressive NHL and whether responses of the magnitude seen in this application could predict for clinical benefit.

The NDA submission contains 2 studies. The major study (CA99002) under consideration is a international, multi-center, open-label, uncontrolled, single arm, phase 2 study using VSLI as a single agent given every 3 weeks to relapsed, aggressive NHL patients who had received at least 2 prior combination therapies including one anthracycline-based therapy previously. The supportive study (DM97-162) is a single center, open-label, uncontrolled, single arm, phase 2 study using VSLI as a single agent given every 3 weeks to relapsed NHL and acute lymphoblastic leukemia (ALL) patients. The primary endpoint of both studies was response rate. Other endpoints included: duration of response, time-to-progression, survival and toxicity.

Study CA99002 enrolled 119 patients. However, the sponsor amended the protocol nine times, including the eligibility criteria, and granted exemptions allowing patients who did not meet the eligibility criteria to be enrolled. As a result of the amendments and exemptions, only 65 (54.6 %) patients enrolled actually met the critical eligibility criteria: had relapsed, aggressive Non-Hodgkin's Lymphoma; received 2 or more prior combination chemotherapies, including 1 prior anthracycline-based therapy for their disease; and had all required baseline examinations, scans and lab values. In addition, the sponsor modified the International Workshop standardized criteria published as "Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas[i]." Revision of standardized criteria in the evaluation of a novel agent prevents comparison to other studies or historical control data. According the review team's analysis, the unconfirmed response rate (complete response (CR) + partial response (PR) + complete response unconfirmed (CRu)) was 21.5% (95% CI 12.3, 33.5) with 1.5% CRs (95% CI 0, 8.3). The confirmed response rate was 12.3% (95% CI 5.5, 22.8), with no confirmed CRs.

Accelerated approval is not a screening process for drug activity. The magnitude of the response rate, duration, and type (CR vs. PR) must be considered in deciding whether the surrogate is reasonably likely to predict clinical benefit.

2 AGENCY APPROVAL REQUIREMENTS

2.1 EFFECTIVENESS REQUIREMENT FOR APPROVAL

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act adding a requirement that, to obtain marketing approval, manufacturers must provide "substantial evidence" of effectiveness. Section 505(d) of the Act defined substantial evidence as "evidence consisting of adequate and well-controlled investigations." The Agency's position regarding the quantity of evidence is that Congress intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. In 1997, the Food and Drug Administration Modernization Act stated that a single trial may suffice if other supportive evidence exists such as evidence from other trials where the drug has been used in different age groups, at different doses, and in different regimens, or different modified release dosage forms. The 1998 Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products states, that for a single trial to be considered sufficient, the single trial must be well-conducted, internally consistent, and demonstrate a compelling result. In general, the FDA has relied on a single adequate and well controlled efficacy study (along with supportive evidence) to support approval in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

The Code of Federal Regulations (CFR), 21CFR 314.126 (b), defines adequate and well controlled studies. Key regulatory points to consider for the present application include:

- The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect…
- The method of selection of subjects provides adequate assurance that they have the disease or condition being studied,…
- The methods of assessment of subjects' response are well-defined and reliable…

2.2 APPROVAL MECHANISMS

Two approval mechanisms exist for agents used to treat serious and life-threatening illness: regular and accelerated. The Agency grants regular approval based on an endpoint which demonstrates clinical benefit or an established surrogate for clinical benefit. Examples of endpoints for regular approval include an improvement in quantity

(e.g., survival or time to progression) or quality of life. The Agency grants accelerated approval (AA) if a drug (or biologic) appears to provide a benefit over available therapy; the benefit is determined by the drug's effect on a surrogate endpoint deemed reasonably likely to predict clinical benefit or on evidence of an effect on a clinical benefit other than survival. One example of an endpoint for AA is response rate.

For AA, the Agency requires additional post-marketing studies to confirm and describe the clinical benefit. The Agency expects that such confirmatory studies to demonstrate clinical benefit will usually be underway at the time of approval. If confirmatory studies are not performed with due diligence or fail to demonstrate clinical benefit, the Code of Federal Regulations describes a mechanism for removing these agents from the market.

2.3 AVAILABLE THERAPY FOR NON-HODGKIN'S LYMPHOMA (NHL)

Because AA requires an advantage over "available therapy", the definition of this term is a critical issue. The Agency's Guidance for Industry: Available Therapy defines available therapy for drugs considered for accelerated approval. The Guidance states "available therapy (and the terms existing treatments and existing therapy) should be interpreted as therapy that is specified in the approved labeling of regulated products, with only rare exceptions.

FDA recognizes that there are cases where a safe and effective therapy for a disease or condition exists but it is not approved for that particular use by FDA. However, for purposes of the regulations and policy statements … only in exceptional cases will a treatment that is not FDA-regulated (e.g., surgery) or that is not labeled for use but is supported by compelling literature evidence (e.g., certain established oncologic treatments) be considered *available therapy*."

To determine whether VSLI meets the criteria for AA, the Agency and ODAC must consider not only approved drugs and biologics but also the published literature.

2.3.1 Recently Approved Therapies for Non-Hodgkin's Lymphoma (NHL)

The Agency has approved and labeled drugs and biologics for single agent and combination use for NHL. Within the past 15 years, the Agency has approved 4 biologic agents for the treatment of NHL. The Agency approved these four agents for the treatment of relapsed follicular NHL, a different indication than is proposed for VSLI. Complete Responses and an improvement in survival have been thought to represent clinical benefit for patients with aggressive NHL.

2.3.1.1 Rituxan

The Agency approved Rituxan based on durable response rates in patients with relapsed or refractory low grade or follicular CD 20+ B-cell NHL. The approval was based on an

efficacy and safety database of 306 patients in 7 studies. The main study for approval was a single arm study involving 166 patients. The overall response rate was 48% with a complete response rate of 6% and a partial response rate of 42%. The median duration of response was at least 9.2 months.

2.3.1.2 Zevalin

The Agency approved Zevalin based on durable response rates in patients with relapsed or refractory low grade follicular or CD20+ transformed B-cell NHL and in patients with rituximab-refractory follicular NHL. The approval was based on an efficacy and safety database of 426 patients in 6 studies. The main trials for approval were 106-04, a single arm, open-label trial in patients with rituximab-refractory follicular NHL and 106-06, a multicenter, randomized, phase 3 active controlled trial comparing Zevalin to Rituxan therapy in patients with relapsed or refractory low grade follicular or CD20+ transformed B-cell NHL . The overall response rates were 74% (18% CR) in the comparison trial and 59% (4% CR) in the single arm trial. The median duration of response ranged from 7.7 to 14.2 months for five studies. The median duration had not been reached for the sixth study.

2.3.1.3 Bexxar

The Agency approved Bexxar based on durable response rates in patients with CD 20+ follicular B-cell NHL with and without transformation whose disease is refractory to Rituxan and had relapsed following combination chemotherapy. The approval was based on an efficacy and safety database of 230 patients in 5 studies. The overall response rates ranged from 47-64% with complete response rates which ranged from 20-33%. The median durations of response were greater than or equal to 1 year.

2.3.1.4 Intron-A

The Agency approved INTRON A (Interferon alfa-2b) recombinant for Injection for the initial treatment of clinically aggressive follicular Non-Hodgkin's Lymphoma in conjunction with anthracycline containing combination chemotherapy in patients 18 years of age or older. The safety and efficacy of INTRON A administered in conjunction with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHVP), a combination chemotherapy regimen, was evaluated as initial treatment in patients with clinically aggressive, large tumor burden, Stage III/IV, follicular Non-Hodgkin's Lymphoma. In a randomized, controlled trial, 130 patients received CHVP therapy and 135 patients received CHVP therapy plus INTRON A therapy. The group receiving the combination of INTRON A therapy plus CHVP had a significantly longer progression-free survival (2.9 years vs. 1.5 years, p=0.0001, log rank test) and median survival (not reached vs. 5.5 years p=0.004, log rank test).

2.3.2 Past Approved Therapies for Non-Hodgkin's Lymphoma

The table below lists drug approvals from 1959 to 1987 for NHL based primarily on preclinical data, anecdotal data concerning treated patients, and a review of the literature.

Table 1 Past Approvals for Non-Hodgkin's Lymphoma (Reviewer Table)

Drug	Approval Date	Indication
Methotrexate	August 10, 1959 (injection)	In combination with other chemotherapeutic agents in the treatment of advanced stage Non-Hodgkin's lymphomas
Cyclophosphamide	November 11, 1959	Alone or in combination for the treatment of Malignant lymphomas, lymphocytic lymphoma (nodular or diffuse), mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma
Vincristine	July 10, 1963	In combination with other chemotherapeutic agents in the treatment of Non-Hodgkin's lymphomas
Vinblastine	November 25, 1965	For the treatment of Non-Hodgkin's lymphomas
Bleomycin	July 31, 1973	Palliative treatment of Non-Hodgkin's lymphomas
Carmustine	March 7, 1977	Non Hodgkin's Lymphoma -as secondary therapy in combination with other approved drugs for patients who relapse while being treated for primary therapy or fail to respond to primary therapy
Adriamycin	December 23, 1987	Non-Hodgkin's Lymphoma

2.3.3 Non-Approved Therapies for Relapsed, Aggressive Non-Hodgkin's Lymphoma

The treatment of relapsed, aggressive NHL is complex and includes chemotherapy regimens that are not specifically labeled for a NHL indication as well as high dose chemotherapy with stem cell transplantation.

