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DepoCyt[®] (cytarabine liposome injection)

**NDA 21-041
Subpart H Phase 4 Commitment**

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Briefing Document for the

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Information Regarding Accelerated Approval Clinical Phase 4 Commitments

I. General Information

A. Drug Name

DepoCyt[®] (cytarabine liposome injection)

B. Indication

Intrathecal treatment of lymphomatous meningitis

C. Accelerated Approval Date

01 April 1999

II. Description of Commitment including titles of individual studies

SkyePharma's Phase 4 commitment, as outlined in the April 1, 1999 approval letter, was to conduct a Phase 4 post-marketing study (Protocol SKY0101-010) and to provide additional information on the pharmacokinetics of DepoCyt (pharmacokinetic protocol SKY0101-011), and submit final study reports to the NDA as a supplemental application. The titles of these studies are the following:

- SKY0101-010: A Randomized Phase 3/4 Clinical Study to Determine the Patient Benefit and Safety of DepoCyt (cytarabine liposome injection) for the Treatment of Neoplastic Meningitis
- SKY0101-011: A Phase 1 Pharmacokinetic Study of DepoCyt (cytarabine liposome injection) in Patients With Leukemic, Lymphomatous, or Solid Tumor Neoplastic Meningitis

It was noted in the approval letter (April 1, 1999) that the studies would be initiated in six months with an interim analysis planned for study SKY0101-010 at approximately the fourth quarter of 2001. If the study proceeded beyond the interim analysis, the study completion date was estimated to be September 2003. However, due to the sponsor-initiated product recall in October 1999, patient enrollment was not able to begin as planned. On March 5, 2001, SkyePharma and Chiron Corporation (the U.S. distributor at that time) resumed commercial distribution of DepoCyt and the studies were opened for enrollment.

As a result of agreements made in an Agency teleconference on March 26, 2002, the number of solid tumor neoplastic meningitis patients to

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be enrolled in study SKY0101-010 was increased such that the power would be adequate to demonstrate a statistically significant difference in the primary endpoint for this subgroup. Reference is made to correspondence with the Agency dated April 21, 2004 that provided enrollment status and May 19, 2004 that requested concurrence from the Division with our plan to close enrollment in the study. The Division concurred with the plan to close enrollment (facsimile dated July 27, 2004).

IIIa. Study SKY0101-010

A. Essentials of Study Design (SKY0101-010)

This trial was a randomized, Phase 3/4, open-label, active-controlled, multicenter study designed to evaluate the clinical benefits of treatment with DepoCyt versus standard care in patients with lymphomatous or solid tumor neoplastic meningitis.

The primary objective of this study was twofold: 1) to confirm the clinical benefits of treatment with DepoCyt versus standard therapy in adult patients with neoplastic meningitis (either solid tumor neoplastic meningitis or lymphomatous meningitis) and/or 2) to confirm the clinical benefits of treatment with DepoCyt versus standard therapy in adult patients with solid tumor neoplastic meningitis. In the case of patients with solid tumor neoplastic meningitis, randomization was between treatment with intrathecal (IT) DepoCyt versus IT methotrexate (MTX). In the case of lymphomatous meningitis, the randomization was between IT DepoCyt and IT cytarabine. The primary efficacy endpoint was progression-free survival (PFS), defined as the time to neurological progression or death.

1. Summary of Study Sites (geography, number)

A total of 45 study sites were initiated and 20 of these did not enroll any patients. Of the 25 study sites that contributed patients to the SKY0101-010 study, two also contributed patients to the SKY0101-011 study. Participating sites were located in the United States, Canada, Ireland, the United Kingdom, France, Belgium, Netherlands, Switzerland, Austria, and Germany.

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2. Patient Population (Eligibility/Exclusion criteria)

Inclusion criteria: Males and females ≥ 18 years of age diagnosed with lymphomatous or solid tumor neoplastic meningitis who had demonstrated positive cerebrospinal fluid (CSF) cytology within 21 days prior to randomization **or** characteristic signs and symptoms of neoplastic meningitis plus a magnetic resonance imaging (MRI) or computed tomography (CT) scan indicating the presence of meningeal tumor.

