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APPLICATION NUMBER: NDA 21041

MEDICAL REVIEW(S)

FDA MEDICAL OFFICER REVIEW JAN 7 1999

DepoCyt (DTC 101, liposomal cytarabine)

NDA # 21041 Submissions dated:
October 2, 1998
October 6, 1998
October 23, 1998
October 26, 1998
November 5, 1998
November 6, 1998

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1. INTRODUCTION

1.1 General information

1.1.1 NDA #: 21041

1.1.2 Drug name:
Generic name: cytarabine liposomal injection (DTC 101)
Trade name: DepoCyt

1.1.3 Applicant: Depotech Corporation
10450 Science Center Drive
San Diego, CA 92121

1.1.4 Pharmacologic Category: Antipyrimidine active in S phase

1.1.5 Proposed Indication: Intrathecal treatment of lymphomatous meningitis

1.1.6 Dosage Form and route of administration: Five ml (10 mg/ml) ready to use vials for intrathecal injection

1.1.7 Important related drugs: DTC 101 is a liposomal form of cytosine arabinoside (Ara-C)

1.2 Background

1.2.1 Regulatory history of DepoCyt and consideration of accelerated approval

On December 18, 1997 NDA 20-198, DepoCyt, for intrathecal treatment of carcinomatous meningitis, was discussed before the Oncologics Drugs Advisory Committee. The committee voted 7 to 3 that the clinical studies supporting this application were not adequate and well controlled; they voted 10 to 0 that the data did not represent substantial evidence of efficacy. After the ODAC meeting, the sponsor submitted additional information and met with the Agency in an unsuccessful effort to convince the Agency that the NDA was approvable. A "not approvable" letter issued on May 22, 1998. After a later meeting, a letter from Robert Temple, MD, the Director of the Office for Drug Evaluation I, encouraged submission of the data from the lymphoma trial:

> "DepoCyt may, however, be approvable for treating lymphomatous meningitis. The results of Study DTC92-001 lymphoma arm are clearly promising, and assuming review of your completed submission does not alter our view of the data, would support an application for accelerated approval in the treatment of lymphomatous meningitis. The experience with Depocyt in carcinomatous meningitis would be considered as part of the safety database and would provide some support for intrathecal anticancer activity. We therefore invite you to submit a formal application for this claim (as a new NDA) ..."

1.2.1.1 Efficacy in carcinomatous meningitis

The FDA assessment of NDA 20-198 for treatment of carcinomatous meningitis is summarized in attached documents: Division Director comments by Bob Delap, MD, the non-approval letter to the applicant dated 5-22-98, and a letter from the Robert Temple, MD, dated 8-26-98.

The major study submitted in the NDA for treatment of carcinomatous meningitis was Study DTC92-001, a randomized study of DepoCyt IT every 2 weeks for 5 doses compared to methotrexate 10 mg IT given twice weekly for 9 doses. Patients with a confirmed cytological complete response were to receive additional IT therapy for several weeks. As prophylaxis against side effects of intrathecal therapy, both groups were to receive identical treatment with corticosteroids on the weeks that DepoCyt was to be administered. Patients could receive additional steroid therapy for breakthrough symptoms of intrathecal therapy. 61 patients were randomized including 31 treated with DepoCyt. Complete cytological response, the primary endpoint, required clearing of the CSF at 4 weeks and confirmation by another sample at 5-6 weeks. Secondary endpoints included change in neurological symptoms and quality of life parameters.

Per protocol criteria for response, there were 3 confirmed complete responses in 31 patients randomized to DepoCyt and 1 confirmed complete response in 30 patients randomized to methotrexate. Additional categories of response were designated: "complete response without confirmation" for patients who never had a confirmation sample collected and "late response" for patients with a positive cytology at 4 weeks which subsequently had negative cytology documented from all previously-positive sites. Using these additional post hoc criteria, 8/31 (26%) responded on DepoCyt and 6/30 (20%) on methotrexate.

The sponsor's most persuasive analysis was an unplanned analysis of time to clinical progression. This analysis was largely based on a global neurological assessments performed by the investigator. The applicant found a significant advantage for the DepoCyt arm (median 58 days on Depocyt versus 30 days for methotrexate, p = 0.007 logrank). Problems with the applicant's analysis are summarized in the following excerpt from Dr. Temple's letter of 8-26-98:

> "Although a global assessment instrument was part of the study, there were no established criteria for evaluating each patient. Moreover, the assessment was not made by a blinded observer and could be changed. As previously acknowledged, in about 16% of the cases the results were retrospectively revised based on other data, suggesting a problem with the method of assessing the global assessment data. Given the open, incompletely specified, and subjective nature of the assessment, we examined the neurologic evaluations for evidence to support the global assessment. We found that in most cases (80%) it was easy to explain the global change by examining the individual exams; i.e. progression on global was well-correlated with progression on one or more neurological scales. This was not true at one site, however, where global and neurologic scale results were quite different, very much in the direction of showing later progression on the global exam for DepoCyt. A log rank test comparing progression by site and treatment showed a significant difference between one study site and the pooled remaining sites. It was this site that was wholly responsible for the favorable global outcome. Analysis of progression at all sites using neurological exam (p = 0.445) and examination of progression using the global exam but excluding this site (p = 0.312) showed no advantage of DepoCyt. With exclusion of the site we found a still higher correlation (93%) between neurological and global assessments. We thus cannot conclude that an advantage of DepoCyt on time to neurological progression has been shown."

1.2.1.2 Safety in carcinomatous meningitis

The toxicity of DepoCyt compared to that of methotrexate was evaluated in the same randomized study of 61 patients with solid tumors involving the meninges and discussed before ODAC in December of 1997. These toxicites were detailed in several FDA reviews. The following is an excerpt from Dr. Delap's review that quotes the applicant's own findings:

"Chemical arachnoiditis was reported more frequently, and occurred with greater severity, in the DepoCyt treatment group. As described in volume 2.9 of NDA [ ](page 066), section 9.18.3.2., "Eleven patients who received only DTC 101 (DepoCyt) and two who received DTC 101 after failing methotrexate developed 2 or more signs and symptoms suggestive of chemical arachnoiditis serious enough to warrant hospitalization. One patient who received methotrexate developed such symptoms, and no patients who crossed from DTC 101 to methotrexate therapy developed arachnoiditis." Similarly, there were three episodes of"life-threatening" chemical arachnoiditis described among the 29 DepoCyt patients, and none in patients who received methotrexate (NDA volume 2.9, page 077).

The applicant has suggested that the increased chemical arachnoiditis on the DepoCyt arm may be explained in part by the fact that the DepoCyt patients received more cycles of treatment than the patients treated on the methotrexate arm of the study. It must be noted, however, that as described above, patients on the methotrexate arm actually received a substantially larger number of intrathecal injections than patients on the DepoCyt arm (since each cycle of DepoCyt treatment consisted of a single intrathecal injection, while cycles of methotrexate consisted of 2-4 intrathecal injections). Also, although patients on both arms of the study received dexamethasone prophylaxis to ameliorate the adverse effects of intrathecal chemotherapy, this dexamethasone prophylaxis was scheduled to coincide with DepoCyt administration (i.e., patients on the DepoCyt arm were always supposed to receive dexamethasone around the time of their DepoCyt injections, while patients on the methotrexate arm were to receive dexamethasone on the same schedule, which did not happen to overlap with all of their scheduled intrathecal injections; see the attached timetables for dexamethasone and study drug administration, Appendix 3 of the study protocol). Finally, patients who developed chemical arachnoiditis were allowed to receive additional "rescue" doses of dexamethasone; as summarized in the NDA (volume 2.9, page 079), "the proportion of patients who received rescue dexamethasone, as generally identified by the site, was: 13/41 (32%) in the DTC 101 group, with 15% of drug cycles rescued, (and) 2/30 (7%) in the methotrexate group, with 3% of drug cycles rescued...". (NOTE: this statistic combines DTC 101 -treated patients from all three strata in the Applicant's study 92-001, i.e. 29 patients with solid tumors, 9 patients with lymphoma, and 3 patients with leukemia). In summary, the data included in this NDA clearly suggest that chemical arachnoiditis is a greater concern with intrathecal DepoCyt administration than with intrathecal methotrexate administration."

1.2.1.3 Subpart H—Accelerated Approval of New Drugs for Serious and Life-Threatening Illnesses

In a letter to the applicant dated August 28, 1998, Dr. Temple suggested that the applicant's encouraging analyses of cytologic response in lymphomatous meningitis might warrant consideration of accelerated approval if FDA review of the data did not alter the results. Therefore, a summary of the regulatory significance of the accelerated approval regulations is pertinent.

Subpart H was finalized on December 11, 1992, and is found starting in 21 CFR section 314.500. There are a 4 critical statements in the regulations:

- This regulation applies to drugs that have been found to "provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)."

- "FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence , to predict clinical benefit ...."

- "Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit... The applicant shall carry out any such studies with due diligence."

- FDA may withdraw approval, following a hearing, if a study fails to verify clinical benefit or if the applicant fails to perform the required postmarketing study with due diligence.

The first test for eligibility of an application under these regulations is that the new drug provides benefit over "existing treatments." The optimal design of a trial would randomize patients to the new drug versus the best "existing" drug. Whether there is an acceptable "existing treatment" is another question. For oncology drug approvals lack of existing treatment means that there are no drugs approved for the indication and that there is no substantial body of literature suggesting effective unlabeled therapy.

The next point is the definition of the word "surrogate." Given the common usage of the term surrogate, one's tendency may be to suggest that one should know with certainty that a surrogate endpoint will reliably predict the ultimate outcome of interest. However, as utilized in these regulations, the surrogate need only be "reasonably likely" to predict benefit, and evidence from any realm of science may be called upon in making this prediction. The Oncology Division has accepted tumor response rates as a surrogate for approval under these regulations on several occasions. It seems likely that the authors of the DepoCyt protocols would have considered complete cytological response rate as an

adequate surrogate since this was the primary endpoint of the study. Although the Oncologic Drugs Advisory Committee will be asked whether complete cytologic response of lymphomatous meningitis is an adequate surrogate endpoint under Subpart H, the Office of Drug Evaluation I and the Division of Oncology Drug Products, after consultation with ODAC's Janice Dutcher, MD, came to a preliminary judgement that it probably was. Dr. Temple, as quoted above, invited the applicant to file the NDA for lymphomatous meningitis. He stated that if the findings were unchanged upon FDA review, the findings "would support an application for accelerated approval in the treatment of lymphomatous meningitis."