Treating physicians most commonly use combination chemotherapy to treat relapsed, aggressive NHL. The table below lists selected combination regimens using marketed agents with overall response rates (ORRs) of 30% or more.

Table 2 Combination Chemotherapy Regimens for Relapsed or Refractory, Aggressive Non-Hodgkin's Lymphoma (Reviewer Table)

Regimen	Response Rate	Reference
IIVP-16	ORR - 47.4%, CR - 21.1%	Engert et al. Leukemia and Lymphoma 1997 vol. 24 pp.513-522.
Idarubicin and high dose Cytarabine	ORR - 61%, CR -59.1%	Dufour et. al. Leukemia and Lymphoma 1996 vol. 22 pp.329-334.
ICE	ORR - 59%, CR -17.9%	Jerkman et. al. Eur J Haematol 2004; 73:179-182
Rituxan-EPOCH	ORR - 68%, CR-28%	Jermann et al. Annals of Oncol 2004; 15:511-516

Modified ICE	ORR - 43.8%, CR -12.5%	Itoh et al. Int J Hem 1998 Dec. 68(4):431-7.
Cisplatin and Fludarabine and Cytarabine	ORR - 48%, CR- 7%	Seymour et al. Cancer 2002 94 (3):585-93.
Taxol plus high dose Cyclophosphamide	ORR - 45%, CR -16%	Younes et al. British Journal of Hematology 1998; 103:678-83.
DHAX	ORR- 50%, CR - 16.7%	Chau et al. British Journal of Hematology 1998; 101:203-4.
Daunosome plus COP-X	ORR - 88%, CR - 18%	McBride et al. Leukemia and Lymphoma 2001 vol. 42 (1-2) pp.89-98.
FLUDAP	ORR - 39%, CR - 15.2%	Child et al. Leukemia and Lymphoma 2000 vol. 37 (3-4) pp.309-17.
Rituxan plus ICE	ORR - 77%, CR - 53%	Kewalramani et al. Blood 2004; 103(10):3684-88.
Mitoxantrone-DHAP	ORR - 41%, CR - 23%	Haq et al. Leukemia and Lymphoma 1999 vol. 35 (5-6) pp.527-36.
Cytarabine and Etoposide	ORR - 66%, CR-33%	Gentet et. al. JCO 1990; 8(4):661-665.
Dexamethasone Cytarabine and Cisplatin	ORR - 67%, CR - 23%	Press et. al. JCO 1991; 9(3):423-31.
Ifosfamide and mitoxantrone	ORR - 47%, CR - 31%	Dovey et al. Hematological Oncology 1990; 8 (4):205-13.
ESHAP	ORR - 53.1%, CR - 31.3%	Wang et al. Japanese Journal of Clinical Oncology pp.33-37
ESHAP	ORR - 72%,	Ezzat et al. Ann Oncol 1994; 5(5):453-456.
VIM	ORR - 60%, CR - 43%	Herbrecht et al. Hematological Oncology 1991;9(4-5):253-7.
Ifosfamide and mitoxantrone	ORR - 48.5%, CR - 30%	Child et al. Hematological Oncology 1991; 9 (4-5):235-44.
VIM3-Cytarabine	ORR - 67%, CR - 17%	Dupriez et al. Hematological Oncology 1991; 9(4-5):259-66.
CCNU and Vinblastine	ORR - 40%, CR - 20%	Palmieri et al. Hematological Oncology 1990;8 (4):179-83.
MACOP-B	ORR - 86%, CR - 72%	Oster et al. Blut 1990; 60 (1):23-7.
Etoposide and Mitoxantrone and Cisplatin and Dexamethasone	ORR - 45.4%, CR - 31.8%	Vitolo et al Haematologica 1991; 76 (1):43-6.
EPIC	ORR - 58%, CR - 28%	Hickish et al. British J of Cancer 1993; 68(3):599-604.
HOAP-Bleomycin	ORR - 46.7%, CR - 33.3%	Liang et al. Cancer Chemother Pharmacol 1988; 22(2):169-71.
Ifosfamide, hydroxyurea and etoposide	ORR - 52.6%, CR - 5.2%	Gasser et al. Cancer Treat Rep 1985; 69(2):225-6.
etoposide and mitoxantrone and Cisplatin and prednisolone	ORR - 61%, CR - 22.2%	Ohnosi et al. Cancer Treat Rep 1987; 71(6):639-41.
Vinblastine, bleomycin and Cisplatin	ORR - 38.5%, CR-0%	Corder et al. Cancer 1984:54(2):202-6
CAMP	ORR - 47%, CR - 27%	Ruit et al. Seminars Oncology 1990;17(6):suppl 10:24-7
NOPE	ORR - 49%, CR - 34%	Bezwoda et al. Leukemia and Lymphoma 1993 vol. 10 (4-5) pp.329-33.
Cyclophosphamide, etoposide,	ORR - 34%	Chao et. al. Blood 1990; 76(7):1293-

procarbazine, prednisone [CEPP(B)]		1298.
DHAP	ORR - 60.5%	Velasquez et al. Blood 1988; 71(1):117-122.
Ifosfamide, methotrexate, and etoposide	ORR - 62%	Cabanillas et al. Blood 1982; 60(3):693-697
P-IMVP-16/CBDCA	ORR - 55.6%, CR - 26.7%	Sawada et. al. Eur J Haematol 2002; 68:354-61
Methotrexate plus adriamycin plus bleomycin plus cyclophosphamide plus vincristine (M-BACOD)	ORR - 88.1%, CR - 78%	Canellos et al. Cancer Treat Rep 1981; 65 (suppl 1)125-9.

The table below lists selected single agent regimens with published overall response rates of 20% or more in relapsed, aggressive NHL.

Table 3 Single Agent Chemotherapy for Relapsed Aggressive NHL (Reviewer Table)

Regimen	Response Rate	Reference
Oral etoposide	ORR - 69%, CR - 12.5%	Shaklai et al. Cancer 1996 77 (11):2313-7.
Gemcitabine	ORR - 66%, CR - 33%	Per Bernell et al. British Journal of Hematology 1998; 101:203-4.
Cytarabine	ORR - 63.6%, CR -45.5%	Peters et al. Neth J Med 1987;30(1-2):64-74
Methotrexate	ORR - 52%, CR - 20.8%	Canellos et al. Cancer Treat Rep 1981; 65 (suppl 1)125-9.
Il-2	ORR - 50%, CR - 50%	Lauria et al. Eur J Can 1991;27(4):521-2.
Rituxan	ORR - 31.8%, CR -4.8%	Rothe et. al. Haematologica 2004:89(7):875-876.
Idarubicin	ORR - 43%	Case et al. Leukemia and Lymphoma 1993; 10 Suppl: 73-79.
Oxaliplatin	ORR - 40%	Germann et al. Ann Oncol 1999; 10(3):351-354.
Rituxan	ORR - 37%, CR - 26.3%	Tobinai et al. Annals of Oncology 2004;15:821-830
Oxaliplatin	ORR - 24%	ASH, 2003 Abs # 2361
Bortezomib	ORR - 20%	ASCO, 2004 Abs. # 6581

2.4 CONFIRMATORY STUDIES

In March 2003, the Agency reviewed the progress of the required confirmatory trials for drugs and biologics granted Accelerated Approval (AA) with the Oncology Drug Advisory Committee (ODAC). At the meeting, the Agency and ODAC discussed the progress of 16 drugs or biologics for 19 oncology indications granted AA since 1992, which had been approved for at least 18 months.[ii] Of the 12 agents, only 4 had completed their required post-marketing studies and been converted to regular approval. The remaining 8 had not. Among the reasons postulated for failure to complete the required confirmatory clinical studies include the difficulty of enrolling to a confirmatory trial once the drug is marketed. At that ODAC meeting, the committee reinforced the Agency's recommendation that the post-marketing studies be ongoing at the time of Accelerated Approval.

The Agency believes that confirmatory trials should be a part of a comprehensive drug development plan. The confirmatory trials should be an integral part of this plan and discussed early in the product's development.

3 NDA SUBMISSION

The NDA submission contains 2 studies; the major study (CA99002) and the supportive study (DM97-162). The primary endpoint of the both studies was response rate. Other endpoints included: duration of response, time-to-progression, survival and toxicity.