Key exclusion criteria: Patients may not have failed to respond (as defined by clearance of the CSF) to > 4 doses of prior intrathecal (IT) MTX or cytarabine therapy or 2 or more doses of prior DepoCyt therapy for prophylaxis against, or treatment of, neoplastic meningitis; and patients may not have received > 4 prior doses of “high dose” intravenous (IV) MTX ($> 500 \text{ mg/m}^2$ per dose) or cytarabine ($> 2 \text{ g/m}^2$ per dose) for prophylaxis against, or treatment of, neoplastic meningitis.

3. Endpoints

The primary efficacy endpoint was progression-free survival (PFS), defined as the time to neurological progression or death.

Secondary efficacy endpoints included time to neurological progression (TNP), survival (meningeal disease-specific and all-cause), cytological response rate, overall assessment of neurological progression, Karnofsky Performance Scores (KPS), Q-TWiST analyses, and improvements in neurological deficits present at Baseline. Safety was assessed by adverse events (AEs), clinical laboratory parameters, physical examinations, and vital signs.

4. Treatment Schema

Patient randomization was stratified by tumor type (lymphomatous vs. solid tumor) and by region (North America vs. Europe). Patients with solid tumor neoplastic meningitis were assigned in a 1:1 ratio to receive DepoCyt or MTX. Patients with lymphomatous neoplastic meningitis were assigned in a 1:1 ratio to receive DepoCyt or cytarabine (ara-C). The dose and frequency of injections for each therapy were as follows: DepoCyt 50 mg once every two weeks; Control (MTX 10 mg or cytarabine 50 mg) twice per week. Treatment was to consist of two phases: 6 Induction Cycles (2 weeks per cycle) and 4 Maintenance Cycles (4 weeks per cycle). All doses of study drug were

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administered intrathecally (either via an intraventricular reservoir or via lumbar puncture). At the completion of treatment, all patients were followed monthly through 1 year after study entry and bi-monthly for the following 12 months for neurological assessments.

5. Efficacy and Safety Monitoring

Efficacy: For the primary endpoint of PFS, neurological assessments were performed at Screening, at the beginning of each treatment cycle, and at each follow-up timepoint. Changes in neurological exams were utilized by the Investigator to support the occurrence (or lack thereof) of neurological progression at the beginning of each treatment cycle.

CSF cytology, KPS, and survival (both all cause and meningeal-disease specific) were evaluated. In addition, adverse events were analyzed (Q-TWiST analysis) to determine the time spent without toxicity.

Safety: Safety was monitored through treatment-emergent adverse events (through 30 days following the last dose of study drug) and survival through approximately two years. Laboratory evaluations were also monitored while patients were receiving treatment.

6. Statistical Design

Because the objective of the study was two-fold, the alpha level required adjustment. Assuming that 60% of all events occurred in the patients with solid tumors, then to have an overall type I error of 0.05, each of the primary efficacy analyses needed to be tested at the 2-sided level of significance of $\alpha = 0.031$. The number of events needed to be observed in the solid tumor group for a hazard ratio of 2.0, a type I error of 0.031, and power of 80% was 75. Therefore, planned enrollment was approximately 80 patients with solid tumor neoplastic meningitis and 40 patients with lymphomatous neoplastic meningitis. Enrollment was to continue until 75 patients with solid tumor neoplastic meningitis reached neurological progression or died within 12 months of study entry.

The primary endpoint was PFS for the efficacy population (all patients who had at least one dose of study drug and at least one post-treatment assessment of a given endpoint) of both disease strata combined. Kaplan-Meier distributions were analyzed using the log-rank test, stratified by disease stratum and region. A Cox regression analysis, considering pertinent baseline variables, also was planned. Patients who had not died or experienced

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neurological progression, or who were lost to follow-up, were censored at the date of last contact. Kaplan-Meier distributions of time to neurological progression, meningeal disease-specific survival, and all-cause survival for the efficacy population also were analyzed using the log-rank test stratified by disease stratum and region. To avoid possible bias that may have occurred as a result of patients in the Control arms (MTX and cytarabine) visiting the clinic more frequently than patients in the DepoCyt arm, the date of the end of the cycle during which neurological progression occurred for patients on both arms was used for “adjusted” analyses. The analysis of PFS was performed with and without this adjustment. Comparisons between treatment groups of proportions of patients with a cytological response were performed using a Cochran-Mantel-Haenszel (CMH) test stratified by disease stratum and region. The time from randomization until a patient’s KPS decreased to $\leq 50\%$ was determined for each patient and evaluated by the Kaplan-Meier method with a log-rank test stratified by disease stratum and region. The differences between DepoCyt and active Control (standard therapy) with respect to KPS at Baseline and change from Baseline at each visit were compared using an analysis of variance (ANOVA) model with disease stratum and region as covariates.