An important point to remember is that the accelerated approval regulations do not weaken the strength of evidence needed for approval. The results from analyses, using the surrogate endpoint, require the same scrutiny and the same degree of certainty as for full approval, using an endpoint representing clinical benefit. Analyses from well controlled clinical trials are required in both cases. Inadequate analyses and poor quality data cannot be rescued by accelerated approval.

Finally, accelerated approval comes with an agreement that the applicant is to conduct a trial(s) to demonstrate that the drug indeed imparts clinical benefit. This could be demonstrated in another stage of disease (e.g., adjuvant) or in a different setting (e.g., combination therapy). If the study is not performed expeditiously or if the results are negative, the regulations outline a procedure whereby FDA may withdraw approval.

1.2.2 Lymphomatous meningitis

Lymphomatous infiltration of the meninges (lymphomatous meningitis or LM) occurs predominantly in non-Hodgkin's lymphoma (NHL) and is seen in 4-15 % of NHL patients (Grossman, 1991; Recht,1991). The likelihood of development of lymphomatous meningitis varies as a function of the NHL histology : diffuse histologies are more commonly associated with LM than nodular histologies (Young, 1978; Levitt, 1980; Recht, 1989); in the more undifferentiated diffuse neoplasms such as lymphoblastic and Burkitt's lymphoma the cumulative risk of LM may be as high as 25 % (Recht, 1991). LM occurs in 20-22 % of AIDS patients with NHL and in 25 % of AIDS patients with primary CNS lymphoma (Chamberlain, 1993). It most commonly develops in the setting of progressive systemic disease (Young, 1971; Recht,1988), although it can be present at the time of initial diagnosis or as a first manifestation of relapse after complete remission.

While patients can present with any neurologic symptom, symptoms of general CNS dysfunction (headache, altered mental status), cranial nerve abnormalities or spinal cord dysfunction are most frequently encountered. The most definitive diagnosis of LM is made by the identification of lymphoma cells in the cerebrospinal fluid (CSF); cytologic examination is positive in more than 90 % of patients with LM if three examinations are performed. Other potential CSF abnormalities in LM may include an elevated protein level (>50 mg/dl), hypoglycoracchia (<40 mg/dl) and elevated beta-2-microglobulin levels. In the patients for whom a spinal tap is contra-indicated (raised intracranial

pressure, coagulopathy, etc), neuroimaging studies, such as contrast-enhanced brain/spine MRI or contrast-enhanced brain CT, can support the diagnosis of LM.

If left untreated, the development of leptomeningeal infiltration by malignant tumor leads to death from progressive neurologic disease, with a median survival of 4 to 6 weeks (Little, 1974); specific data for the natural history of lymphomatous meningitis do not seem to exist. Reported median survivals for treated LM range from 2 to 10 months (Chamberlain, 1997; Chamberlain, 1994, Young, 1979; Recht, 1988; Raz, 1984, Griffin, 1971); if the meningeal lymphomatous disease is controlled by treatment, the majority of LM patients will die from progressive systemic disease (Chamberlain, 1997; Young, 1979; Recht, 1988; Raz, 1984).

The literature on treatment of LM is characterized by a paucity of randomized or even of single-arm prospective trials. Based on these limited data, the current 'aggressive' approach to LM constitutes of :

1. radiation therapy of symptomatic sites in the neuraxis and of all bulk disease evident on neuroimaging studies
2. intrathecal chemotherapy, often administered through an intraventricular catheter with subcutaneous reservoir (Ommaya device). Methotrexate and ara-C are the most frequently administered intrathecal antineoplastic agents in LM and are used in a variety of doses and schedules (Chamberlain, 1997; Chamberlain, 1993; Sandor, 1998, Siegal, 1994). With respect to the design of this trial, it is important to note that reports of LM patients treated with ara-C only as first-line intrathecal chemotherapy are extremely rare (Ziegler, 1971; Fulton, 1982)

Using the combined chemo/radiotherapy approach, neurologic symptoms improved or stabilized in 80 % of patients; however, fixed neurologic deficits tend not to improve on treatment (Recht, 1988). Cytologic CSF clearance on a first-line intrathecal chemotherapy regimen was reported in 73 to 100 % of treated patients (Chamberlain, 1997; Chamberlain, 1993; Siegal, 1994). Unfavorable prognostic factors include age, poor performance status, moderate to severe cranial nerve deficits and systemic progressive disease (Mackintosh, 1982; Grossman, 1993).On the other hand, coadministration of systemic chemotherapy (Siegel, 1994; Chamberlain, 1997) and presence of LM at the time of initial NHL diagnosis (Recht, 1988; Recht, 1991) are likely to have a positive impact on the outcomes of patients with leptomeningeal metastases. Patients with LM in the context of primary CNS lymphoma seem to do better than patients with secondary CNS lymphoma (Mackintosh, 1982; Sandor, 1998).

The following issues pertinent to the review of the submitted data are apparent from the literature :

- an optimal 'standard of care' treatment for LM has never been prospectively defined; the most common approach is a combination of radiation therapy to symptomatic sites and bulk disease and intrathecal chemotherapy (most

commonly either MTX only or MTX/Ara-C combination). Ara-C only as a first line intrathecal treatment has only been reported in a small number of patients

- LM often presents in the context of systemic relapse and most treated patients die of systemic disease. Therefore, overall survival should not be considered a primary endpoint in the evaluation of an intrathecal treatment

- There is no agreement in the literature how response to treatment of leptomeningeal metastases should be assessed. As an illustration, the response criteria of the most important prospective series in leptomeningeal metastases are summarized in table 1.

- In randomized trials in LM, the distributions of age, performance status, systemic disease, important to severe cranial nerve deficits, systemic chemotherapy and primary CNS lymphoma need to be assessed in the two treatment groups

Publication	Complete response	Partial response	Stable disease	Comment
Hitchins, 1986 (solid tumors and lymphoma)	Clinical improvement + negative CSF cytology + normal CSF chemistry for > 4 wks	Clinically improved or stable + negative CSF cytology + >50 % improvement CSF chemistry for > 4 wks	Clinically stable + negative CSF cytology + stable CSF chemistry for > 4 wks	
Grossman, 1993 (solid tumor and lymphoma)	Normal neurologic exam + negative CSF cytology + normal CSF Glc/TP + no meningeal masses for > 4 wks	Neurologic improvement + 50 % decrease CSF tumor cells OR 50 % shrinkage of masses for > 4 wks	Neurologically stable + <50 % decrease and < 25 % increase of CSF tumor cells or masses for > 4 wks	Too stringent : no patient had CR or PR
Chamberlain, 1998 (NSCLC)	If initially positive CSF cytology: Negative ventricular + lumbar cytology 1 wk apart If initially negative CSF cytology: Normal neurologic exam	If initially positive CSF cytology: Conversion to suspicious on ventricular + lumbar cytology 1 wk apart If initially negative CSF cytology: Incomplete resolution of clinical signs	NR If initially negative CSF cytology: No change in neurologic signs	Striking correlation between cytologic CR and clinical + radiologic PR)
Chamberlain, 1993 + 1997 (lymphoma)	Two consecutive negative CSF (both ventricular and lumbar sampling) cytologies > 1 wk apart	Conversion from positive to suspicious CSF cytologies on two consecutive samples (both ventricular and lumbar)		
Siegal, 1994 (lymphoma)	Negative CSF cytology >4 times for >4 weeks + neurologic stabilization/improvement + no meningeal masses	Residual meningeal masses or residual CSF tumor cells + neurologic stabilization/improvement		

Table 1. Response criteria as used in published prospective trials of neoplastic meningitis

1.2.3 Pharmacology

Ara-C, the active ingredient of DTC 101, is an antipyrimidine active in S phase which cytotoxicity is function of both drug concentration and duration of exposure. However, after intrathecal (IT) administration, the half-life of Ara-C is only 3.4 hours. The rationale behind the current study is that a slow-release formulation of Ara-C able to maintain cytotoxic CSF concentrations for prolonged periods of time may be a more effective treatment for LM than normal Ara-C.

DTC 101 is an injectable suspension of Ara-C encapsulated into multivesicular lipid-base particles (DepoFoam) for sustained release. Preclinical studies of intrathecal administration of DTC 101 in rats revealed that this encapsulation indeed resulted in a 55-fold increase in CSF half-life. A phase I study in neoplastic meningitis in humans revealed a MTD of 75 mg IT; pharmacokinetic analysis showed that after a single IT dose of 50 mg (as used in the current study) cytotoxic concentrations of Ara-C above 0.1 mcg/ml were present in the CSF for more than 14 days.

2. CLINICAL STUDY

The data under review are the data of the lymphomatous meningitis patients of protocol DTC 92-001. This protocol, entitled 'A randomized clinical study to determine the efficacy and safety of DepoFoam encapsulated cytarabine (DTC 101) relative to standard therapy for the treatment of neoplastic meningitis in patients with leukemia, lymphoma or solid tumors' was originally designed for meningeal leukemia, meningeal lymphoma and meningeal carcinomatosis. However, as only the lymphomatous meningitis data are currently being reviewed, the following description will only highlight the protocol characteristics relevant for this patient group.

2.1 Study objectives

1. The first objective was to determine the effectiveness of DTC 101 for the treatment of lymphomatous meningitis relative to standard intrathecal chemotherapy (Ara-C).
   Primary efficacy endpoints : response rate, time to complete response, duration of complete response, time to relapse.
   Secondary efficacy endpoints : changes in neurological symptoms/signs and changes in quality of life measurements.