Reviewer's Comment: Time to progression and survival in a single arm study cannot be used for registration purposes.

3.1.1 Study CA99002

The major study submitted for review was CA99002 entitled "Pivotal Phase II Multicenter study of Vincristine Sulfate Liposomes Injection in Diffuse large B-cell Non-Hodgkin's Lymphoma." This study was an international, multicenter, open-label, single arm, single agent study of VSLI in patients with relapsed, aggressive Non-Hodgkin's Lymphoma who had received at least 2 prior combination therapies, including one prior anthracycline-based therapy.

3.1.2 Eligibility Criteria

The sponsor amended the protocol 9 times between September 30, 1999 and August 10, 2001. These changes included the eligibility criteria. The major enrollment criteria from the final version (version 9) included:

- Patient has histologically-confirmed aggressive de novo or transformed Non-Hodgkin's Lymphoma as defined by the REAL/WHO classification. Specifically:
    - Diffuse large B-cell Lymphoma
      Primary Mediastinal large B-cell Lymphoma with sclerosis'
      Intravascular Large B-cell Lymphoma
      Immunoblastic B-cell Lymphoma

T-cell rich B-cell Lymphoma
Anaplastic large B-cell Lymphoma
- Peripheral T-cell Lymphoma, not otherwise specified
- Anaplastic large null/T-cell Lymphoma

- Patients who have had prior involved-field irradiation may be included, provided irradiated area is not the only source of measurable disease. Patients who have had total body irradiation as part of high dose therapy and stem cell transplantation are eligible.
- Patient's performance status ECOG <= 3
- Patient has 2 or more prior courses of combination chemotherapy from the time of diagnosis of de novo aggressive lymphoma or from the time of biopsy-proven transformation from an indolent lymphoma.
- Patients' first and second-line treatment must have been combination chemotherapy. The first-line therapy must have been an anthracycline containing regimen.
- Patient has had at least a minor response (MR) to first-line therapy.
- Patients must have measurable disease. Measurable disease is defined as bidimensionally measurable lesions with clearly defined margins that are ≥ 2 cm in the largest dimension determined, for example, by physical examination, X-ray, CT scan or MRI. A CT scan will be required for baseline tumor evaluation of enrolled patients.
- Patient must not have had radiotherapy, chemotherapy, immunotherapy, and/or alternative anti-cancer treatments or corticosteroids (> 10 mg/day of prednisone or equivalent), within the past 4 weeks.
- Patient must not have had major surgery within 4 weeks of enrollment (excluding that for diagnosis).

Reviewer's Comment: Nine amendments made between the original protocol (dated Sept, 30, 1999) and final protocol (Aug, 10, 2001,) which included multiple amendments made to the inclusion/exclusion criteria. These included: histologic criteria, changes to requirements for prior chemotherapies, changes to requirements for prior response, changes to measurable disease, and concerning concomitant treatment with steroids.

Two amendments involved changes to histologic criteria. One amendment included patients with other aggressive de novo (i.e., peripheral T-cell lymphoma, not otherwise specified and anaplastic large null-/T-cell lymphoma) and transformed NHL. However, the protocol did not define clear criteria for defining transformation in the absence of biopsy confirmation.
Another amendment allowed patients to be eligible when there is evidence of follicular lymphoma on any area of the biopsy. However, no clear criteria were provided on how response would be assessed in patients with mixed NHL, composite or discordant NHL.

Reviewer's Comment: In addition, the sponsor granted exemptions so patients could be enrolled in this trial. Unfortunately all these changes and exemptions resulted in a heterogeneous population. For approval consideration, especially on the basis of a single arm trial in a limited patient population, the study population should be well-defined and

reasonably homogeneous. Ensuring a homogenous population provides for some of the requirement of the single arm trial being "adequate and well controlled."

The sponsor granted exemptions so patients could be enrolled in this trial. Some exemptions were reflected in later amendments. Below is a list of selected exemptions granted.

a) Not fulfilling inclusion/ exclusion criteria at baseline:

- patients whose first and second line treatments were not combination regimens but who at least had 2 prior combination regimens (2 patients; 1 patient with exemption);
- platelets counts were below entry limits with no or unknown bone marrow involvement (2 patients with exemptions);
- bone marrow biopsy not performed (3 patients: 2 with exemptions) or not within 3 weeks of first VSLI dose (8 patients: 6 with exemptions);
- an indicator lesion which had received previous radiotherapy was chosen (9 patients: 3 with exemptions);
- washout period less than 4 weeks from previous treatments (7 patients: 6 with exemptions and 5 with progressive disease, 2 without evidence of progressive disease);
- HIV testing not done (3 patients);
- laboratory tests not performed within 48 hours of first VSLI dose (2 patients: 1 with exemption);
- ALT not measured at baseline to determine eligibility (1 patient);
- recent excision of cutaneous squamous cell carcinoma (1 patient with exemption); and
- neurologic disorders unrelated to chemotherapy (1 patient with syringomyelia).

b) Patients recruited prematurely under certain new criteria which were later allowed by protocol amendments approved by IRB (3 patients; all with exemptions).

Central Pathology Review

Site investigators determined whether a patient was eligible for enrollment. Investigators determined whether histological eligibility for entry into the study was met by the review of the patient's pathology reports available on site. A retrospective centralized review of patient's histological diagnosis was carried out by 2 pathologists, Drs. Randy Gascoyne and Mukesh Chhanabhai, at the British Columbia Cancer Agency (BCCA) and University of British Columbia, Vancouver, Canada.

Patients were not withdrawn from the study if deemed ineligible by Central Pathology Review.

3.1.3 Study Design

The study protocol stated that all patients would receive 2.0 mg/m^2 every 2 weeks IV over one hour. Two weeks constituted a cycle. The protocol also stipulated that treatment would continue for 2 cycles following a confirmed response up to a maximum of 12 cycles. Treatment beyond 12 cycles was permitted; however this required a consensus opinion from the sponsor, medical monitor, and the investigator.

Dose Escalation

Dose escalations were not permitted.

Dose Reduction Guidelines

- Toxicities were assessed using the NCI Common Toxicity Criteria. Patients were allowed to have a maximum of three dose reductions using the criteria and dose schedule.

Concomitant Therapy

Administration of any other investigational drug or biological agent during the course of the study resulted in termination of the patient from the study.

Removal from Study

The following criteria outlined some of the reasons for removal from the study.

- Patients who, during the course of the study, do not follow the protocol for the study will be removed from the investigation
- If a patient experiences a grade 4 non- hematological or biochemical toxicity
- The need for additional systemic anticancer therapy, radiation therapy to any disease site (disease progression) or surgical removal of any of the indicator lesions
- Administration of any other investigational drug or biological agents during the course of this study
- Disease progression

3.1.4 Efficacy Analysis: Schedule

Response was assessed on the basis of clinical, radiologic, and pathologic (bone marrow) criteria. The protocol required thoracic, abdominal and pelvic CT scans for all patients. The protocol specified that assessment of disease response by imaging should be performed at start of treatment, every 4 weeks (every 2 cycles) and at the end of study.

The protocol required bone marrow biopsies and serum lactate dehydrogenase (LDH) within 3 weeks of study drug administration. A bone marrow aspirate and biopsy would only be performed to confirm a CR if they were initially positive or if clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

3.1.4.1 Primary Efficacy Parameter:

Version 9 of the protocol defined the primary efficacy endpoint as the objective response rate (ORR). The ORR was defined as the proportion of patients whose best responses were complete response (CR), complete response unconfirmed (CRu), or partial response (PR) in the intent-to-treat (ITT) population.

Reviewer's Comment: Initially, response was defined as CR and PR. In an amendment, CRu was later included as part of the definition of response. The protocol did not stipulate that responses had to be confirmed. Another amendment stipulated that an additional efficacy analysis will be done for patients who meet evaluability criteria.

The patient's best response was determined by an Independent Review Panel (IRP). The treating Investigators (INV) also assessed response and made treatment decisions accordingly.

The protocol stated that responses would be determined according to the criteria proposed in the report of an International Workshop. However, the sponsor modified the International Workshop Criteria for this study. The sponsor stated that justifications for these modifications include:

"1. That some lesions could not be measured accurately. Percentage increases or decreases (as used for some response categories) can only be calculated when accurate bidimensional measurements are possible.
2. That a minimum of 1 and a maximum of 6 lesions (called "indicator" lesions) would be identified and measured accurately throughout the study and used for all subsequent comparisons.
3. That up to 6 lesions were to be chosen from the largest dominant nodes or nodal masses, splenic or hepatic nodules.
4. That measurements were not required for all other lesions ("Non-indicator" lesions), but they were "assessable" and tracked for changes in status (increased, decreased,stable/present, resolved/absent)."

The protocol stipulated that for purposes of this study, 1.5 cm was defined as the upper limit of normal lymph node size. To optimize reliability in determining response, indicator lesions had to have a minimum size of 2 cm in at least one dimension.