The safety population included all patients who had received any study drug. No formal statistical tests were performed on safety variables.

B. Date of Initiation (SKY0101-010)

Study Initiation (date of first patient’s enrollment): July 3, 2001

C. Accrual (SKY0101-010)

(If applicable, progress since discussion at March 2003 ODAC meeting on Accelerated Approval)

A total of 103 solid tumor and 25 lymphoma subjects were enrolled. Of these, 100 solid tumor and 24 lymphomatous neoplastic meningitis patients were treated and analyzed.

D. Estimated Timeline for Study Completion (SKY0101-010)

Study Completion (date of last patient observation): November 23, 2004

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E. Estimated Timeline for Submission of Study Results (SKY0101-010)

Results of studies SKY0101-010 and SKY0101-011 are planned for submission by the end of 2005.

IIIb. Study SKY0101-011

This study was an open-label, multicenter CSF pharmacokinetic study of DepoCyt in adults with solid tumor, lymphomatous, or leukemic meningitis.

The primary objective of this study was to evaluate the CSF pharmacokinetics of free and total cytarabine following intraventricular administration of DepoCyt, 50 mg. The data collected from the prior population-based pharmacokinetic study of DepoCyt administered at 50 mg (DTC 92-001) will be combined with this dataset as part of the analyses.

The secondary objectives of this study were to:

- Determine the CSF pharmacokinetics of free and total ara-C following lumbar sac administration of DepoCyt, 50 mg;
- Further evaluate the safety of DepoCyt in adult subjects with neoplastic meningitis.

A. Essentials of Study Design (SKY0101-011)

1. Summary of Study Sites (geography, number)

Two sites in Europe enrolled subjects.

2. Patient Population (Eligibility/Exclusion criteria)

Inclusion criteria: Males and females ≥ 18 years of age diagnosed with lymphomatous or solid tumor neoplastic meningitis who had demonstrated positive CSF cytology within 21 days prior to randomization **or** characteristic signs and symptoms of neoplastic meningitis plus an MRI or CT scan indicating the presence of meningeal tumor.

Key exclusion criteria: Patients may not have failed to respond (as defined by clearance of the CSF) to > 4 doses of prior intrathecal (IT) MTX or cytarabine therapy or 2 or more doses of prior DepoCyt therapy for prophylaxis against, or treatment of, neoplastic meningitis; and patients may not have received > 4

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prior doses of “high dose” intravenous (IV) MTX (> 500 mg/m² per dose) or cytarabine (> 2 g/m² per dose) for prophylaxis against, or treatment of, neoplastic meningitis.

3. Endpoints

The primary objective of this study was to determine the CSF pharmacokinetics of free and total ara-C following intraventricular administration of DepoCyt, 50 mg. The primary endpoints were the PK parameters of CSF cytarabine. The secondary endpoints were CSF cytarabine concentration following lumbar sac administration of DepoCyt, 50 mg, and the evaluation of safety through assessment of adverse events.

4. Treatment Schema

All patients received DepoCyt. Treatment consisted of two phases: 6 Induction Cycles (2 weeks per cycle) and 4 Maintenance Cycles (4 weeks per cycle). All doses of study drug were administered intrathecally (either via an intraventricular reservoir or via lumbar puncture).

5. Efficacy and Safety Monitoring

Efficacy was not monitored. Safety was monitored through evaluation of adverse events.

6. Statistical Design

Cerebrospinal fluid samples obtained during Cycles 1 and 2 will be analyzed for free cytarabine and total cytarabine (supernatant and pellet) concentrations.

Separate pharmacokinetic analyses will be performed for subjects receiving DepoCyt via intraventricular injection and subjects receiving injection into the lumbar sac. To assess the pharmacokinetics of DepoCyt following intraventricular administration at a dose of 50 mg, the measurements of drug concentrations obtained in the present study will be combined with those obtained from subjects receiving DepoCyt via the intraventricular route in a previous pharmacokinetic population study (Protocol 92-001). The previous study employed identical dosing, sampling intervals, sampling handling procedures, and analytical methods as the current study. For subjects treated via lumbar sac injection in this study, these results will be combined with comparable data from the prior study and these results analyzed separately.