2. The second objective was to determine the safety of DTC 101 relative to Ara-C.
   Safety parameters : incidence of adverse events, changes in laboratory parameters

3. The third objective was to compare the need for additional oral steroids (dexamethasone) for symptomatic control of drug-related toxicities

2.2 Study design

The study was an open-label, randomized, multicenter study to determine efficacy and safety of intrathecal DTC 101 relative to that of intrathecal Ara-C for the treatment of cytologically proven lymphomatous meningitis. Patients were accrued prospectively, were randomized at a 1:1 ratio and were stratified by AIDS-related and by non-AIDS-related lymphomatous meningitis. The original study plan required a minimum of 20 patients (at least 10 non-AIDS LM patients) in each arm.

2.2.1 Inclusion Criteria

- Histologically proven diagnosis of lymphoma (AIDS or non-AIDS related) and positive CSF cytology (either ventricular or lumbar) documented within 14 days prior to entry.

- No compartmentalization of the CSF flow as documented by radioisotope Indium^{111} or Technitium^{99}-DTPA flow study in patient in whom cerebrospinal fluid analysis, myelograms, computerized axial tomographic or MR imaging scans suggested a CSF blockage. (This requirement was dropped after protocol amendment March 11 1996)
- 3 years of age or older.
- An expected survival of at least 2 months.
- Karnofsky Performance Status > 50%.
- Laboratory values as follows:

Platelet Count	$\geq 80{,}000/mm^3$
WBC Count	$\geq 3{,}000/mm^3$ (or ANC $\geq 1{,}000mm^3$)
Serum creatinine	≤ 2 x upper limit of normal
Total bilirubin	≤ 3 x upper limit of normal
SGOT	≤ 3 x upper limit of normal
LDH	≤ 3 x upper limit of normal
Alkaline phosphatase	≤ 3 x upper limit of normal
Blood Glucose	≤ 150 mg/dl

- Free of uncontrolled infection except HIV.
- In the event that the patient received any prior intrathecal treatment, he/she must have recovered from any toxicity attributed to that therapy.
  Any patient with a history of a serious NEUROLOGICAL (grade 4) adverse event related to any previous chemotherapy, administered either systemically or intrathecally at any dose, were to be excluded from the study.
- The experimental nature of this therapy must be fully understood by the patient (or responsible next-of-kin) and an "Informed Consent Form" must be signed

2.2.2 Exclusion Criteria

During the study treatment periods patients were NOT to receive

- intrathecal chemotherapy with any other agent except the study drug to which the patient is randomized.
- concurrent high-dose IV methotrexate (>500 mg/m^2/day), IV ARA-C (> 2 grams/m^2/day), high-dose thiotepa (> 300 mg/m^2/day) or investigational chemotherapy by either short or prolonged IV infusions for treatment of active disease outside of the meninges.
- simultaneous whole brain or entire neuraxis irradiation therapy and intrathecal study therapy.

(Patients may receive partial brain or limited-field spinal irradiation to symptomatic and bulky sites during study treatment. Patients may have received whole-brain, limited-field brain or craniospinal irradiation prior to enrollment. However if more than 14 days have elapsed from the initial cytologic diagnosis, a repeat CSF cytology is required).

- A history of a serious NEUROLOGICAL (grade 4) adverse event related to any previous systemic or intrathecal chemotherapy

- Prior treatment with intrathecal Ara-C (but may have received prior intrathecal MTX or may have received intrathecal Ara-C prophylactically).
- Any recent serious medical complication(s) making the patient considered medically unstable.
- Pregnant or breast feeding.
- Being of child-bearing potential without using methods to prevent pregnancy.
- Compartmentalization requiring VP shunt
  Use of any investigational drug therapy within 14 days prior to study entry or during study
- Unable to undergo repeat clinical neurological examinations, radioisotope, MR and CT brain scans, and other diagnostic procedures required by the protocol.

2.2.3 Early removal of patients from protocol

- Patient request, with documented reasons;
- If at any time, in consultation with the study chairman, continued participation in the study was determined not to be in the best interest of the patient;
- Development of a grade 4 or intolerable adverse event;
- Initiation of craniospinal or whole brain irradiation;
- Development of CSF compartmentalization, i.e. obstructive hydrocephalus or spinal cord block;
- Development of a significant intercurrent illness;
- Deterioration in the patient's disease status such that chemotherapy was no longer indicated.

2.2.4 Treatment

Patients were randomized to one of two treatment arms.

- Patients randomized to DepoCyt (DTC 101) received DTC 101, 50 mg by IVT or LP injection once every 14 days for 2 doses (induction). Those responding at the end of induction were to receive 50 mg once every 14 days for 3 doses, and 50 mg every 28 days for 1 dose (consolidation). Patients who did not relapse during the consolidation period received 50 mg once every 28 days for four additional doses (maintenance).
- Patients randomized to uncapsulated Ara-C received 50 mg by IVT or LP injection twice every 7 days for 28 days for 8 doses (induction). Those responding at the end of induction were to receive 50 mg once every 7 days for 5 doses, followed by 50 mg once every 2 weeks for 3 doses (consolidation). Patients who did not relapse during the consolidation period received 50 mg once every 28 days for four additional doses (maintenance).

All patients were to receive concurrent treatment with dexamethasone, 4 mg bid PO or IV x 5 days, to minimize symptoms associated with chemical arachnoiditis. Moreover, additional cycles of dexamethasone, 4 mg bid PO or IV x 5 days were allowed for breakthrough toxicities during any other week of the study.

2.2.5 Dose modifications

- Neurotoxicity : If a patient developed altered mental status and the recommended work-up was negative (repeat CSF flow, contrast-enhanced brain CT/MRI, CSF culture), the dose of study therapy was to be reduced by 50% and treatment continued.
- Hematologic Toxicity : In patients not receiving concurrent systemic chemotherapy and developing myelosuppression (WBC < 1500/mm^3 or platelets < 30,000/mm^3), treatment could be delayed until WBC and platelet counts returned to baseline if urgent clinical treatment for the meningeal disease was not required.
- CNS Infection : In the event of a CNS infection, study drug was to be discontinued. Patients who demonstrated a complete response to IT study therapy could continue into the consolidation or maintenance periods following CSF bacteriologic cure (confirmed by culture). CSF cytopathology also was to be repeated: if positive, the patient was to return to an induction regimen, and if negative, to consolidation or maintenance.

2.2.6 Evaluation for efficacy

Table 2 represents a timetable for the collection of study parameters as outlined in the protocol.

Evaluation	Baseline	Day 1 of each cycle	End of treatment	Follow-up **
CSF cytology	X	X (every 2 cycles after 2 months)	X	X (for CR patients only)
CSF flow study	X*	If clinically indicated		If clinically indicated
CT/MRI brain	X	If clinically indicated		If clinically indicated
CT myelogram/MRI spine	If clinically indicated	If clinically indicated		If clinically indicated
History/physical exam (including KPS)	X	X	X	X
Neurologic exam	X	X	X	X
Quality of life (FACT-CNS)	X	At end of induction and during maintenance only	X	
Mini Mental State Examination	X	At end of induction, end of consolidation, end of maintenance only	X	X
Hematology (peripheral blood)	X	X	X	If abnormal
Chemistry (peripheral blood)	X	X	X	If abnormal
Chemistry (CSF)	X	X (every 2 cycles after 2 months)	X	X (for CR patients only)
Urinalysis	X	X	X	If abnormal

*Only if CSF blockage suggested by CSF analysis or by radiologic tests; this radioisotope Indium^{111} or Technitium^{99}-DTPA flow requirement was dropped after protocol amendment March 11 1996

** follow-up every four weeks for all patients; for patients in complete remission (CR) every four weeks for the first three months, every three months afterwards for maximum one year

2.2.7 Efficacy considerations

Efficacy (primary study objective) was based primarily on response rates, as well as time to response and duration of response.

Response was defined in terms of both CSF cytology and neurologic status.

a) CSF cytology :

The protocol required an initial assessment of cytologic response to be made after 4 weeks of induction therapy (day 29) based on a CSF sample drawn from a single site of choice previously documented to be positive (lumbar or intraventricular).

If the CSF cytology remained positive : the patient was considered to have demonstrated "no response (NR)" and was to discontinue study treatment.
If CSF cytology was negative at this site and there was no evidence of progressive disease, negative cytology must then be confirmed.

Confirmatory CSF samples were scheduled between weeks 5 and 6 (day 32) from all sites previously documented as positive (lumbar and/or intraventricular) and were required to be negative before the patient could be considered a "complete responder (CR)".

If any CSF sample demonstrated positive cytology : the patient was regarded as a "non-responder (NR)" and was to discontinue study treatment.
If all CSF samples were cytologically negative and there was no evidence of progressive disease, the patient was regarded as a "complete responder (CR)" and continued with consolidation/maintenance therapy.

Duration consolidation/maintenance/follow-up, CSF cytology only needed to be checked periodically at a single site of choice previously documented to be positive.

Definition of response based on CSF cytology were:

- Negative cytology: absence of malignant cells or of cells suspicious for malignancy in the CSF. "Atypical" or "abnormal" results were classified as negative.
- Positive cytology: presence of "malignant" cells or cells "suspicious for malignancy" in the CSF.

A local cytopathologist at each participating institution was required to determine the CSF cytology during the study, when the investigator needed an immediate result upon which to base his/her decision as to whether to continue study treatment. In addition, a blinded independent cytopathology review was required by protocol. This evaluation, not the local cytopathology review, was clearly stated to be final for purposes of the efficacy review.

b) Assessment of neurologic status:

A standardized neurological examination including the Mini-Mental State Examination was performed at baseline and at regular intervals throughout the treatment and follow-up. Improvement or worsening of neurological signs or symptoms from the baseline score were evaluated. If there was either cytologic or neurological disease progression consistent with leptomeningeal metastases sufficient to contemplate a change in intrathecal chemotherapy, the patient was to discontinue study treatment.
It is important to note that most patients with neoplastic meningitis have fixed neurologic deficits that do not improve even when the CSF is cleared of malignant cells by therapy, and thus improvement in neurologic symptoms and signs is not routinely anticipated.

c) Definitions of Response

'Complete Response (CR)' was defined as

- TWO consecutive negative CSF cytologies at least 3 days apart (cytologic);
- No evidence of clinical disease progression (neurologic).

