6 February 2003

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Supervisory Health Science Administrator
Advisors and Consultants Staff
FDA, CDER, ORM
HFD-21, Room 1093
5630 Fishers Lane
Rockville, MD 20852-1734

RE: NDA 21-041 DepoCyt® Phase IV Commitments

Dear Dr. Somers:

As requested in your letter dated January 23, 2003, enclosed are 40 copies (and 2 electronic copies in Microsoft Word) of the background package for the Oncologic Drugs Advisory Committee meeting scheduled March 12-13, 2003. SkyePharma will be presenting and update on its Phase IV commitments of NDA 21-041, DepoCyt (cytarabine liposome injection) for the intrathecal treatment of lymphomatous meningitis.

As requested, both the paper and electronic copies have been marked "AVAILABLE FOR PUBLIC DISCLOSURE IWTHOUT REDACTION" as described in the Guidance for Industry "Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of New Drugs and Convened by the Center for Drug Evaluation and Research, Beginning on January 1, 2000."

Speakers and presenters from SkyePharma are as follows:

Gordon L. Schooley, Ph.D.
Senior Vice President
Global Clinical and Regulatory Affairs
SkyePharma Inc.

Stephen B. Howell, M.D.
Professor of Medicine
Director, Cancer Pharmacology Program
University of California, San Diego

Please let me know if you require any further information in preparation for the ODAC meeting.

Regards,

Gordon L. Schooley, Ph.D.
Sr. Vice President
Global Clinical and Regulatory Affairs

INFORMATION REGARDING ACCELERATED APPROVAL CLINICAL PHASE 4 COMMITMENTS

I. General Information

A. Drug Name: DepoCyt® (cytarabine liposome injection)

B. Indication: DepoCyt is indicated for the intrathecal treatment of lymphomatous meningitis. Neoplastic meningitis is an orphan indication with an estimated incidence of 1,200 cases/year.

C. Accelerated Approval Date: April 1, 1999. DepoCyt was approved on the basis of a pivotal trial in 28 patients with lymphomatous meningitis supported by data from a Phase 1 trial (19 patients), two additional pharmacokinetic trials (11 and 13 patients), and a randomized prospective controlled trial (61 patients) and subsequent open-label trial (89 patients) in patients with solid tumor neoplastic meningitis.

II. Description of Commitment including titles of individual studies

SkyePharma committed to conducting a Phase IV Post-Marketing study (Protocol C0101-010) and a pharmacokinetic sub-study titled "A randomized clinical study to determine the patient benefit and safety of DepoCyt (Cytarabine Liposomal Injection) for the treatment of solid tumor neoplastic and lymphomatous meningitis." These studies were to be initiated within six (6) months. The original estimated dates for the study timeline are as follows:

Start date:	September 1999
Interim Analysis:	4th Quarter 2001 (after 50% of events)
Enrollment Completion:	September 2003

SkyPharma also estimated 6 months for final data analysis and 3 months for study report completion.

The following amendments were made to the Protocol:

1. The Pharmacokenetic study was in incorporated into the Phase IV Post-Marketing study (Protocol C0101-010).
2. Protocol was subsequently categorized as a Phase III/IV study, so as to simultaneously pursue an indication in patients with solid tumor neoplastic meningitis. The title of the amended study is "A randomized phase III/IV clinical study to determine the patient benefit and safety of DepoCyt (cytarabine liposome injection) for the treatment of neoplastic meningitis".

3. Sample size was changed from approximately 100 patients total to enroll patients until 75 patients with solid tumor neoplastic meningitis achieved the clinical endpoint of neurological progression or death. This is estimated to be a total of 110 patients.
4. The interim analysis was eliminated.
5. Addition of European clinical study sites.
6. Stratified randomization for North America vs. Europe.

III. Study Details

A. Essentials of Study Design

1. Summary of Study Sites

Forty-three (43) study sites are currently participating in the Phase III/IV trial. A summary of participating sites is in Appendix 1:

a. 18 study sites are currently participating in the U.S.
b. 2 study sites are currently participating in Canada
c. 24 study sites are currently participating in Europe

2. Patient Population

The trial is open to adult patients with lymphomatous or solid tumor neoplastic meningitis documented within 21 days of randomization by either:

a. positive CSF cytology for lymphoma or solid tumor neoplasm **OR**
b. characteristic signs and symptoms of neoplastic meningitis **PLUS** an MRI or CT scan indicating the presence of meningeal tumor.

3. Endpoints

The primary endpoint is progression-free survival defined as the time to neurological progression or death.