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Summary statistics for CSF levels (n, mean, standard deviation, median, minimum and maximum) will be shown for cycle 1 and cycle 2. In addition, the PK parameters, C_{max} , T_{max} , $t_{1/2}$, AUC_{0-last} , and $AUC_{0-\infty}$, will be summarized for cycle 1 and cycle 2.

B. Date of Initiation (SKY0101-011)

The first patient was enrolled in this trial on September 3, 2004.

C. Accrual (SKY0101-011)

(If applicable, progress since discussion at March 2003 ODAC meeting on Accelerated Approval)

Enrollment in study SKY0101-011 completed in March 2005. A total of 12 subjects were treated and provided PK samples for analysis. Patient follow up is complete.

D. Estimated Timeline for Study Completion (SKY0101-011)

Enrollment and patient follow up is complete. Analysis of pharmacokinetic samples is ongoing.

E. Estimated Timeline for Submission of Study Results (SKY0101-011)

Results of studies SKY0101-010 and SKY0101-011 are planned for submission by the end of 2005.

IV. Other Issues

A. Difficulties encountered in conduct/accrual/completion of trials

1. Changes in medical practice

A. Commercial Availability of DepoCyt in The United States

With the initial approval and subsequent commercial availability of DepoCyt for the treatment of lymphomatous neoplastic meningitis in the United States and Canada, there appeared to be a shift in the standard treatment of patients inflicted with neoplastic meningitis. From early on there was a great deal of interest among clinicians to initiate DepoCyt treatment in patients with lymphomatous neoplastic meningitis without having to enroll them in this controlled, randomized clinical trial. Considering that a lymphoma patient

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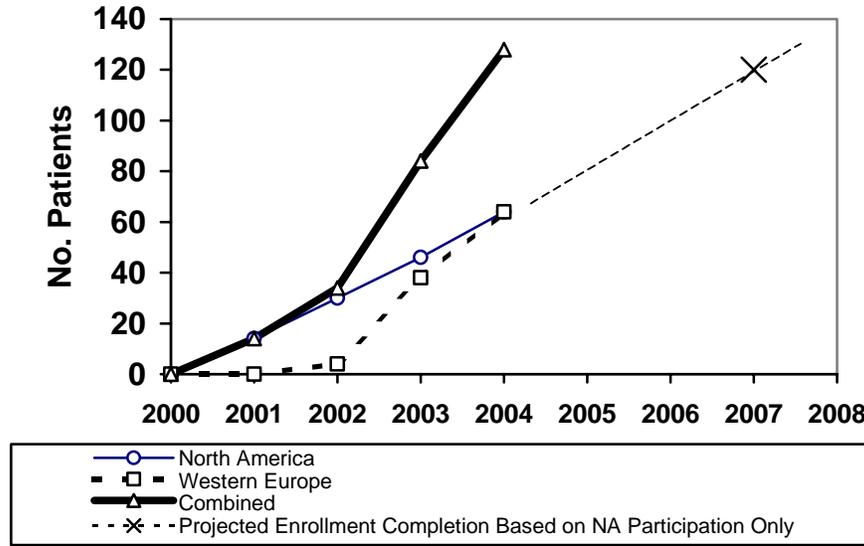
could be randomized to cytarabine, which requires four times more clinic visits than if treated with DepoCyt, many of the U.S. investigators queried to participate in this trial chose not to.

Similarly, as part of the consent process, patients were informed of the treatment options that were available to them other than participating in this controlled study. These options included off-study treatment with commercially available DepoCyt without the patient having to contemplate treatment with cytarabine or methotrexate, both of which would be administered twice weekly.

Although both of these issues were potentially hindrances to site recruitment and study enrollment, 12 institutions in North America were eventually recruited *and* contributed patients. At the rate of recruitment achieved in 2002 at the North American sites, however, the commitment to enroll 100 patients could not be met in a timely fashion without expansion of the trial to another facilitative region. Thus, a decision was made to add sites in Europe, with the FDA's agreement, where the product was initially in a pre-approval stage and continuing to undergo various stages of marketing authorization in the various countries. As these sites were added and recruitment was initiated in Europe, it became apparent that SkyePharma's post-approval timeline commitment could and would be met (Figure 1 below).