'No Response (NR)' was defined as

- Positive cytology in any of the CSF samples taken either at the end of the Induction period (day 29) or between weeks 5 and 6 (days 32-35: confirmatory samples) (cytologic);
- Evidence of progression of leptomeningeal metastases (neurologic).

'Time to Complete Response' was defined as the duration, in days, between the first day of study treatment and the first negative cytology that is subsequently documented to be a CR by the confirmatory cytology exams (cytologic) with no evidence of progression of leptomeningeal metastases (neurologic).

'Duration of Complete Response (Remission)' was defined as the duration, in days, between the first negative cytology (that is subsequently documented to be a CR by the confirmatory cytology exams) and

- the first subsequent positive cytology that is subsequently documented to reflect disease relapse by a confirmatory cytology exam (cytologic);
- evidence of progression of leptomeningeal metastases (neurologic).
- death, whichever comes first (this third possibility was not present in the original protocol, but was added afterwards during data analysis)

'Time to Disease Relapse' was defined as the duration, in days, between the first day of study treatment and

- the first positive cytology subsequent to the patient having achieved a CR(cytologic);
- evidence of progression of leptomeningeal metastases (neurologic).

Secondary measurements of efficacy were :

- Changes in neurological symptoms and signs
- Changes in quality of life measurements :
  - Prospectively defined instruments of quality of life were : Karnofsky Performance Score, Mini Mental State Examination and FACT-CNS scale (FACT-G scale plus an study-specific additional concerns subscale)
  - Retrospectively, a Q-TwiST analysis was added in which the time period is calculated in which a patient is alive and free of symptoms due to toxicity or disease progression
- Data were collected on progression of systemic disease and overall survival

2.2.8 Safety considerations

Safety was the second objective of the study. Safety parameters were

- Incidence of adverse events.
  An 'adverse event' was defined as any experience affecting a person's health. The severity of the adverse event was graded according to the CALGB Expanded Common Toxicity Criteria and the relationship to the study drug was assessed by the investigator.
  A 'serious adverse event' was defined as a life-threatening, permanently disabling event, requiring in-patient hospitalization or death. It also included congenital anomaly, a new cancer or overdose. An 'unexpected adverse event' for DTC 101 was defined as one that was not observed in the phase I study (headache, fever, meningismus, nausea/vomiting, photophobia, back pain, dehydration, hyponatremia, tinnitus, dizziness, confusion and encephalopathy); an 'unexpected adverse event' for Ara-C was defined as one that was not reported in the literature (seizures, leukoencephalopathy, paraparesis, myelosuppression, anemia, stomatitis, mucositis, hepatic dysfunction, alopecia and dermatitis).

- Changes in laboratory parameters

The third objective was to compare the need for additional oral steroids (dexamethasone) for symptomatic control of drug-related toxicities.

2.2.9 Statistics

This is an open-label randomized clinical trial comparing efficacy and safety of intrathecal DTC 101 versus intrathecal uncapsulated Ara-C in the treatment of lymphomatous meningitis. Patients were stratified into 'AIDS-related lymphoma' versus 'non-AIDS-related lymphoma'. Enrollment was planned to continue until at least ten non-AIDS-related lymphoma patients were assigned to each study treatment and until at

least twenty total patients were enrolled in each treatment arm. With an expected size of about 20 patients per group, true response rates of 90% versus 40%, 75% versus 20% and 60% versus 10% were calculated to be distinguishable with 80% power at an alpha level of .05.

3. FDA REVIEW OF DATA

3.1 Patient characteristics and trial conduct

Between March 24 1994 and August 11 1998 33 lymphomatous meningitis patients were enrolled in the trial. Seventeen patients were randomized to DTC 101 and sixteen patients were randomized to uncapsulated Ara-C. Patient characteristics of the two groups are shown in table 3.

	DTC 101	Ara-C
Total number	17	16
AIDS-related lymphoma	2	3 (2 evaluable)
Median age (years)	60	53.5
Karnofsky: median / mean	70% / 75%	70% / 69 %
Stable systemic disease	5	2
Progressive systemic disease	4	6
Prior intrathecal chemo	3	5
CNS radiation prior to study entry: - prior to diagnosis of LM - after diagnosis of LM	 4 4	 4 1
CNS radiation during study - any time during study - prior to response evaluation	 3 3	 1 1
Concurrent systemic chemotherapy	9	4
Primary CNS lymphoma	6	2
Intraparenchymal brain lymphoma	1	1
Cranial nerve palsies	5	8
CSF compartmentalization (nr/nr tested)	1/9	0/11

Table 3. Patient characteristics

From this table it is apparent that some bad prognostic factors (as discussed in 1.2.1) have an unequal distribution in the two patient groups:

- in DTC 101 group : higher median age
- in Ara-C group : more progressive systemic disease, more cranial nerve palsies, less concurrent chemotherapy, less primary CNS lymphoma

The distribution of AIDS- and non-AIDS-related lymphoma and performance status was comparable in the two arms.

Of the 33 patients, 31 received intrathecal study treatment. One DTC 101 patient (25LN230) and one Ara-C patient (25LA169) did not receive any study drug after enrollment for various reasons; these two patients will be excluded from all subsequent analyses. Three patients (2 Ara-C, 1 DTC 101) are still under active protocol treatment.

One DTC 101 patient (31LN225) entered on study should have been considered ineligible. The patient had CSF compartmentalization as shown by a positive CSF flow study at day −12. In the absence of demonstration of a restored CSF flow prior to study entry, this is a formal exclusion criterion (patient received WBRT starting on day 1).

3.2 Efficacy evaluation

3.2.1 Primary efficacy endpoints

3.2.1.1 Response rates

The protocol definition of CR (complete response) is discussed in 2.2.7. Briefly, a patient is said to have a CR at the end of the induction period if (a) there is no evidence of clinical neurologic progression and (b) the CSF cytologies, read by a blinded central pathologist, have converted to negative on two separate occasions (at least 3 days apart) and at all initially positive sites.

The FDA assessment of the response results is shown in table 4. Only in 13/31 patients can the response be evaluated without encountering protocol violations; only 2 of these 13 patients had a CR by protocol definition. The reader is encouraged to study table 4 in detail, as a careful assessment whether and which protocol violations can be acceptable, will be crucial for all further efficacy evaluations. The following protocol violations were separately listed :

- forbidden concomitant treatment: high-dose MTX/Ara-C, WBRT (whole brain radiation therapy)
- absence of central pathology review: crucial slides of the initial sample and/or of samples for response assessment were either not read or reported 'non-evaluable'
- not all initial sites checked: while the patient initially had positive cytology at lumbar and at intraventricular (Ommaya) sites, only the response of one site was checked
- initial site not checked: while the patient initially had positive cytology at the lumbar or at the intraventricular (Ommaya) site, only the response of the other site (initially negative or unknown) was checked
- supplementary site checked: while a positive cytology initially only was documented at one site, the response was also checked in the other site (initially negative or unknown)
- late sample: end of induction sample was taken at $\geq$ day 40 (instead of day 29)

- no confirmatory sample: no confirmatory sample taken
- late confirmatory sample: confirmatory sample taken at ≥ day 40 (instead of day 32).

The different protocol violations are separated per patient. For example, in patient 25LA168 the cytology of the initially positive site was not checked, no confirmatory CSF sample was drawn and central pathology review was missing; however the patient could be said to have obtained a CR if all these violations were considered acceptable.

In order to allow an assessment of the relative importance of the central pathology review, a comparison of central and of local pathology results was made. This comparison made clear that the central pathologist read more CSF samples as positive than the local pathologists. Of all 218 cytology samples for which local and central review was available, 36 (16.5 %) were read as positive by the central pathologist and negative by the local pathologists; only in 7 (3.2 %) the sample was read as positive by the local pathologist and as negative by the central pathologist. Most important for the determination of the response rate is the likelihood that the central pathology review, if it had been available, would have read a sample as positive in cases in which the (only available) local pathology reading was 'negative' or 'atypical' ('atypical' by protocol was considered negative). In the samples for which central and local review were available, 55 % of the 'atypical' cytologies in the local review were read as positive by the central reviewer, whereas 23 % of the 'negative' cytologies were read as positive by the central reviewer (table 5). In the 8 patients for which only local pathology review was available, 1 patient had an 'atypical' reading and 7 patients had a negative cytology reading.

	Total	Central review: 'negative'	Central review : 'positive'
Local review: 'negative'	140	108 (77 %)	32 (23 %)
Local review: 'atypical'	11	5 (45 %)	6 (55 %)

Table 5. Comparison of local and central pathology results

The importance of a confirmatory negative cytology sample has been discussed in the literature (Chamberlain, 1993) and is also apparent from the available data. In 4 of the 8 patients from whom a confirmatory sample is lacking, the subsequent CSF sample taken 11-14 days later was read as positive (indicated by (d) in table 4).