4. Treatment Schema

Lymphoma patients are randomized (1:1) to DepoCyt or cytarabine. Solid tumor patients are randomized (1:1) to DepoCyt or methotrexate. Randomization is further stratified by region (U.S. vs. Europe). Treatment consists of two phases: 6 Induction cycles (2 weeks per cycle) and 4 Maintenance cycles (4 weeks per cycle). DepoCyt patients are treated once at the beginning of each Induction cycle and once at the

beginning of each Maintenance cycle. Cytarabine and methotrexate patients are treated twice per week during Induction and once per week during Maintenance. At the completion of treatment, all patients are followed monthly through 1 year after study entry and bi-monthly for the following 12 months for neurological assessments.

5. Efficacy and Safety Monitoring

CSF cytology, laboratory assessments, and neurological assessments prior to each treatment cycle. In addition, adverse events are monitored through 30 days following the start of the patient's final treatment cycle.

6. Statistical Design

The study is designed to have an 80% power of detecting a 50% reduction in the rate at which solid tumor patients suffer neurological progression. The estimated number of necessary events is 75. Accrual of both solid tumor and lymphomatous meningitis patients will continue until 75 solid tumor patients have suffered neurologic progression or have died. Anticipated total accrual of patients with either lymphomatous or solid tumor neoplastic meningitis is 110 based on the observation that approximately two-thirds of the patients accrued to the trial thus far have solid tumor neoplastic meningitis and one third lymphomatous meningitis. An intent-to-treat (ITT) analysis will consider all patients randomized and analyzed according to the drug of randomization irrespective of whether or not they actually received the drug to which they were assigned. Kaplan-Meier distributions will be analyzed using the log-rank test for progression-free survival (time to neurological progression or death).

B. Date of Initiation

Identification of investigators began immediately after DepoCyt approval in April of 1999. The study was ready for patient accrual in October 1999. However, available supplies of DepoCyt were recalled in October 1999, and no drug was available for 18 months until FDA approved reintroduction to the market in March 2001. Trial preparation was reactivated immediately thereafter and the first patient was enrolled on 03 July 2001.

C. Accrual

As of 31 January 2003, 49 patients have been enrolled, 12 of which were enrolled with lymphomatous neoplastic meningitis.

Enrollment status:
2001: 16 patients
2002: 27 patients
2003: 40 patients to be enrolled (6 patients were enrolled by 31 Jan 2003)
2004: 27 patients to be enrolled
Total: 110 patients

D. Estimated Timeline for Study Completion

The current enrollment rate is sufficient to meet SkyePharma's enrollment commitment by August 2004.

Start date:	March 2001
Interim analysis:	Eliminated as per agreement with FDA
Enrollment Complete:	August 2004
Last patient visit:	Approximately March 2005
Report Completion:	August 2005 – approximately 6 months Following the last patient visit
Total elapsed time:	Approximately 4-1/2 years (identical to the original commitment)

E. Estimated Timeline for Submission of Study Results

The study calls for a two-year follow-up period following randomization. However, due to the severity of the disease under study, the likelihood of a patient failing to reach neurological progression or death within 6 months after receiving initial treatment is low. It is anticipated that the clinical database could be closed Q2 2005 should all participating patients reach the primary endpoint by March 2005. Should this occur, the study results would be available by the third quarter of 2005. This is approximately 4-1/2 years of elapsed time from the study start, which is same elapsed time as the original Phase IV commitment of March 1999. The final clinical study report could be submitted to FDA within one month following report completion. However, should one or more of the patients enrolled after the first quarter of 2003 have progression-free survival for two years following randomization, there could be a respective delay in the analysis of the data. For this reason, the proposed timeline to provide study results is between approximately Q3 2005 and Q1 2007.

IV. Other Issues

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

1. Changes in medical practice

With the initial approval and commercial availability of DepoCyt for the treatment of lymphomatous neoplastic meningitis in the United States and Canada, there appears to have been a shift in the standard treatment of patients inflicted with this disease. There is certainly interest among clinicians to initiate DepoCyt treatment in patients with lymphomatous neoplastic meningitis without enrolling them in this controlled, randomized clinical trial. Considering that a lymphoma patient could be randomized to ara-C in this trial, which requires 4 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 are informed of the treatment options that are available to them other than participating in this controlled study. These options include off-study treatment with commercially available DepoCyt without the patient having to worry about being randomized to ara-C or methotrexate, both of which are administered twice weekly.

Although both of these issues are potentially hindrances to study enrollment, 18 U.S. institutions have been recruited and the rate of enrollment in the U.S. appears to be in-line with enrollment in the prior Phase III controlled studies. In addition, European sites were recently added to the study, which should aid in completing the study within the currently specified timelines since DepoCyt, although approved in Europe for lymphomatous meningitis patients, is not yet distributed by SkyePharma's. European licensee.

2. Safety considerations

The safety of the trial is continuously monitored and there have been no reasons to believe that safety would adversely effect the study completion timelines.