Reviewer's Comment: The International Workshop defines normal lymph node size as 1.0 cm in certain circumstances. A paper by Grillo-Lopez et al. postulates that increasing the size of a "normal lymph node", leads to the complete response rate increasing.[iii] *Revision of standardized criteria in the evaluation of a novel agent prevents comparison to other studies or historical control data.*

The protocol stated that indicator lymph nodes followed for response had to measure at least >2.0 cm in at least one diameter. Splenic and hepatic nodules could be included among the 6 indicator nodes.

Modifications
Below are two key modifications made concerning the definitions for the various response categories.

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of lactate dehydrogenase (LDH) if definitely assignable to NHL.

Reviewer's Comment: The International Workshop required normalization of all biochemical parameters not just LDH.

2. All lymph nodes and nodal masses must have regressed to normal size (=1.5 cm in their greatest transverse diameter).

Reviewer's Comment: This requirement differs from the International Workshop in that the International Workshop allowed that some lymph nodes less than 1.5 cm to be abnormal and involved with disease. The Workshop stipulated that these nodes must regress to = 1.0 cm to be considered normal or by more than 75% in the sum of the products of the greatest diameters.

Reviewer's Comment: The criteria for PR allow a patient to be declared as having a PR based on a 50% or greater decrease in the SPD of the indicator lesions while demonstrating stable disease (or no evidence of progressive disease) in the non-indicator lesions. Thus not all disease had to decrease even if clearly abnormal at study start.

3.1.4.2 Secondary Efficacy parameter definitions

The secondary efficacy endpoints were duration of response, time to progression, and overall survival.

Reviewer's Comment: As stated above, time to-progression and overall survival in a single arm trial cannot be used for registration purposes.

3.1.4.3 Primary Analysis

The protocol stipulated that primary efficacy analysis will be performed on the (ITT) population rate of responders, where a responder is defined for this analysis as a patient who achieves a CR, Cru or PR.

Reviewer's Comment: Based on the sponsor's proposed indication, for regulatory purposes the primary analysis of interest is based on those patients who meet the major eligibility criteria.

3.1.4.4 Independent, Blinded Assessment of Response

The sponsor utilized an Independent Review Panel (IRP) to assess a patient's best response. The IRP review was designed to overcome bias in the determination of efficacy by the clinical site investigators and to apply a modified form of the International Workshop criteria for tumor response. The review process consisted of a central radiology review by a single radiologist followed by a final assessment of response by a team of oncologists.

Four versions of the charter were in effect during the IRP process. They are listed in the Appendix.

Reviewer's Comment: The FDA review was unable to verify that the charter for the Independent Review Panel (IRP) was followed because the sponsor retrospectively changed the charter during the course of the review. The charter was amended three times (on 8.13.2002, 9.9.2002, and 1.22.2003) to reflect how the IRP evaluations were actually being performed. Failure to follow the version of the charter in effect at the time of the review is a protocol violation. A complete list of all of the protocol violations for individual subjects was not provided.

The Perceptive Informatics/PAREXEL (PIP) Medical Diagnostics Core Imaging Laboratory Operations Manual, Version 1.0, is dated 6.26.2002. This is almost one year after the first IRP radiology readings were performed in July 2001. This PIP Manual describes the instructions to the clinical sites for acquiring imaging studies, receipt of imaging data by Perceptive Informatics, Inc., (PII), the downloading and archiving of images, and the procedure for the conduct of the independent review. It is unclear what procedures were used prior to the date that this manual went into effect.

Reviewer Comment: Because of the retrospective changes to the charter and the absence of a PIP Manual prior to the start of the independent review, the IRP results may not be reliable with regard to confirmation of tumor response to therapy. In order to confirm reliability, readjudication of the IRP results for each subject using the final version of the charter may be necessary.

Central Radiology Review

CT scans were the primary imaging modality to be reviewed by the IRP radiologist. Occasionally, MRI scans were also reviewed. For a few subjects, plain films were also provided. According to the sponsor, the use of these x-rays was not covered by the

charters. Results of other imaging studies, in the redacted clinical reports, were also given to the IRP oncologists.

For Centralized Review Charter (CRC) Definitions and Indicator Lesion Measurement Rules, please see the Appendix.

The following provisions were important to consider in the review of this application:

- Provision that all study images undergo preliminary review by the contract research organization (CRO) or Perceptive Informatics/PAREXEL prior to review by the IRP
- Procedure for PII Imaging Research Associates (IRAs) to select Indicator lesions, perform cross-product measurements, and prepare images for analysis by the IRP radiologist
- Provision that the IRP radiologist review the preliminary cross-product measurements generated by the PII IRAs for the Baseline and follow-up examinations, and either accept or modify the measurements
- Procedure for the IRP radiologist to enter the cross-product measurements, along with qualitative comments, into the image analysis database
- Provision that once the review is complete, the IRP radiologist should sign off using a unique password, locking the dataset so that no further changes could be made
- Results of radiology review forwarded to the oncologists for determination of overall tumor response
- Procedure for the IRP oncologists to review all cases concurrently

Reviewer's Comment: From review of the imaging database, the first IRP radiology review may have occurred on 7.11.2001. However, the PII Manual did not go into effect until almost one year later. Furthermore, the PII Manual is not clear as to whether the radiology readings were locked after evaluation of each individual time point, or after a series of time points had been read. The submission does not state what PII procedures were in effect for the receipt, archiving, and quality control of images data, or the selection, measurement, and documentation of measurements for Indicator lesions prior to 6.26.2002.

Central Oncology Review

Response evaluation by independent oncology reviewers were done as follows:
The imaging studies were reviewed by an independent radiologist who wrote the IRP RAD report. Two independent oncology reviewers then looked at the imaging report and the clinical information and gave their assessment. If they were concordant, that was listed as the final opinion. If they were discordant, a third independent oncology reviewer assessed the scans and clinical information. The majority out of the 3 was considered the final opinion. If there was still discordance, a fourth oncology reviewer was used to conduct an unblinded adjudication review. This fourth adjudicator reviewer was usually the same as the third oncology reviewer. If a finding of response were based

on radiographic evidence only, the date of response would be the image date. If physical examination findings were factored into the assessment, the date of response/ progression might have been either the date of the clinical visit or the date of the images. Once concordant PD was declared, no further concordance was required. The IRP oncologists were to provide an assessment at each visit, even if the protocol did not require a formal response assessment. The assessment of Unable to Evaluate was used in the absence of response, stable disease, or progression.

4 RESULTS

4.1 PATIENT ENROLLMENT AND DEMOGRAPHICS

The intent to treat (ITT) population consisted of 119 patients enrolled in 42 centers from the United States, Canada and the Czech Republic. The mean age of patients overall was 58 years with a range of 25 to 87 years. The majority of the patients were male (54%) and Caucasian (82%). Baseline ECOG performance status score was = 2 in 94% of patients.

4.2 ANALYSIS POPULATIONS

Per the protocol the ITT population was the primary efficacy population. All patients who received any therapy constituted the safety population. An evaluable population and other subsets were examined by the sponsor for secondary variables and for sensitivity analyses.

Reviewer's Comment: The review team considers only those patients who were deemed "Definite Eligible" by the Central Pathology Review, those patients who did not have major protocol violations, and those patients who had all baseline examinations, scans, and lab measurements to be eligible for assessment of response rate for the proposed indication.

4.3 BASELINE DISEASE CHARACTERISTICS

Histologic Review

The table below shows the results of the centralized pathology review according to the Central Pathology Review Final Histological diagnosis sheet. The Final Histological Diagnosis worksheet only designated patients as "definite eligible", "probable eligible", and "ineligible". No other categories were allowed.

Reviewer's Comment: For review purposes, the review team analysis considers only 89 patients (74.8 %) identified as "Definite Eligible" by Central Pathology Review. Central Pathology review identified 30 patients (25.2%) as "ineligible" or "probable eligible". The majority of patients deemed ineligible for this study by Central Pathology review had low grade histology on biopsy specimens.

Table 4 Central Pathology Review -Final Histologic Diagnosis (Appendix E.1.2.13) (Reviewer's Table)

Histologic Type	N=119	%
Definite Eligible	**89**	**74.8**
Probable Eligible/Ineligible	**30**	**25.2**
Indeterminant	3	2.5
Missing	2	1.7

Reviewer's Comment: Initially only patients with relapsed de novo aggressive NHL were allowed into the study. A subsequent amendment permitted the inclusion of patients with other aggressive de novo (i.e., peripheral T-cell lymphoma, not otherwise specified and anaplastic large null-/T-cell lymphoma) and transformed NHL. Typically in patients with low grade NHL, the diagnosis of transformation is made by definitive biopsy. Although the protocol allowed patients with a diagnosis of transformed lymphoma to be enrolled in the study, the protocol did not define the enrollment criteria for transformation in the absence of a definitive biopsy. Not all enrolled patients had a diagnosis of aggressive NHL by biopsy.