		1. RESPONSE (PROTOCOL)	2. DISCONTINUATION	3. FORBIDDEN CONCOMITANT TREATMENT	4. NO CENTRAL PATHOLOGY REVIEW	5. NOT ALL INITIAL SITES CHECKED	6. INITIAL SITE NOT CHECKED	7. SUPPLEMENTARY SITE CHECKED	8. LATE SAMPLE	9. NO CONFIRMATORY SAMPLE	10. LATE CONFIRMATORY SAMPLE
1	25LA165				CR						CR
2	25LA167	NR									
3	01LN205	CR									
4	03LN208									CR (d)	
5	04LN209	NR	Death d21								
6	19LN213				CR						CR
7	29LN214	NR									
8	19LN216	CR (f)									
9	38LN217				CR	CR				CR (d)	
10	04LN220				CR						CR
11	03LN222			HD MTX/ARA-C	CR						CR
12	26LN223	NR									
13	31LN225			WBRT	CR						CR
14	04LN226				CR						CR
15	29LN232									CR (d)	
16	29LN230	—									
17	29LN233										CR
18	25LA166	NR	Death d13								
19	54LA168				CR		CR			CR	
20	25LA169	—									
21	19LN206	NR									
22	19LN207	NR	d17 (a)								
23	20LN210							NR (g)			
24	19LN211					CR					
25	24LN212	NR									
26	25LN215										CR
27	13LN218	NR	d13 (b)								
28	12LN219						CR				CR
29	26LN221									CR	
30	03LN224	NR	d16 (c)								
31	51LN227					CR			CR	CR	
32	62LN229						CR			CR (d)	
33	38LN231	NR	d14 (e)								

Table 4. Cytologic response evaluation (legends and footnotes on next page)

Table 4. Cytologic response evaluation – legends and footnotes

Data of patients randomized to DTC 101 (1-17) are printed in bold, while data of patients randomized to Ara-C (18-33) are printed in normal characters.

Column 1 (evaluable patients per protocol) contains the cytological response of those patients in whom the response assessment was done according to the original protocol (15 patients). Column 2 gives information on those patients who discontinued the treatment during the induction phase (6 patients). Column 3 to 10 deal with the different protocol violations encountered during response assessment.

(a) 19LN207 discontinued day 17 because of lack of response (positive CSF cytology and neurologic progression per original CSF), negative CSF cytologies on day 33 and 93 during IT MTX treatment

(b) 13LN218 discontinued treatment day 13 due to right arm paresis (drug-related ?) 24 hour after 3rd IVT treatment with Ara-C. MRI negative for brachial plexus tumor.

(c) 03LN224 discontinued day 16 because of neurologic progression

(d Negative cytology end of induction, no confirmatory sample but positive cytology of subsequent CSF sample (11-14 days after end of induction)

(e) 38LN231 discontinued day 14 because of clinical progression

(f) 19LN216 had a confirmatory sample at day 37 instead of day 32-35; while this was a technical protocol violation, the delay was less important than in all other patients with a late confirmatory sample ($\geq$ day 40)

(g) 20LN210 only had positive cytology documented at IVT site prior to start of protocol; however also a CSF cytology by lumbar puncture (LP) was checked at day 34; while the IVT cytologies were negative, the LP cytology was positive for lymphomatous cells

3.2.1.2 Time to complete response, duration of complete response, time to relapse

The protocol definitions of 'time to complete response' and 'duration of complete response' are discussed in 2.2.7. For 'time to relapse' not only cytologic relapse or neurologic progression (as per protocol) but also death was considered a terminating event.

Results are shown in table 6. Time to response, time to cytologic progression, time to neurologic progression and duration of response were calculated for all patients who potentially could be considered CR if protocol violations were ignored (see 4.2.1). Time to death was calculated for all patients. Following remarks need to be made:

- for the calculation of time to response, no interim cytology during the first cycle of Ara-C was taken into consideration to allow objective comparison between Ara-C and DTC 101 (given the more frequent administration schedule of Ara-C, CSF cytology samples were available earlier in the Ara-C group than in the DTC 101 group)
- because of discrepancy in results of local and central pathology review, results for 'time to last negative cytology' and 'time to cytologic progression' are split in 'local' and 'central' review. Where available, the central pathology results were used as a basis for further calculations.

3.2.2 Secondary efficacy endpoints

3.2.2.1 Changes in neurological symptoms/signs

Neurological assessments were carried out by the study investigators. These assessments were used for the determination of response and time to neurologic progression. Where a global neurologic assessment was missing in the original CRF, the reassessment of the neurologic status by the sponsor's medical officer was used. Where there was a disagreement between the global neurologic assessment per original CRF and a reassessment of the neurologic status by the sponsor's medical officer, the original CRF assessment was used. By that analysis, median time to neurologic progression for the 33 treated patients, irregardless of their response status, was 76.5 days in the DTC 101 group and 51 days in the Ara-C group. No statistical significance was claimed by the sponsor.

3.2.2.2. Quality of life measurements

Prospectively defined quality of life instruments were the Karnofsky performance score (KPS), the mini mental state examination (MMSE) and the FACT-CNS score (patient questionnaire).

The reader is invited to study the frequency with which these measurements were scheduled by protocol (see table 2). The submitted data only allow a comparison of

baseline and of end-of-induction results for all three instruments as only data on very few patients are available for the consolidation, maintenance, end of treatment and follow-up time points. There are several reasons for this absence of data at later time points:

- as the majority of patients progressed during study (only three patients completed the protocol), the number of patients at later time points became very small
- the patient's debilitating condition frequently prohibited the completion of the FACT-CNS questionnaire and the MMSE.

Results for the baseline and end-of-induction scores for the three instruments are shown in table 7 and are summarized in the following paragraph and in table 8 :

a) KPS :

- for 15/16 DTC 101 patients baseline and end-of-induction KPS scores were available. Mean scores were 76 % at baseline and 78.6 % (+2.6 %) at end-of-induction; median scores were 70 % at baseline and 70 % (+10 %) at end-of-induction.
- For 8/15 Ara-C patients baseline and end-of-induction KPS scores were available. Mean scores were 71 % at baseline and 62.5 % (- 8.5 %) at end-of-induction; median scores were 65 % at baseline and 50 % (- 15 %) at end-of-induction.

b) MMSE :

- for 9/16 DTC 101 patients baseline and end-of-induction MMSE scores were available. Mean scores were 24.8 at baseline and 25.2 (+0.4) at end-of-induction; median scores were 29 at baseline and 24 (-5) at end-of-induction.
- for 4/15 Ara-C patients baseline and end-of-induction KPS scores were available. Mean scores were 26.5 at baseline and 28 (+1.5) at end-of-induction; median scores were 27.5 at baseline and 29 (+ 1.5) at end-of-induction.

c) FACT-CNS :

- for 7/16 DTC 101 patients baseline and end-of-induction FACT-CNS scores were available. Mean scores were 107 at baseline and 118 (+11) at end-of-induction; median scores were 110 at baseline and 117 (+7) at end-of-induction.
- for 6/15 Ara-C patients baseline and end-of-induction FACT-CNS scores were available. Mean scores were 99 at baseline and 94 (-5) at end-of-induction; median scores were 97 at baseline and 101 (+4) at end-of-induction.

	DTC 101 (n=16)		Ara-C (n=15)	
	Number of patients	Change in absolute value	Number of patients	Change in absolute value
KPS mean score	15	+ 2.6 %	8	- 8.5 %
KPS median score	15	+ 10 %	8	- 15 %
MMSE mean score	9	+ 0.4	4	+ 1.5
MMSE median score	9	- 5	4	+ 1.5
FACT-CNS mean score	7	+ 11	6	- 5
FACT-CNS median score	7	+7	6	+ 4

Table 8 Trends in change of quality of life data during induction period

		RESPONSE AS PER PROTOCOL	ALL RESPONSES (WITH PROTOCOL VIOLATIONS)	TIME TO RESPONSE (from day 1)	TIME TO LAST NEGATIVE CYTOLOGY (from day 1)		TIME TO CYTOLOGIC PROGRESSION (from day 1)		TIME TO NEUROLOGIC PROGRESSION (from day 1)	TIME TO DEATH	TIME TO RELAPSE	DURATION OF RESPONSE (from first negative cytology)
					local	centri	local	centri				
1	25LA165		CR	17	89	NR	96	NR	96	170	96	79
2	25LA167	NR	NR						190	294(cens)		
3	01LN205	CR	CR	15	62	43	NA	62	75	75	62	47
4	03LN208		CR	15	43	29	NA	43	78	78	43	28
5	04LN209	NR	NR						21	21		
6	19LN213		CR	15	221	60	NA	82	124	580	82	67
7	29LN214	NR	NR						114	114		
8	19LN216	CR	CR	18	52	52	NA	NA	51	54	51	33
9	38LN217		CR	14	29	25	41	41	23	42	41	9
10	04LN220		CR	14	93	NR	125	NR	91	239	91	77
11	03LN222		CR	29	407	121	NA	157	218	481(cens)		128
12	26LN223	NR	NR						432(cens)	432(cens)		
13	31LN225		CR	16	40	NR	NA	NR	41	64	41	25
14	04LN226		CR	15	63	63	NA	NA	74	87	87	59
15	29LN232		CR	16	70	28	NA	42	56(cens)	56(cens)	42	26
16	29LN233		CR	15	45	45	NA	NA	53(cens)	53(cens)	53(cens)	38(cens)
17	25LN230	—	—									
18	25LA166	NR	NR						6	13		
19	54LA168		CR	15	30	24	NA	NA	38	38	38	23
20	25LA169	—	—									
21	19LN206	NR	NR						64	64		
22	19LN207	NR	NR						14	162		
23	20LN210	NR	NR						51	51		
24	19LN211		CR	29	203	169	231	203	231	1121(cens)	203	174
25	24LN212	NR	NR						148	382		
26	25LN215		CR	13	218	218	NA	NA	218	577	218	205
27	13LN218	NR	NR						10	44		
28	12LN219		CR	16	125	125	NA	NA	130	130	130	114
29	26LN221		CR	30	30	30	NA	NA	34	34	34	4
30	03LN224	NR	NR						16	177		
31	51LN227		CR	15	40	40	NA	NA	55	55	55	40
32	62LN229		CR	16	165	137	227	NR	121	282(cens)	121	105
33	38LN231	NR	NR						15	59		

Table 6. Time to response, time to relapse, duration of response (legends – see next page)

Table 6. Time to response, time to relapse, duration of response – legends

Data of patients randomized to DTC 101 (1-17) are printed in bold, while data of patients randomized to Ara-C (18-33) are printed in normal characters.

Following abbreviations are used : NA, not applicable; cens, censored.