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Figure 1. SKY0101-010 Regional and Total Enrollment (Actual and Projected in the Absence of the Addition of European Sites)



B. Regional Differences in Medical Approach (Prior and Concurrent Therapies, Route of Study Drug Administration) to Patients with Neoplastic Meningitis

By region, there were differences in medical practice in the way some of the treatments were used in this population. With respect to prior therapy, there were larger number of patients in North America given prior radiation therapy compared to that in Europe.

There were also imbalances between the two regions regarding the route of administration of DepoCyt. In North America, all patients received their study medication via intraventricular administration (using Ommaya catheter) whereas in Europe the proportion of patients who received study treatment via lumbar puncture exclusively or intraventricular injection was balanced.

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C. Availability and Use of High-Quality Imaging Equipment for the Diagnosis of Neoplastic Meningitis

Higher resolution imaging equipment became more widely available and utilized for the diagnosis of neoplastic meningitis since the initiation of the pre-approval study. Importantly, these imaging techniques were regularly being utilized in the diagnosis of neoplastic meningitis in the absence of positive cytology, which is demonstrated in only 45 – 70% of cases on initial presentation¹. As such, this change in practice was incorporated into the SKY0101-010 study, where patients could be enrolled if they presented with a positive MRI or CT imaging scan in the presence of neurological signs and symptoms indicative of meningeal involvement. Generally, the disease state of patients with parenchymal enhancement is considered advanced². As such, patients so afflicted have a poorer prognosis than those presenting with only positive cytology.

2. Safety considerations

None

3. Other

A. Inclusion of Solid Tumor Patients in the Study Population

During discussions with FDA regarding the SKY0101-010 study, it was clear that enrolling a sufficient number of lymphomatous neoplastic meningitis patients would not allow for rapid enrollment; certainly completion of a study requiring the initial sample size (approximately 100 patients) to show a 50% improvement in progression-free survival over an active comparator would have taken at least 10 years (and based on actual accrual rates of 24 lymphoma patients in the SKY0101-010 study, 15 years is likely a more realistic estimate). As such, during discussion of study design, agreement was obtained with FDA to include solid tumor patients and to analyze both disease strata in a combined fashion so that a statistically meaningful comparison

¹ Chamberlain MC. Neoplastic Meningitis. *Seminars in Neurology* 2004;24:363-374

² Schumacher M, Orszagh M. Imaging techniques in neoplastic meningitis. *Journal of Neuro-Oncology* 1998;38:111-120

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could be made. Thus, the overall SKY0101-010 study results will include a different population than the study supporting the initial approval and surrogate claim.

B. Pursuit of a Claim in Solid Tumor Neoplastic Meningitis

In 2002, SkyePharma and FDA agreed to enroll enough solid tumor patients in the SKY0101-010 trial to support an additional claim in the indication of solid tumor neoplastic meningitis (the study was subsequently powered at 80% to detect a 50% improvement in the solid tumor stratum). With this change, total enrollment was anticipated to terminate with approximately 110 patients. In fact, since the post-approval commitment to finish this study could still be met, enrollment was kept open slightly longer than anticipated to increase representation of lymphoma patients in the study.

C. Pharmacokinetic Commitment

The pharmacokinetic study was initially structured as an addendum to protocol SKY0101-010. However, there was difficulty in recruiting sites to the PK component of a randomized study. Therefore, the open-label, uncontrolled PK trial (SKY0101-011) was initiated shortly after completion of enrollment in the SKY0101-010 trial. Three sites from the controlled trial participated in the Phase 1 trial, and two of the three sites enrolled a total of 12 patients. Data from these 12 patients will be analyzed with data from a prior PK study to further characterize the cytarabine CSF PK profile of DepoCyt.

D. Product Unavailability

A recall of both lots distributed between April and October 1999 was initiated when the free cytarabine content was found to be out of specification during stability studies. These results were unexpected and atypical of prior history with the product. SkyePharma conducted a lengthy and rigorous investigation of possible sources of product instability and discovered that the problem was caused by a slight change in the composition of one of the lipids due to a minor change in a single step of the manufacturing process used by the lipid supplier. A comprehensive investigation report was submitted to FDA in July 2000 documenting the single cause for the recall and corrective and preventive actions taken by the Sponsor. SkyePharma met with FDA in September 2000 and when additional stability data became available, FDA approved resumption of commercial distribution in March 2001. As a result of

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this issue, DepoCyt was not available for conduct of the post-marketing trial for a period of 18 months.

B. Other Applicant Concerns

None