3. Other: Product unavailable

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

B. Other Applicant Concerns

None

APPENDIX 1

ACTIVE CENTERS

PROTOCOL SKY010-010

Appendix 1: Active Centers Protocol SKY0101-010

Investigator			Center No.	Institution	City	Country
William	Shapiro	MD	2	Barrow Neurological Institute	Phoenix	USA
Pamela	New	MD	3	University of Texas Health Science Center	San Antonio	USA
Pamela	Khosla	MD	5	Rush Cancer Institute	Chicago	USA
Surasak	Phuphanich	MD	6	H. Lee Moffitt Cancer Center and Research Inst.	Tampa	USA
Eric	Wong	MD	9	Beth Israel Deaconess Medical Center	Boston	USA
Benjamin	Lawler	MD	10	Marshfield Clinic	Marshfield	USA
Paul	Moots	MD	19	Vanderbuilt University Medical Center	Nashville	USA
Kurt	Jaeckle	MD	23	Mayo Clinic	Jacksonville	USA
Deborah	Blumenthal	MD	27	Huntsman Cancer Institute	Salt Lake City	USA
Marc	Chamberlain	MD	28	USC	Los Angeles	USA
Subramanian	Hariharan	MD	29	JFK Neuroscience Institute	Edison	USA
Lynne	Taylor	MD	30	Virginia Mason Medical Center	Seattle	USA
Lynn	Ashby	MD	36	Straub Clinic and Hospital	Honolulu	USA
Jeffrey	Olson	MD	37	Windship Cancer Institute	Atlanta	USA
David	Irwin	MD	38	Alta Bates Comprehensive Cancer Center	Berkeley	USA
Thomas	Coyle	MD	39	SUNY Upstate Medical University	Syracuse	USA

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Investigator			Center No.	Institution	City	Country
George	Marcoullis	MD	40	Comprehensive Cancer Center	Bronx	USA
David	Linch	MD	56	UCL	London WC1E 6HX	United Kingdon
A.Y.	Rostom	MD	50	The Royal Marsden Hospital	Surrey, SM2 5PT	United Kingdom
Thomas A.	Lister	MD	51	St. Bartholomew's Hospital	London EC1A 7BE	United Kingdom
Peter	Johnson	MD	53	Southampton General Hospital	Southampton S016 6YD	United Kingdom
David	Spooner	MD	57	Queen Elizabeth Hospital	Birmingham B15 2TH	United Kingdom
Ann	Hunter	MD	63	Leicester Royal Infirmary	Leicester LE1 5WW	United Kingdom
Simon M.G.J.	Daenen	MD	49	Kliniek University Hospital	9713 GZ Groningen	The Netherlands
Albert	Twijnstra	MD	54	University Hospital of Maastricht	6202 AZ Maastricht	The Netherlands
Christiana	Sessa	MD	45	Ospedale San Giovanni	Bellinzona	Switzerland
John	Crown	MD	58	St. Vincent's Hospital	Dublin 4	Ireland
Simus	O'Reilly	MD	64	Cork University Hosptial	Wilton, Cork	Ireland
Maccon	Keane	MD	65	University College Hospital	Galway	Ireland
Brian	Moulton	MD	68	Irish Clinical Oncology Research Group	Dublin 2	Ireland
Dieter	Hoelzer	MD	52	Klinilum der J.W. Goethe-Universitat	60590 Frankfurt	Germany
Mathias	Schmid	MD	59	Unilkinilum Ulm D-89070	Ulm	Germany

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Investigator			Center No.	Institution	City	Country
Dirk	Behringer	MD	60	Universitatsklinikum-Freiburg	D-79106 Freiburg	Germany
K.	Hossfeld	MD	61	Medizinische Universitatsklinik	D-20246 Hamburg	Germany
Kurt	Possinger	MD	62	Charite University Hospital Mitte	D-Berlin	Germany
Jean-Louis	Misset	MD	43	Hopital Saint-Louis	75010 Paris	France
Jean-Pierre	Droz	MD	44	Center Leon Berard	Lyon	France
Sopie	Taillibert	MD	46	Chu Pitie-Salpetriere Hospital	Paris Cedex F-75651	France
Jean-Luc	Harousseau	MD	47	Centre Hospitalier Universitaire	44093 Nantes Cedex 1	France
Bertrand	Coiffier	MD	48	Centre Hospitaliere	F-69495 Pierre-Benite	France
Rena	Buckstein	MD	22	Toronto Sunnybrook	Toronto	Canada
David	Eisenstat	MD	34	Regional Cancer Centre CancerCare Manitoba	Winnipeg	Canada
Dominique	Lossignol	MD	41	Institut Jules Bordet	Bruxelles B-1000	Belgium