		KPS		MMSE		FACT-CNS	
		BASELINE	END OF INDUCTION	BASELINE	END OF INDUCTION	BASELINE	END OF INDUCTION
1	**25LA165**	**80**	**90**	**29**	**24**	**83**	**117**
2	**25LA167**	**100**	**100**	**ND**		**ND**	
3	**01LN205**	**70**	**90**	**27**	**28**	**91**	**109**
4	**03LN208**	**70**	**70**	**19**	**20**	**110**	**125**
5	**04LN209**	**60**	**NA**	**30**	**NA**	**113**	**NA**
6	**19LN213**	**60**	**90**	**ND**		**ND**	
7	**29LN214**	**60**	**70**	**26**	**22**	**89**	**ND**
8	**19LN216**	**70**	**60**	**ND**		**126**	**113**
9	**38LN217**	**80**	**80**	**18**	**NR**	**ND**	
10	**04LN220**	**70**	**60**	**30**	**30**	**ND**	
11	**03LN222**	**100**	**100**	**29**	**30**	**134**	**136**
12	**26LN223**	**100**	**100**	**29**	**30**	**151**	**152**
13	**31LN225**	**60**	**60**	**ND**		**ND**	
14	**04LN226**	**50**	**50**	**4**	**21**	**56**	**74**
15	**29LN232**	**70**	**70**	**30**	**22**	**NR**	**NR**
16	**29LN233**	**100**	**90**	**29**	**ND**	**NR**	**NR**
17	**25LN230**	**–**	**–**	**–**	**–**	**–**	**–**
18	25LA166	70	NA	NR	NA	108	NA
19	25LA168	90	50	NR	NR	129	111
20	25LA169	–	–	–	–	–	–
21	19LN206	60	50	ND		ND	
22	19LN207	50	NA	ND		ND	
23	20LN210	60	50	23	29	70	72
24	19LN211	70	80	27	30	91	105
25	24LN212	80	90	30	ND	95	ND
26	25LN215	50	50	21	INVALID	88	74
27	13LN218	70	NA	27	NA	94	NA
28	12LN219	100	90	28	29	112	105
29	26LN221	60	40	28	24	103	97
30	03LN224	80	NA	21	NA	ND	NA
31	51LN227	60	NR	27	ND	91	ND
32	62LN229	50	NR	29	ND	NR	NR
33	38LN231	80	NA	29	NA	NR	NA

Table 7. Quality of life data

Legends :
Data of patients randomized to DTC 101 (1-17) are printed in bold, while data of patients randomized to Ara-C (18-33) are printed in normal characters. Following abbreviations are used : NA, not applicable; NR, not reported

The sponsor did not claim statistical significance for the differences in the change of MMSE and FACT-CNS scores between the two treatment arms. However, statistical significance was claimed for the difference in change of the KPS scores between DTC 101 and Ara-C ($p \leq 0.041$). FDA does not concur with the interpretation of statistical significance given the multiplicity of analyses and the amount of missing data.

The sponsor added an retrospective instrument to the quality-of-life analysis : the Q-TWiST analysis. This analysis calculates the time period in which the patient is alive and free of symptoms due to toxicity or disease progression. This information is received from the difference in the area under the curve between progression-free survival and duration of treatment-related toxicity. The sponsor submitted the following results from this analysis:
- if only grade 3-4 treatment-related adverse events were taken into account, this symptom-free time period was 54 days for Ara-C and 98 days for DTC 101;
- if all treatment-related adverse events were taken into account, this symptom-free time period was 10 days for Ara-C and 59 days for DTC 101.
The sponsor did not claim statistical significance for these differences. Given the time constraints and the lack of apparent significance FDA did not attempt to duplicate this analysis.

3.2.2.3 Survival data

Collection of survival data was a secondary efficacy endpoint. As pointed out in the introduction, since the majority of treated LM patients in the literature are reported to have died from systemic lymphoma, the importance of overall survival as an efficacy endpoint for an intrathecal treatment should not be overestimated.

The survival data per patient are indicated in table 6. At the time of analysis, 5/16 DTC 101 patients and 2/15 Ara-C patients are reported to be alive (censored). Table 9 gives the overall survival data for the two treatment groups.

	DTC-101	Ara-C
Median overall survival (days)	82.5	64
Mean overall survival (days)	177.4	212.5
6 months survivors	5/16 (31 %)	4/15 (27 %)
12 months survivors	3/16 (19 %)	3/15 (20 %)

Table 9. Overall survival data

The majority of patients on both treatment arms died from progressive systemic disease. Of the 11 deceased DTC 101 patients, 6 died from systemic disease and 4 from a combination of systemic and meningeal disease. Of the 13 deceased Ara-C patients, 8 died from systemic disease and 2 from a combination of systemic and meningeal disease. No toxic deaths were reported.

3.3 Safety evaluation

The second objective of the study was to compare the safety profile of DTC 101 administered intrathecally as compared to intrathecal chemotherapy with Ara-C.

3.3.1 Extent of exposure

The mean treatment exposure per patient to DTC 101 was longer than to Ara-C : while on the DTC 101 arm 16 patients received a total of 83 cycles (5.2 cycles/patient), the 15 patients on the Ara-C arm only received a total of 51.75 cycles (3.45 cycles/patient).

3.3.2 Adverse events

3.3.2.1 Frequency of adverse events and drug-related adverse events

Analysis of adverse events was done on data from the 14 DTC 101 patients (74 treatment cycles) and the 13 Ara-C patients (44.5 treatment cycles) for whom data were already submitted in NDA 20798. As the adverse event data on the 4 patients recently entered into the trial were only submitted three weeks prior to the scheduled ODAC meeting, FDA did not include these into the following analysis.

Adverse events reported for at least 10% of patients are presented in table 28 (taken from the applicant's submission). Adverse events that occurred in at least 50% of patients treated with DTC 101, irrespective of whether they were drug-related or not, included asthenia, fever, headache, neutropenia, and confusion. For ara-C, adverse events reported for at least 50% of patients included asthenia, fever, and nausea.

Body System/COSTART Term	DTC 101 (N = 14)	Ara-C (N = 13)
Body as a Whole		
Pain back	5 (36)	3 (23)
Pain	5 (36)	5 (39)
Death	6 (43)	5 (39)
Headache	7 (50)	3 (23)
Fever	7 (50)	7 (54)
Asthenia	8 (57)	10 (77)

Body System/COSTART Term	DTC 101 (N = 14)	Ara-C (N = 13)
Cardiovascular System		
Tachycardia	0	3 (23)
Digestive System		
Monilia oral	1 (7)	3 (23)
Anorexia	2 (14)	3 (23)
Diarrhea	3 (21)	4 (31)
Constipation	4 (29)	3 (22)
Vomiting	4 (29)	6 (46)
Nausea	4 (29)	7 (54)
Hemic and Lymphatic System		
Anemia	1 (7)	4 (31)
Thrombocytopenia	4 (29)	5 (39)
Neutropenia	7 (50)	3 (23)
Metabolic and Nutritional Disorders		
Hyperglycemia	3 (21)	2 (15)
Edema peripheral	5 (36)	5 (39)
Nervous System		
Paresthesia	0	3 (23)
Anxiety	1 (7)	3 (23)
Reflexes decreased	1 (7)	3 (23)
Gait abnormal	2 (14)	5 (39)
Meningismus	3 (21)	0
Vertigo	3 (21)	1 (8)
Neuropathy	3 (21)	1 (8)
Hypesthesia	3 (21)	2 (15)
Agitation	3 (21)	2 (15)
Insomnia	3 (21)	3 (23)
Somnolence	4 (29)	4 (31)
Convulsion	5 (36)	1 (8)
Dizziness	5 (36)	3 (23)
Confusion	7 (50)	3 (23)
Respiratory System		
Pneumonia	1 (7)	3 (23)
Cough increased	3 (21)	3 (23)
Dyspnea	4 (29)	3 (23)
Skin and appendages		
Sweating	1 (7)	3 (23)
Special Senses		
Deafness	4 (29)	3 (23)
Urogenital System		
Urinary incontinence	2 (14)	5 (39)
Urinary tract infection	4 (29)	3 (23)

Table 28: Frequency of adverse events reported by $\geq$ 10% of patients

The risk of a patient suffering from an adverse event correlates with the duration of his/her on-study time. As there is a clear discrepancy in on-study time and number of treatment cycles per patient between the two arms, the following analysis focuses on the frequency of adverse events 'per cycle' instead of 'per patient'.

Table 10, taken from the applicant's submission, reports the frequency of drug cycles in which the most common (reported by at least 10 % of patients) drug-related adverse events occurred.

	CALGB Toxicity Grade by Cycle									
	DTC 101 N = 74					Ara-C N = 44.5				
Grade of Toxicity	1	2	3	4	All Grades	1	2	3	4	All Grades
Headache	7[2] (9)[3]	9 (12)	4 (5)	0 (0)	20 (27)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)
Nausea	1 (1)	6 (8)	0 (0)	0 (0)	7 (9)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)
Vomiting	0 (0)	5 (7)	1 (1)	0 (0)	6 (8)	1 (2)	1 (2)	0 (0)	0 (0)	2 (4)
Asthenia	0 (0)	1 (1)	1 (1)	0 (0)	2 (3)	1 (2)	2 (4)	1 (2)	0 (0)	4 (8)
Fever	1 (1)	3 (4)	2 (3)	0 (0)	6 (8)	1 (2)	1 (2)	0 (0)	0 (0)	2 (4)
Pain	0 (0)	3 (4)	1 (1)	0 (0)	4 (5)	1 (2)	1 (2)	0 (0)	0 (0)	2 (4)
Meningismus	0 (0)	1 (1)	2 (3)	0 (0)	3 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Confusion	1 (1)	2 (3)	2 (3)	0 (0)	5 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Somnolence	2 (3)	2 (3)	2 (3)	0 (0)	6 (8)	0 (0)	1 (2)	1 (2)	0 (0)	2 (4)
Neutropenia	0 (0)	0 (0)	0 (0)	4 (5)	4 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 10. Frequency of drug cycles in which adverse events occurred by study drug and grade; all drug-related[1] adverse events reported by ≥ 10% of patients.