Another amendment allowed patients to be eligible when there is evidence of follicular lymphoma on any area of the biopsy.

Reviewer's Comment: No clear criteria were provided on how response would be assessed in patients with mixed NHL, composite or discordant NHL.

Prior Lymphoma Therapy:

Patients received both single agent and combination chemotherapy as prior therapies before receiving VSLI. Single agent therapies included rituximab, irinotecan, ifosfamide, fludarabine, ribavarin, liopsomal doxorubicin, temozolamide, cyclophosphamide, gemcitabine, and oral etoposide. Combination chemotherapy included well-known regimens such as MIME, ESHAP, CEPP, BEAM, mini-BEAM, CVPP, Hyper CVAD, TTR, M-BACOS, M-BACOD as well as lesser known regimens.

The table below shows the distribution of the numbers of chemotherapy/immunotherapy regimens received by patients prior to trial entry. The majority of patients had between 2 and 4 regimens prior to trial entry. The range of prior therapies was 1 to 10.

Table 5 Prior Therapy Regimens in ITT population (Reviewer's Table)

Number of Prior Chemotherapy regimens	**N=119**	**%**
1	1	0.8
2	23	19.3
3	39	32.8
4	27	22.7
5	13	10.9
6	8	6.7
7	4	3.4
8	1	0.8
9	1	0.8
10	2	1.7

Derived from dataset PR_THER.xpt

The table below shows the mean and median numbers of chemotherapy/immunotherapy regimens received by patients prior to trial entry.

Table 6 Summary of the Number of Prior Therapies (Reviewer's Table)

Mean	3.8
Median	3.0
SD	1.7
Range	1-10

Protocol Violations and Deviations

The FDA assessed the inclusion and exclusion criteria and found violations and deviations such that some patients were ineligible for the trial. The table below summarizes the study protocol deviations and violations for Study CA99002 after assessment by the FDA. The inclusion and exclusion criteria are worded as in the criteria listed in the Protocol CA99002, version 9.0.

Table 7 Study CA99002 Agency Review of Inclusion and Exclusion Criteria and Protocol Violations (Reviewer's Table)

Inclusion (I) or Exclusion (E) Criteria	**Number of Patients with Violations (%) (n=119)**
(I) Patients with histologically confirmed (by Central Pathology Review) aggressive de novo or transformed NHL, as defined by the REAL/WHO classification	30 (25.2)
(I) Patients who have had prior involved-field irradiation may be included, provided the irradiated area is not the only source of measurable disease.	3 (2.5)
(I) Patients must have measurable disease. Measurable disease is defined as at least one bidimensionally measurable lesion with clearly defined margins that are ≥ 2cm in the largest dimension determined by physical examination, or CT exam.*	8 (6.2)
(I) Patients must have 2 or more prior courses of combination chemotherapies from the time of diagnosis of de novo aggressive lymphoma or from the time of biopsy-proven transformation from an indolent lymphoma**	4 (3.4)
(I) Patient's first and second-line treatment must have been combination chemotherapy. The first-line therapy must have been an anthracycline containing regimen.	5 (4.2)
(I) Hematology lab test requirements granulocytes ≥ 0.5 x 10^9/L platelets ≥ 50 x 10^9/L	2 (1.7)
(I) Biochemistry lab test requirements total bilirubin = 2 times ULN ALT and alkaline phosphatase = 4 times ULN	1 (0.8)
(E) Patients known to be HIV positive. Serology evaluation is mandatory prior to enrollment	2 (1.7)
(E) Radiotherapy, chemotherapy, immunotherapy, and/or alternative anti-cancer treatments (including investigational drugs) or corticosteroids (>10 mg/day of prednisone or equivalent), within the past 4 weeks.***	8 (6.7)
(E) Patients with any previous malignancies with less than a 5-year complete remission interval, except for curatively resected basal cell carcinoma or curatively resected in situ carcinoma of the uterine cervix which has been excised.	1 (0.8)
(E) Neuromuscular impairment at screening or prior grade 3 or 4 sensory or motor neuropathy related to chemotherapeutic treatment	2 (1.7)

* For consistency the Agency considered that measurable disease defined only by radiologic films to be determined by the IRP radiologist and measurable disease defined only by physical examination to be determined by the investigator.

** This list does not include those patients deemed by Central Pathology Review to have low grade, indeterminate, missing, or in need of another biopsy to confirm diagnosis.

*** This list includes those patients who had therapy within 4 weeks and no subsequent radiological films to document progression. Two patients on the list have no clear stop date of their last prior treatment so it is not possible to tell if the patient had four weeks between therapies. In the absence of definitive information, I have categorized these patients as having had their therapy within the last 4 weeks. This list does not include those who received steroids, or radiation as treatment of their lymphoma while on study.

Reviewer's Comment: The Agency judged the following to be major protocol violations: those patients whose pathology was not "Definite Eligible" by Central Pathology Review (30 patients); who had no measurable disease (8 patients); those who did not have 2 or

more prior courses of combination chemotherapies (4 patients); whose first-line therapy was not an anthracycline containing regimen (5 patients); and who received chemotherapy, radiotherapy and immunotherapy or corticosteroids within the past 4 weeks (8 patients). Major protocol violations were seen in 54 unique patients (45.3%). Exclusion of 54 patients left only 65 patients. This number represents a fairly small database considering recent approvals for NHL.

Treatment Discontinuation

The primary reason for discontinuation was disease progression or relapse (61%). Other reasons for discontinuation were adverse events (15%), withdrawn consent (5%), death (5%), patient ineligibility (3%) and other (6%). Six patients (5%) were discontinued from the study due to death.

4.4 EFFICACY

Study Population

All enrolled patients were required to have the following prior to study drug administration.

Within 3 weeks of initiation of VSLI treatment:

- Lymphoma History
  -Histologic type of lymphoma
  -number of prior treatment regimens and categorical type (e. g., radiation, combination chemotherapeutic regimens)
  -time to current relapse
  -stage of disease at diagnosis and at study enrollment
- Medical history and physical examination, including tumor measurement of palpable or visual lesions, and vital signs (blood pressure, pulse rate, temperature, and respiration). Baseline signs and symptoms should be recorded using the NCI toxicity grading criteria
- Neurological examination (by Investigators) - monitoring of symptoms and neurologic examination (deep tendon reflexes, tests for sensory and motor impairment, and coordination/ balance)
- Performance status (ECOG rating scale)
- Weight (in street clothes, without shoes). Calculation of BSA (not to be recalculated for subsequent cycles unless there is a change of ≥ 10%)
- Height
- Concurrent diseases and conditions
- Concomitant drugs
- CT scan of the area with disease involvement (with contrast). Every effort should be considered to ensure uniformity of scanning procedures. The Sponsor will provide guidelines to ensure the uniformity of scanning

Every 4 weeks during the course of the study, the protocol required all patients to undergo tumor measurements using an appropriate imaging technique.

Sample size estimates
It was proposed that a 30% response rate (CR+ CRu + PR) in evaluable patients in the patient population represented a clinically significant result. Assuming the true response rate was 30%, this would require 81 patients. It was anticipated that this would require the treatment of approximately 100 patients assuming a 20% drop-out rate..

Data Analysis Plan
The primary efficacy endpoint was the total number of documented responses (CR, CRu and PR); each patient's best response would be used. Estimates of the secondary endpoints (median duration of response, time to progression and survival) would be obtained using Kaplan Meier methods.

Efficacy Analyses

The following analyses listed are the sponsor's and FDA's efficacy analyses. The first table below contrasts the IRP best response results according to INEX and the review team's assessment of eligible enrollees. All CR, CRu and PR were verified by the FDA using datasets and patient data listings. The primary efficacy endpoint was objective response rate (CR + CRu + PR).

Reviewer's Comment: The review team reviewed the datasets and case reports. We did not agree that the response assessment could be performed for certain patients. According to the International Workshop, response was to be assessed on the basis of clinical, radiologic and pathologic (bone marrow) criteria. Patients who did not have baseline examination, chest, abdomen, and pelvic CTs as required by the protocol and bone marrow cannot be assessed for response. The requirement was that all be done within 21 days. The sponsor granted a number of exemptions. We reviewed the exemptions and did not agree that scans or bone marrow biopsies obtained more than 8 weeks prior to study entry were useful in this study for assessment.

Two patients did not have a baseline examination performed nor did they have an exam until after VSLI had been administered. Complete staging with CT scans of chest, abdomen and pelvic scans were not performed for 3 patients. Complete staging with baseline bone marrow biopsy were not performed for 9 patients within 8 weeks prior to study enrollment. One patient did not have a baseline LDH drawn. In addition, 10 patients did not have baseline neurologic examinations to allow an assessment of the neurologic toxicity of VSLI. Thus a minimal required staging workup was missing for 23 (19.3%) patients.