[1] Includes all adverse events that were possibly, probably or definitely drug-related, or for which relationship to drug could not be determined.

[2] Number of cycles in which the AE of the specified type and grade occurred.

[3] Percent of total cycles on which the AE occurred.

The assessment by the investigator of the relationship of an adverse event to the study drug was sometimes debatable. For example, neutropenia was an adverse event in at least one cycle in 7 patients on the DTC 101 arm (6 grade 4, 1 grade 3) and in 3 patients on the Ara-C arm (2 grade 4, 1 grade 3). Although 9 of these 10 patients received concomitant intravenous chemotherapy, neutropenia was considered drug-related in 4 patients; the rationale to consider (only) a subset of these adverse events as drug-related is unclear. Interestingly, in the only patient without concomitant intravenous chemotherapy, the neutropenia was not even considered as possibly drug-related, but was attributed to prior radiotherapy.

Nonetheless, a notable difference is observed in the frequency of headache, nausea, vomiting, meningismus and confusion between the two groups. This impression of a higher incidence of (investigator-determined) drug-related adverse events in the DTC 101 arm from table 9 is confirmed by the analysis shown in figure 1 (taken from the applicant's submission). Figure 1 presents a graphic display of the number of patients suffering drug-related adverse events per cycle. The pre-study frequencies of disease-related adverse events are shown for comparison.

Figure 1 also shows that the number of patients reporting an adverse event was less in any treatment cycle compared to the pre-study period. The frequency of adverse events did not increase in later treatment cycles.

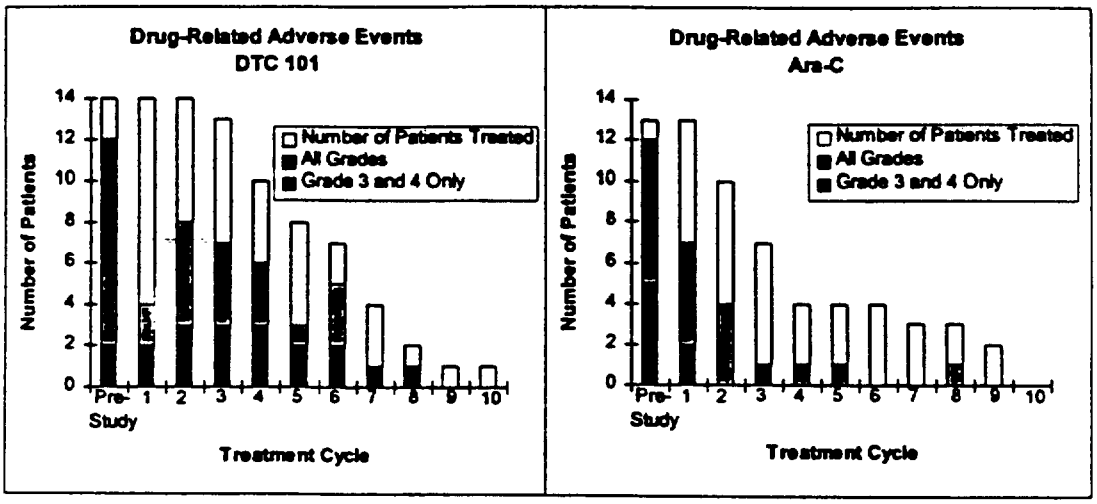

Figure 1. Number of patients suffering disease-related adverse events prior to the start of treatment and drug-related adverse events following the start of treatment by cycle

The height of the open bar indicates the number of patients treated in that cycle, the height of the lightly shaded portion of the bar indicates the number of patients who suffered any grade of the AE, and the darkly shaded portion indicates the number of patients whose AE was grade 3 or 4. The number of patients with AEs in the pre-study period is shown for reference.

3.3.2.2 Adverse events linked to disease symptoms

Nausea/vomiting and headache are among the most common adverse events reported in the study. They can be disease-related symptoms caused by lymphomatous meningitis or can be drug-related symptoms caused by chemical arachnoiditis. Figure 2 illustrates the evolution of these adverse events during treatment for the two patient groups. The frequency with which nausea/vomiting was reported decreased in both arms; the favorable evolution of the frequency of headache was clear for the Ara-C group but was

questionable for the DTC 101 group. It should be noted that the extent to which concomitant medication (steroids, anti-emetics, analgesics) is responsible for a favorable evolution of these adverse events during treatment is unknown.

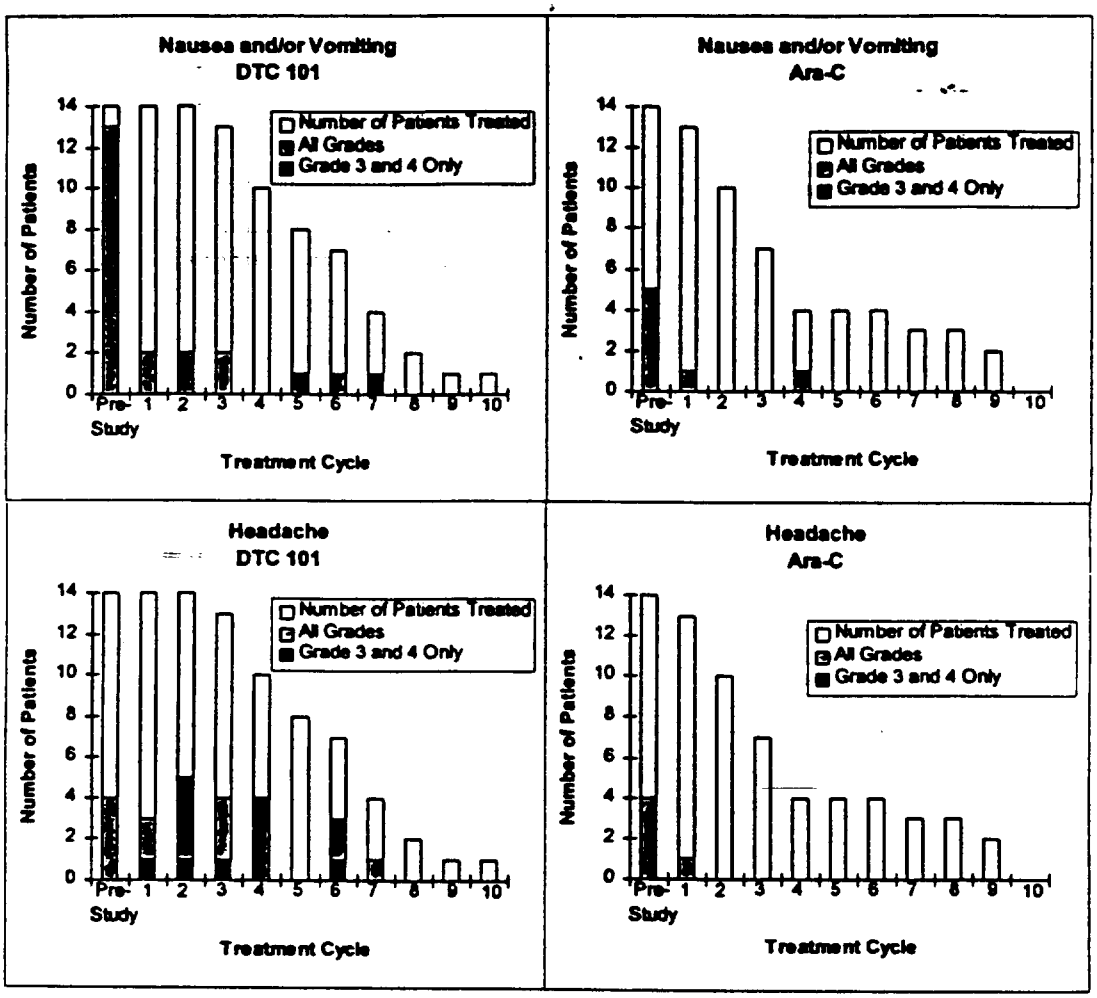

Figure 2. Number of Patients within a Cycle with AEs as a Function of Severity and Study Drug

The height of the open bar indicates the number of patients treated in that cycle, the height of the lightly shaded portion of the bar indicates the number of patients who suffered a grade 1 or 2 AE, and the darkly shaded portion indicates the number of patients whose AE was grade 3 or 4. The number of patients with AEs in the pre-study period is shown for reference.

Chemical irritation of the meninges (chemical arachnoiditis) is a well-known side-effect of intrathecal chemotherapy; as already alluded to above, its symptoms/signs are difficult to distinguish from the symptoms/signs of the neoplastic meningitis itself. The sponsor used a (retrospectively defined) algorithm that scored patients as having arachnoiditis if following symptoms/signs were present :

- either neck rigidity OR neck pain OR meningismus

- or any TWO of following : nausea, vomiting, headache, fever, back pain or CSF pleocytosis.
The grade of the arachnoiditis was scored as equal to the highest grade of the adverse effects on which the arachnoiditis diagnosis was based. Figure 3, taken from the applicant's submission) depicts the number of patients with arachnoiditis by cycle and grade (without regard to investigator's assessment of relationship to study drug).