The decision was made that the FDA analysis would count only those patients who were deemed "Definite Eligible," those who did not have major protocol violations and those who had all pertinent baseline studies pertaining to the assessment of VSLI for the treatment of NHL. The analysis was performed on 54.6% of those enrolled. The FDA

analysis in the table does not take into consideration the review team's concerns about the adequacy of the IRP assessment.

Reviewer's Comment: In the table below, the review team's analysis does not include one patient deemed a responder by the sponsor, as this patient's complete data requires further inquiry to determine if the patient is eligible for response.

Table 8 Unconfirmed Response Rate – Best Response (Reviewer's Table)

Best IRP Confirmed Tumor Response during Study	**Sponsor's analysis[a] (ITT) (%) N=119**	**95% CI**	**FDA Analysis[b] (evaluable) (%) N=65**	**95% CI**
Complete Response (CR)	4 (3.4)	[0.9,8.4]	1 (1.5)	[0,8.3]
Complete Response unconfirmed (CRu)	4 (3.4)	[0.9,8.4]	1 (1.5)	[0,8.3]
Partial Response (PR)	22 (18.5)	[12.0,26.7]	12 (18.5)	[9.9,30]
Objective Response (ORR)	30 (25.2)	[17.7,34]	14 (21.5)	[12.3,33.5]

[a] source from Table 15, Main report, Clinical Study CA99002

[b] Includes those patients who had complete baseline staging, those who did not have major protocol violations, and those patients who were considered definite eligible by Central Pathology Review Final Report. The analysis uses the IRP final Adjudication as listed in the sponsor's report.

The table below contrasts the results according to INEX and the review team's assessment for IRP designated confirmed responders.

Reviewer's Comment: The FDA analysis in the table does not take into consideration the review team's concerns about the adequacy of the IRP assessment.

Table 9 Confirmed Response Rate (Reviewer's Table)

Best IRP Confirmed Tumor Response during Study	**Sponsor's analysis[a] (ITT) (%) N=119**	**95% CI**	**FDA Analysis[b] (evaluable) (%) N=65**	**95% CI**
Complete Response (CR)	4 (3.4)	[0.9,8.4]	0 (0)	[0,5.5]
Complete Response unconfirmed (CRu)	4 (3.4)	[0.9,8.4]	1 (1.5)	[0,8.3]
Partial Response (PR)	22 (18.5)	[12.0,26.7]	7 (10.8)	[4.4,20.9]
Objective Response (ORR)	30 (25.2)	[17.7,34]	8 (12.3)	[5.5,22.8]

[a] source from Table 15, Main report, Clinical Study CA99002

[b] Includes those patients who had complete baseline staging, those who did not have major protocol violations, and those patients who were considered definite eligible by Central Pathology Review Final Report. The analysis uses the IRP final Adjudication as listed in the sponsor's report.

The review team had concerns about the IRP process and decisions. Among those were the reason for the fourth adjudicator, how the fourth adjudicator was chosen among the 3 adjudicators, and concerns about possible overriding of the modified Cheson criteria as defined in the charter and whether certain findings were overlooked.

The table below illustrates one case where the review team had concerns about the IRP adjudication.

Table 10 Patient Deemed a Responder by IRP (Reviewer Table)

Issue	Case Report Forms	FDA Assessment
Absence of measurable disease at baseline of least 2.0 cm.	The patient had 2 sites of disease; 1 node on physical exam and a mediastinal mass. The IRP radiologist did not believe that the mediastinal mass could be measured (Appendix E.2.3.9). The only other site of disease was a right submandibular node measuring between 1.0 -1.5cm throughout the course of the study. IRP declared PR based on absence of non-indicator lesion being followed on scan.	The protocol stated that enrolled patients should have had measurable lesions at least 2.0cm in one diameter at baseline to be followed. The IRP should have declared this patient ineligible for response since this patient did not meet the criteria for response.

Study Conduct Issues

The study had a number of issues in study conduct. Listed below are some examples.
1) Consent forms not signed before baseline study investigations performed (5 patients) or not using latest version of consent form (3 patients).

2) Neurological assessments were omitted at one or more visits post baseline (17 patients) or did not have any neurological assessments performed during the follow- up period after VSLI treatment had stopped (5 patients). Neurological examinations were performed by nursing staff (2 patients).

Reviewer's Comment: The lack of documented exams interferes with a true assessment of the toxicity of VSLI.

3) Bone marrow biopsy not performed to confirm complete response: 2 patients, one of which had the biopsy performed at a different site from that at baseline which was positive for disease.

4) Radiotherapy permitted during the study without withdrawing a patient from the study. This patient had radiotherapy to a spinal lesion which was present at baseline and an exemption was granted to allow continuation in the study as there was not evidence of progressive disease.

Reviewer's Comment: A spinal lesion requiring radiotherapy treatment during the study should have mandated study withdrawal. A spinal lesion requiring urgent radiotherapy during the study likely signals progressive disease.

5) Full set of chest, abdominal and pelvic scans not performed as mandated by protocol at one or more visits (12 patients: 8 patients had evidence of disease shown by other means, e. g., PET or ultrasound scans);

Reviewer's Comment: Lack of following the protocol's directives regarding scans interferes in any assessment of the true efficacy of VSLI.

6) CT scans to confirm Investigator determinations of complete or partial response performed late, i.e. e., after 4 or 8 weeks depending on protocol version patient recruited under (6 patients);

7) CT scans not performed during study to track disease (3 patients) or later than the 8 weeks schedule as specified by protocol (2 patients);

Reviewer's Comment: Lack of following the protocol's directives regarding scans interferes in any assessment of the true efficacy of VSLI.

8) Inconsistent imaging modalities used to track disease when PET scans or ultrasound have been used instead of CT scans or MRIs (6 patients);

Reviewer's Comment: Lack of following the protocol's directives regarding scans interferes in any assessment of the true efficacy of VSLI.

9) CT scans performed without contrast (5 patients: 4 with exemptions) or using 7.5 mm thickness instead of 5 mm thickness (2 patients with exemptions);

10) Weight not recorded for dose calculations at drug administration visits (10 patients) and dose not adjusted for weight decrease of = 10% (2 patients).

11) One patient's chart revealed that the patient was also concurrently enrolled in 2 other studies: (1) Procrit study and (2) central venous catheter study.

Reviewer's Comment: This patient should not have been on multiple studies and enrolled in this registration study.

12) Two patients received corticosteroids (> 10 mg prednisone) as treatment for lymphoma during the study. Another received several days of corticosteroids (> 10 mg prednisone) for thrombocytopenia. Another received corticosteroids (> 10 mg prednisone) for pain. Three additional patients received additional steroids for pneumonia, pulmonary toxicity, and exacerbation of breathing problems.

Reviewer's Comment: The numbers of patients for each of the individual concerns is small compared to total enrollment. However, the presence of these issues combined with the number of patients who did not have documented evidence of relapsed, aggressive NHL as defined by the Central Pathology Review, coupled with the number of patients who did not have the underlying requisite scans, laboratory data, and examination, and the modification of the International Workshop criteria leaves the review team to question whether this study can be considered adequate and well-controlled.

4.4.1 Duration of Response

Duration of response was calculated as the time from first documentation of response until first documentation of relapse/progression. From the tables above, the sponsor and review team did not always agree about the response analysis. The table below shows the sponsor's and the review team's.

Table 11 Duration of Response (Reviewer Table)

Duration of response (days)	**Sponsor Analysis [a]** **IRP Review** **N=30**	**FDA Corrected [b] Sponsor Analysis** **IRP Review** **N=30**	**FDA Confirmed [c] Analysis** **N=8**
Absolute Mean[d]		81.4 [49.8, 113.0]	130.1 [44.9, 215.3]
Absolute Median[d]		56.5	89
KM Estimated Median	> 85[e], [72.0, -]	72 [37.0, -]	93 [43.0, -]

[a] source: Table 18, 5.3.5.2 Study CA 99002, Main report

b Five patients with duration less than 16 weeks were terminated for toxicity etc., hence these patients were counted as relapsed/progressed

c the FDA adjudicated response

d Response Duration not censored

[e] the median duration of response was not reached and upper limit of the 95% CI could not be calculated

The table below shows some of the patients who were censored in the sponsor's analysis.

Table 12 Twenty Censored Patients in Sponsor's Duration of Response Analysis (IRP best response designated patients)

Reason for treatment cessation/study participation	Number of patients	Additional Comments
Underwent Bone Marrow transplant	2	
Neuropathy	6	One patient withdraws from study on the same day that his treating physician/investigator notices a new 1.0 cm node and declares PD. However IRP does not declare Progressive Disease (PD) yet because the size of the new node is not > 1.5 cm. One patient removed from study is declared to have PD 5 days later by his treating physician/investigator based on gallium scan. Since the IRP RAD does not read Gallium scans, no IRP judgment can be made. One patient removed for persistent GI problems/neuropathy and per IRP is in CR. However 20 days later, patient has a biopsy of duodenum with a diagnosis of large cell lymphoma. One patient taken off study by investigating/treating physician is declared PD but no explanation given. According to study report patient is taken off for neuropathy. Another patient taken off study by investigating/treating physician is declared PD but no explanation given. According to study report patient is taken off for neuropathy. One patient is taken off based on site radiologist determination of worsening of CT scan yet the reason for

		removal is listed as neuropathy.
Thrombocytopenia	1	
Investigator took patient off study	1	No reason
Withdrew Consent	1	
Relapse	3	One patient is noted by his treating physician/investigator to have a new node on physical exam yet is coded as censored as opposed to relapsed in the database as IRP has not declared PD but PR. Investigator takes patient off study. A second patient is noted by his treating physician/investigator to have a new node on physical exam yet is coded as censored as opposed to relapsed in the database as IRP has not declared PD but PR. Investigator takes patient off study. One patient is noted by his treating physician/investigator to have a right inguinal node yet is coded as censored as opposed to relapsed in the database. The IRP RAD does not agree based on review of pelvic films. The investigator removes the patient from study 6 days after films.
Patient choice/neuropathy	1	This patient is declared to have PD by his treating physician/investigator 6 days after being declared CR by IRP based on Gallium scan results.
Completion of study	5	

4.5 STUDY DM97-162

Reviewer's Comment: The sponsor submitted this study as supportive evidence. Due to a lack of Central review for pathology or radiology, Case Report Forms, use of standardized criteria for response such as the International Workshop, the use of this study for support of the previous study is questionable.

This study was a single center, open-label, single agent, single arm study of VSLI in patients with relapsed lymphoma and acute lymphoblastic leukemia which enrolled 135 patients with refractory or relapsed NHL or with relapsed or refractory ALL.

Dose and schedule administration were similar to those described for CA99002.

The population enrolled in this study was slightly different from those enrolled in CA99022. Listed below are the major eligibility criteria:

- Patients with relapsed intermediate or low grade Non-Hodgkin's lymphoma (must have had CR or PR to initial therapy). Must not have had refractory lymphoma (defined as progressive disease, MR, or NR, to initial therapy)
- Must not have received any anti-cancer treatment within the past three weeks.

- Must have a new extent of disease work-up within 3 weeks prior to treatment and have bidimensionally measurable disease.
- Performance status < 3 Zubrod.
- Patients who have as result of prior vinca alkaloids grade 3 or 4 sensory neuropathy are not eligible.

Response Criteria were based on bi-dimensionally measurable and unidimensionally measurable parameters.

Efficacy Results

In this study, 132 patients received at least 1 dose of VSLI and constitute the ITT population. The median age was 62 years (range: 20-86 years). Fifty five percent were male and seventy-nine were Caucasian. Performance status was mostly = 2 (84%). Patients with a diagnosis of NHL were 116, of which 97 patients had aggressive lymphoma; while 16 patients had a diagnosis of ALL.

Primary Endpoint: Objective Response Rate

The ORR in the aggressive NHL population was 29% with a 95% CI of [22.2, 42].

Reviewer's Comment: The review team has not conducted an assessment of eligibility and major protocol violations as was performed for CA99002. However, this was a single center, investigator-sponsored study where all patients did not have Case Report Forms completed. Therefore some of the documentation is incomplete and it may be difficult to validate these results.

4.6 SAFETY OF VSLI

4.6.1 Safety Results

The primary analysis was performed on the 119 patients treated in the pivotal trial. Patients completed a median of 4.0 cycles of therapy. The planned median dose for VSLI was 1.0 mg/ m^2/week and the percent of planned dose intensity was 96.4%. The most common cause of dose delay was due to neuropathy followed by hematologic toxicity and both constituted approximately 70 % of the delays. Neuropathy was also the most common cause of dose reductions. Thirteen percent of the dose reductions were at least 0.24 mg/ m^2. The common grade 3 or grade 4 toxicities were neutropenia (21.8 %), weakness (21.0 %), hypesthesia (14.3 %), anemia (12.6 %), paresthesia (11.8 %), thrombocytopenia (10.1 %), fatigue (6.7 %), constipation (5.0 %), and areflexia (5.0 %). The clinical toxicity is mostly neurological.

4.6.2 Dosing Delays and Reductions

Dose delays were seen in 20% of the population. Nineteen patients (16%) had one dose delay, 4 patients (3%) had 2 dose delays and 1 patient (1%) had more than 3 dose delays.

The most common cause of dose delay was due to neuropathy (48.5 %), followed by hematologic toxicity (21.2%). Of the 24 patients who had a dose delay, 18 were discontinued from treatment without receiving another dose of VSLI. Treatment was discontinued due to progressive disease in 8 of the patients (including 2 patients with an unspecified reason for dose delay) and 7 of the patients with a dose delay were withdrawn due to neuropathy. One patient with an unspecified reason died after a dose delay of 7 days.

Approximately 33% of patients underwent dose reductions. Neuropathy was the most common reason for dose reduction. Reasons for dose reduction are summarized in the table below.

Table 13 Reasons for Dose Reduction

Reason for Dose Reduction	Number (%) of Dose Reductions (n=39)
Neuropathy	20 (51.3)
Hematologic toxicity	7 (17.9)
Abdominal pain and cramping, and neuropathy	1 (2.6)
Neuropathy and weight loss	1 (2.6)
Neuropathy, weight loss, and clostridium difficile diarrhea	1 (2.6)
Weight loss and hematologic toxicity	1 (2.6)
Nonhematologic toxicities	1 (2.6)
Hepatic toxicity	1 (2.6)
Unspecified	6 (15.4)

Source: Table 13, Study Ca99002-Main Report.

Of the 45 patients with a dose modification, most patients (69%) had a single dose reduction or a dose delay.

4.6.3 Adverse Events (AEs) and Serious Adverse Events (SAEs)

The common all grade adverse events were hypesthesia (63.9 %), paresthesia (63 %), weakness (59.7 %), constipation (56.3%), areflexia (50.4 %), fatigue (44.5 %), hyporeflexia (44.5 %), peripheral sensory neuropathy (38.7 %), anemia (34.5 %) and nausea (34.5%). The common grade 3 or grade 4 toxicities were neutropenia (21.8 %), weakness (21.0 %), hypesthesia (14.3 %), anemia (12.6 %), paresthesia (11.8 %), thrombocytopenia (10.1 %), fatigue (6.7 %), constipation (5.0 %), and areflexia (5.0 %). The clinical toxicities were mostly neurological and hematological. The majority of patients (73%) reported at least one Grade 3/4 AE as their worst severity.

The hematological toxicities of anemia and neutropenia occurred most frequently in the same patients; 19 patients (16%) experienced both AEs during the study. Anemia, neutropenia and thrombocytopenia occurred in 9 patients (8%) during the study. These hematological events (especially neutropenia) were occurring at Grade 3 or 4 severity in a larger proportion of patients compared with adverse events in the other systems. Of the 26 patients with Grade 3 or 4 neutropenia, 10 had prior bone marrow transplant. Many of the patients who experienced Grade 3 or 4 anemia or thrombocytopenia, were the same as those with Grade 3 or 4 neutropenia.

Serious Adverse Events
The commonest SAEs were general disorders and site administration (11.8%), respiratory, thoracic, and mediastinal disorders (9.2%), infection (9.2%), gastrointestinal (6.7%) and nervous system (6.7%).

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Ten patients (8%) died within 30 days of the last VSLI dose, or an AE that began within 30 days of the last dose. None of the deaths was associated with VSLI treatment.

The majority of AEs that occurred on study were in the nervous and gastrointestinal systems. AEs reported in ≥10% of patients were: peripheral sensory neuropathy (55% of patients), fatigue (26%), constipation (24%), pyrexia (20%), paresthesia (20%), alopecia (20%), nausea (18%), hypoesthesia (15%), weakness (14%), febrile neutropenia (13%), stomatitis (12%), and vomiting (10%). One patient had Grade 4 peripheral motor neuropathy. Common Grade 3 AEs (≥ 5% of patients) were: peripheral sensory neuropathy (13%), fatigue (9%), weakness (5%), and limb pain (5%). Hematologic tests showed a high incidence (50- 60%) of worsening of hematologic toxicity grades on study, primarily 1- or 2- grade changes.

Thirteen patients (10%) were withdrawn from study due to AEs (all neuropathies).

5 CONFIRMATORY TRIAL

The sponsor has not initiated a confirmatory study.