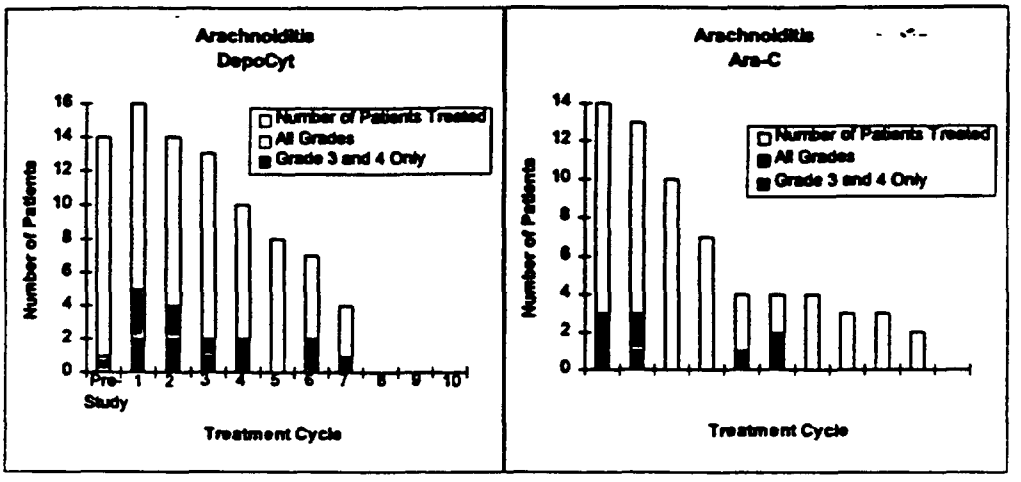

Fig. 3 Number of patients with arachnoiditis by cycle and grade

The height of the open bar indicates the number of patients treated in that cycle, the height of the lightly shaded portion of the bar indicates the number of patients who suffered any grade of the AE, and the darkly shaded portion indicates the number of patients whose AE was grade 3 or 4. The number of patients with arachnoiditis in the pre-study period is shown for reference.

Based on these data, a comparison of the frequencies (per cycle) of on-study arachnoiditis in the two treatment groups leads to the following table :

Arachnoiditis	DTC 101 (n cycles: 74)	Ara-C (n cycles: 44.5)
all grades	16 (22 %)	6 (13 %)
grade 3 and 4	6 (8 %)	3 (7 %)

Table 11. Frequency of on-study arachnoiditis

It should be noted that the algorithm used appears to have a low threshold for identifying arachnoiditis : for example, a combination of nausea/vomiting or nausea/fever was already sufficient for the diagnosis of arachnoiditis. Such low threshold has the hypothetical pitfall that false positive events can obscure a difference between arms if one exists.

No evidence of cumulative toxicity was found in any of the adverse event analyses described above. For that reason, the longer on-study time and the higher number of cycles of the DTC 101 patients per se cannot explain the higher frequency per cycle of adverse events in the DTC 101 arm.

3.3.2.3 Deaths and other serious adverse events

Eleven out of sixteen DTC 101 patients and thirteen out of fifteen Ara-C patients have died during the treatment and follow-up periods. The sponsor did not report any toxic death. However, the cause of death of one patient (04-LN-209) on the DTC 101 arm is a matter of discussion. This patient, with ocular, nasopharyngeal and CNS involvement, died at day 21 after coffee ground emesis and guaiac positive stools were noted; no autopsy was performed and the cause of death was classified as 'related to systemic disease and neoplastic meningitis'. In the absence of more data the possibility of a relationship with the treatment cannot be excluded (drug-induced intestinal obstruction? gastro-intestinal bleeding precipitated by steroids?).

No serious adverse events related to study drug were observed during the 44.5 cycles of Ara-C. As to the 74 DTC 101 cycles, besides the discussion of the cause of death of patient 04-LN-209, two other possibly related serious adverse events were reported (intestinal obstruction and hydrocephalus).

3.3.3 Dexamethasone use

The third study objective was to compare the need for additional oral steroids for symptomatic control of drug-related toxicities. To minimize symptoms associated with chemical arachnoiditis, the protocol required all patients to receive dexamethasone 4 mg bid po or iv for the first five days of each cycle. Moreover, additional cycles of dexamethasone, again 4 mg bid po or iv for five days, were allowed for breakthrough toxicities during any other week of the study.

Treatment compliance for the required dexamethasone use during the first 5 days of each cycle was higher in the DTC 101 group than in the Ara-C group : dexamethasone was given as recommended in 71/74 (95 %) of DTC 101 cycles and in 36/44.5 (80 %) of Ara-C cycles. The additional and the total use of dexamethasone were also higher on the DTC 101 arm, as can be deduced from table 12.

	DTC 101	Ara-C
50 mg/cycle	9 pts	6 pts
100 mg/cycle	4 pts	2 pts
Median dose per cycle (mg)	69	46
Dose range per cycle (mg)	27-147	7-136
Median/mean induction dose (mg)	128 / 145	104 / 140

Table 12. Total dexamethasone use (pts: patients)

4. FDA CONCLUSIONS

The study under review was an open-label, randomized, multicenter study to determine efficacy and safety of intrathecal DTC 101 relative to that of intrathecal Ara-C for the treatment of cytologically proven lymphomatous meningitis. The study is being reviewed as the pivotal trial for accelerated approval with response rate as a surrogate endpoint for overall benefit.

Evaluation of response rate is very difficult in this trial due to multiple protocol violations with regard to administration of forbidden therapies, inadequate collection of CSF samples and lack of crucial central pathology review data. In the absence of sufficient data acquired by strict protocol criteria, response determination is a matter of interpretation and clinical judgment. For practical purposes, FDA would propose four different interpretation scenarios:

1. only patients for whom response data were collected according to the protocol and strictly meet protocol response criteria are considered to have cytologic response

2. patients who, as only protocol violation, had (a) late confirmatory CSF sample(s) confirming the negative cytology at day 29 are also considered to have cytologic response.

3. patients who, as only protocol violations, had (a) late confirmatory CSF sample(s) confirming the negative cytology at day 29 and a lack of central pathology review data, are also considered to have cytologic response

4. only the ineligible patient is excluded – all other protocol violations are ignored

These four different scenarios would lead to the following interpretations of the response rates:

Scenario	DTC 101		Ara-C	
	ITT	Evaluable	ITT	Evaluable
1	2/17 (12%)	2/6 (33%)	0/16 (0%)	0/7 (0%)
2	3/17 (18%)	3/7 (43%)	1/16 (6%)	1/8 (12.5%)
3	7/17 (41%)	7/11 (64%)	1/16 (6%)	1/8 (12.5%)
4	11/17 (65%)	11/15 (73%)	7/16 (44%)	7/15 (47%)

Table 13 Comparison of response rates in different interpretation scenarios.
ITT : intention-to-treat

The fourth scenario clearly is unacceptable for FDA. The FDA considers scenarios 2 and 3 to be potentially acceptable. Due to the discordance between central and local pathology review as discussed in 3.2.1.1, scenario 3 may somewhat overestimate the true response rate. Although FDA acknowledges that in every scenario response rates for DTC 101 are higher, it is clear that in some scenarios the number of evaluable patients becomes very small. Moreover, there is a clear imbalance between the two groups in the number of potential responders that were made unevaluable by major violations of the CSF sampling protocol guidelines (7 Ara-C versus 3 DTC 101 patients – see table 4 colum 5-6-9).

Medians were calculated in scenario 2 and 3 for time to complete response, duration of complete response and time to relapse of the responding DTC 101 patients (table 13). For Ara-C, no medians could be calculated as only one patient could be considered having a CR; the outcomes of that patient is also given in table 14.

	Scenario 2		Scenario 3	
Treatment	DTC 101	Ara-C	DTC 101	Ara-C
Number of responders	3	1	7	1
Time to response (days)	15 (median)	13 (n=1)	15 (median)	13 (n=1)
Duration of response (days)	38 (median)	205 (n=1)	59 (median)	205 (n=1)
Time to relapse (days)	53 (median)	218 (n=1)	82 (median)	218 (n=1)

Table 14 Time to response, duration of response, time to relapse

For the 33 treated patients, regardless of their response status, the time to neurologic progression was 78 days on the DTC 101 arm and 51 days on the Ara-C arm. The median overall survival was 82.5 days on the DTC 101 arm and 64 days on the Ara-C arm. No statistical significance was claimed by the sponsor for any of these two parameters.

Quality-of-life results (KPS, MMSE, FACT-CNS) after the first 4 weeks of treatment were lacking in the majority of patients. Even during the first study month, a comparison between day 1 and day 29 results were only available in 23/31 patients for KPS, in 13/31 patients for MMSE and in 13/31 patients for FACT-CNS. Given the amount of missing data and the multiplicity of analyses, FDA does not concur with the interpretation of statistical significance for the difference in change of the KPS scores in favor of DTC 101.

Adverse events and drug-related adverse events were observed more frequently in the DTC 101 arm than in the Ara-C arm. Even after adjustment for the number of treatment

cycles, the frequency of all listed drug-related adverse events (with the exception of asthenia) is higher on the DTC 101 arm than on the Ara-C arm and a larger fraction of them reached grade 3 or grade 4. This is in particular true for nausea/vomiting and for headache. Two serious adverse events were reported on the DTC 101 arm and none on the Ara-C arm; moreover for one patient on the DTC 101 arm, given lack of more detailed information, one cannot exclude the possibility that death was drug-related.

ODAC recommendations

The Oncologics Drugs Advisory Committee met on November 16 1998 to evaluate whether it could recommend accelerated approval for DTC101 in the treatment of lymphomatous meningitis based on study DTC 92-001 discussed above.

The committee agreed (7 yes, 1 no) that complete cytologic response with the absence of neurologic progression is a surrogate endpoint that is reasonably likely to predict benefit in patients with lymphomatous meningitis treated with intrathecal therapy.

The committee was undecided (4 yes, 4 no) whether study DTC 92-001 was an adequate and well-controlled study for the purpose of evaluating response in lymphomatous meningitis.

The committee agreed (7 yes, 0 no, 1 abstain) that the response rates, and/or other factors, for DepoCyt and Ara-C in study DTC 92-001 support that DepoCyt provides a meaningful advantage over "existing treatments". The more convenient treatment schedule for DepoCyt was mentioned several times during the discussion as an 'other factor' providing meaningful advantage over "existing treatments".

Considering the balance of efficacy and toxicity demonstrated in the trials, the committee recommended (6 yes, 1 no, 1 abstain) accelerated approval for DepoCyt for intrathecal treatment of lymphomatous meningitis.

5. FDA REVIEW OF PROPOSED PACKAGE INSERT

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/ A Staten

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