6 CONCLUSION

In summary, the sponsor has submitted an international, multicenter, single arm study in relapsed, aggressive NHL for accelerated approval (AA) based on response rate. The review team questions whether the data from this small clinical study meet those requirements. The study included only 65 patients (54.6% of the study population) whom FDA found to be evaluable for an AA claim, i.e., who met all of the following criteria:

- who were deemed definitely eligible by the Central Pathology Review,
- who did not have major protocol violations, and
- who had all baseline examinations, scans, and lab measurements to be eligible for assessment of response rate for the proposed indication

The review team also had concerns about the exemptions granted, how the study was conducted, about the IRP process and adjudication, revision of the standardized criteria which prevented comparison to historical controls, and the magnitude of these responses.

In the AA evaluable population in this study, the unconfirmed response rate (complete response (CR) + partial response (PR) + complete response unconfirmed (CRu)) was 21.5% (95% CI 12.3, 33.5) with 1.5% CRs (95% CI 0, 8.3). The confirmed response rate was 12.3% (95% CI 5.5, 22.8), with no confirmed CRs. The study response rates consist mostly of PRs of short duration.

Considerations for the Division and deliberations of ODAC include the following issues. Drugs considered under accelerated approval should demonstrate an improvement over "available therapy." The Committee should consider if the sponsor has demonstrated in this single arm trial that VSLI represents an improvement over available therapy cognizant of the activity of multiple drugs and drug combinations in this disease setting as reported in the literature. A second area of deliberation should focus on the use of a surrogate endpoint (response rate). Accelerated approval is not a screening process for drug activity. For accelerated approval, the surrogate must be "reasonably likely to predict clinical benefit." The Committee should consider not only the magnitude of the response rate but the data which indicates that this RR is comprised primarily of PRs. The Agency believes that the duration of any response rate must be considered in assessing the potential clinical relevance of any claimed benefit.

7 APPENDIX

Independent Review Charter

- Medical Imaging Charter (MIC), Version 1, dated 1.11.2001
    - As part of the ongoing quality assurance program, provided for 20% of all imaging time points to be double-read, i.e. read by two IRP radiologists
    - Definitions for the IRP radiology review—
        - Measurable and Non-measurable disease
        - Selection criteria for Indicator and Non-Indicator lesions
        - Lesion boundary and measurement rules
    - Definitions for the IRP oncology review—
        - Response assessment using modifications of the criteria in the article by Cheson et al.
    - Version of the independent charter that was in effect when the IRP radiologist began his review in July 2001

- Centralized Review Charter (CRC), Version 1, dated 8.13.2002
    - Portion of the IRP radiology review that occurred prior to the date this charter went into effect:
        - Imaging studies for 62 subjects
            - 53 fully reviewed
            - 9 partially reviewed
    - Change in both the title and the format of the charter
    - Change regarding the review of imaging studies so that all images would be single-read (because there was only one IRP radiologist performing the reviews)
    - Addition of a statement that the radiologic response to therapy would be according to the article by Cheson et al.
    - Discretionary statement for the IRP radiologist regarding:
        - Whether a new lymph node > 1.5 cm in diameter represented new disease, or a brief explanation if it was not considered to be new disease
        - Whether to consider reappearance of a lymph node that had disappeared to be evidence of new disease, because this situation had arisen for one subject (05-01)
    - Amendment of how to evaluate previously confluent lesions that separated at a subsequent time point (new procedure for these “sub-lesions” no longer to be measured separately, but to be followed qualitatively)
    - Amendment of Indicator lesion boundary rules for a lesion that become unmeasurable and then reappeared at a later time point (new

procedure for these lesions to be considered new lesions and evidence of progressive disease)
  - Addition of statement that enlargement of any organ due to diffuse infiltrative involvement should also be noted at baseline and followed
  - Statement that the IRP radiologist was not allowed to change lesion measurements in previously completed radiology forms, but to note disagreements in the analysis forms
  - Inclusion of the names of the IRP oncologists
  - Addition of information on the blinding of the IRP oncology determinations and the quality assurance process

- CRC, Version 1.1, dated 9.9.2002

  - Addition of training process for IRP oncologists prior to the start of the review (to reflect training that had already been given)
  - Addition of a 4th level review by the third IRP oncologist in cases where all three IRP oncology readings were discordant in the determination of response (an additional step necessitated by the occurrence of situations where the three did not agree)
  - Addition of statement regarding the requirement that the IRP oncologists record their overall response determination, as well as the date of response and date of progression, in the analysis form

- CRC, Version 1.2, dated 1.22.2003

  - Removal of the statement that Dr. Bruce Peterson was to be used only for the third (and fourth) review because this did not reflect reality (since he had also been used for the first and second reviews)

Table 14 CRC Radiographic Definitions:

Term	Definition
Measurable Disease	Determined at baseline Lesions $\geq$ 2 cm in the longest transverse diameter Lesions measurable in 2 dimensions

Term	Definition
Non-Measurable Disease	Uni-dimensional measurable disease Lesions < 2 cm in greatest diameter at baseline Diffuse organ enlargement Bone lesions Leptomeningeal disease Ascites Pleural/pericardial effusion Imflammatory breast disease Lymphangitis cutis/pulmonitis Cystic lesions Abdominal masses not confirmed and followed by imaging techniques No specfic mention of pulmonary metastases

Term	Definition
Indicator Lesions	Selected by the IRP radiologist from the baseline examination Minimum of 1 measurable lesion up to a maximum of 6 measurable lesions Choice independent from selection of lesions at the clinical sites Selection based on size, with larger preferred over smaller, and suitability for accurate repeated measurements Selected from disparate regions of the body Should include mediastinal and retroperitoneal areas of disease, whenever these sites are involved Should not be in areas of know treatment with radiation therapy Sum of the cross-products (SPD) for all Indicator lesions calculated at baseline All Indicator lesions identified from baseline examination followed at subsequent time points SPD compared to that from the baseline examination Reappearance of lesions at follow-up time points determined to be progressive disease at the discretion of the IRP radiologist

Term	Definition
Non-Indicator Lesions	All measurable lesions (≥ 2 cm) not designated as Indicator lesions Non-measurable lesions Lymph nodes 1.6 to 1.9 cm in greatest transverse diameter Number of Non-Indicator lesions per organ or lymph node group recorded for baseline examination For follow-up time points, Non-Indicator lesions assessed qualitatively or quantitatively by total number of lesions per organ or lymph node group Tumor burden: increased, unchanged, decreased, or disappeared compared to the previous time point Changes in organomegalies identified and recorded
New Lesions	Lymph nodes > 1.5 cm at the discretion of the IRP radiologist Explanation in comments for lymph nodes > 1.5 cm not considered new disease
Reappearance of lesions	At the discretion of the IRP radiologist whether a lymph node that has disappeared at a previous time point and reappeared constitutes progressive disease

Table 15 CRC Radiographic Tumor Evaluation

Time point	Assessment

Time point	Assessment
Baseline	Indicator Lesions • Minimum of 1, maximum of 6, lesions recorded • Sum of cross-products for all Indicator lesions calculated and reported Non-Indicator Lesions • Number of lesions per organ or lymph node recorded; not measured • Enlargement of any organ due to diffuse infiltrative involvement noted
Follow-up	Indicator Lesions • Sum of cross-products measured for comparison to baseline • Reappearance of lesions = PD, at the discretion of the IRP radiologist Non-Indicator Lesions • Assessed qualitatively or quantitatively by total number of lesions per organ or lymph node group • Changes in previously identified organomegalies noted • New sites of disease identified o Lymph nodes > 1.5 cm = PD, at the discretion of the IRP radiologist

CRC Indicator Lesion Measurement Rules

- Lesions were to be measured using the slice where the lesion was the largest.
- Measurement were to be made using the longest diameter of the lesion as the primary length, and the widest portion of its perpendicular diameter as

the orthogonal length, using the orthogonal measurement tool in a proprietary program, Cheshire.

- All available tools (e.g., magnification, window/level, calibrated circle) were to be utilized to obtain accurate lesion measurements.
- In cases where a lesion has a hypervascular component, the area was to be included in the lesion measurements, both at baseline and for follow-up time points.
- When lesion boundaries were located in the liver, they were to be assessed during the portal venous phase of the CT scan.
    - If the boundaries of the lesion could not be determined at baseline, a different lesion was to be selected for measurement.
    - If the lesion in question was the only measurable lesion, the best assessment as to the size of the lesion was to be made, and documented in the comments section of the analysis form.
- When Indicator lesions became confluent on a subsequent time point, the best assessment as to the individual lesion boundaries was to be made and measurement of lesions performed.
    - If the lesions definitely could not be separated and no measurements could be made, a qualitative assessment was to be performed and documented in the comments.
- If an Indicator lesion became unmeasurable due to poor imaging quality, an overall qualitative assessment of the case was to be performed.
    - Measurement of the remaining Indicator lesions, if present, and the sum of the cross-products were still to be generated.
- In the case where an Indicator lesion became unmeasurable on a follow-up time point, the lesion was to be assessed qualitatively and excluded from the sum of the cross-products from that time point on
    - If the lesion reappeared at a subsequent time point, it was to be considered a new lesion.

8 REFERENCES

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