This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Zimmerman
8/9/02 09:50:54 AM
CSO

Ning Li
8/16/02 01:20:32 PM
BIOMETRICS

Alla Shapiro
8/27/02 02:26:15 PM
MEDICAL OFFICER

MEETING MINUTES

MEETING DATE: May 29, 2002 **TIME:** 9am **LOCATION:** room 6002 (G)

Drug Name: Gliadel **NDA:** 20-637/S-016 **Type of meeting:** end of review

Sponsor: Guilford **Preparation package:** dated March 19 and April 1, 2002

FDA Invitees, titles and offices:
Robert Temple, M.D., Director, ODE1
Richard Pazdur, M.D., Division Director
Alison Martin, M.D., Medical Team Leader
Alla Shapiro, M.D., Medical Officer
Jan Buckner, M.D., ODAC representative (pre-meeting)
Gang Chen, Ph.D., Statistical Team Leader
Ning Li Chu, Ph.D., Statistical Reviewer
Paul Zimmerman, R.Ph., Project Manager
(attendees are bolded)

Sponsor, titles and offices:
Craig R. Smith, M.D., Chief Executive Officer
Enoch Bortey, Ph.D., Associate Director, Biostatistics
Dana Hilt M.D., Vice President, Clinical Research
Louise M. Peltier, Senior Director, Regulatory Affairs
Steve Piantadosi, M.D., Ph.D., Johns Hopkins Oncology Center (Consultant)
—
—

Meeting Objective(s):
To discuss sNDA statistical analyses

QUESTIONS for DISCUSSION with FDA RESPONSE:

Question 1:
Guilford performed the Cox Multivariate Analysis using the covariates specified in the statistical analysis plan (country, age, KPS, and tumor type) and arrived at a statistically significant result (p=0.03;). According to the Division's letter, its analysis did not produce a statistically significant treatment effect for Gliadel (p=0.16). We have attempted to understand how the Division arrived at a different p value than Guilford but have not been able to do so. Please explain the method used to arrive at the Division's result and comment on how it conforms with the statistical analysis plan.

FDA response:
The protocol-specified analysis for the primary efficacy endpoint, overall survival, showed no significant difference between study arms with a p-value of 0.08. The analysis you refer to is a secondary endpoint, albeit prespecified. The p value is 0.044 (not 0.03) according to the sponsor's analysis.

The FDA performed an exploratory Cox Multivariate Analysis using the three covariates that are well-known prognostic factors for the primary endpoint of survival (and cited in the protocol). The resulting p-value is not significant at p=0.16. While country is of interest, it is not a known prognostic factor.

We note that the SAP provided for a variety of multiple secondary endpoints. There was no explicit ranking (other than prioritizing overall survival in patients with GBM which was associated with a p=0.20), or provisions for multiplicity. We also note that when we look at the refractory setting, the GBM population is the responsive subgroup and the indication was limited to this population.

Further details of the analysis are available, including a SAS output. In our analysis, age was treated as a continuous variable (not binary, as in the sponsor's analysis), while KPS and tumor type were categorized similarly to those used in the sponsor's analysis (KPS: $\leq$ 70 vs. >70; tumor type: nonGBM vs. GBM). It is a common statistical practice to treat age as a continuous variable since categorization may lose important information. If age is cut per sponsor's analysis, the resulting p-value for the treatment effect is 0.08. The SAP did not provide subcategories within the prespecified covariates.

The applicant presented an overhead of a graph depicting Survial Time (months 0-26) vs Survival Probability (0.0-1.0) of GBM and Non-GMB with Placebo or Gliadel. See the attached graph.

Question 2:
The adjustment for tumor histology in the statistical analysis plan was prespecified as the Cox Model. We do not understand how the Division concluded that the 10 anaplastic oligoastrocytoma patients were largely responsible for any Gliadel effect. Please explain how the Division arrived at its conclusion.

FDA response:
The impact of tumor histology was examined in several ways -- the Multivariate Cox Model (see question 1) and also by the univariate stratified logrank (p=0.14) which was prespecified in the SAP. In both of these analyses, tumor histology is defined as GBM vs. nonGBM.

Additional exploratory analyses were undertaken to assess the potential impact of the nonGBM group. The observed difference between the arms in the primary endpoint of survival was small (median of approximately 2 months). A difference of this magnitude could be due to imbalances between the arms in strong prognostic factors, particularly histology, as noted by the two ODAC neurooncologists.

Within the nonGBM patients, the greatest imbalance was noted to be in patients diagnosed as anaplastic oligoastrocytoma (total of 11 patients -- 8 randomizing to Gliadel and 3 to placebo – see table below). This group was therefore chosen to be censored in a sensitivity test (subgroup analysis) looking at impact of imbalances in favorable histology patients on the primary outcome variable. The p value for the analysis of survival excluding 11 patients is p=0.18, rather than p=0.08.

	Gliadel N=120	Placebo N=120
Glioblastoma Multiforme	101	106
Non-GBM		
• Anaplastic Oligodendroglioma	6	5
• Anaplastic Oligoastrocytoma	8	3
• Anaplastic Astrocytoma	1	1
• Other (favorable)	0	1
Pleomorphic xanthoastrocytoma	1	1
PNET	1	0
Astrocblastoma	0	1
Astrocytoma gemistocytic	0	1
Metastases	2	1
TOTAL	120	120

The applicant presented an overhead of page 11 of 32 of the SAP/RPR 132596-T-301, approval date 03November 1999 (revised version) regarding the "Potential effect of covariates on primary efficacy parameter will be studied through:

- A logrank stratified on each covariate……
- A Cox propor tional hazards model with all covariates….

See the attached page.

Question 3: (The FDA response was provided to the applicant but not discussed at the meeting.) In light of the prespecified statistical analysis plan (which does not call for censoring deaths), why did the agency censor deaths in its analysis of the secondary endpoints noted in the "not approvable" letter?

FDA response:
Time to deterioration in KPS and time to deterioration in neurocognitive function were prespecified secondary endpoints and included death as an event.

The FDA conducted a sensitivity test to examine the impact of death on the conclusion of significance in preventing deterioration of the specified clinical parameters. With death censored, the significance of any difference between the arms is lost. This indicates that these endpoints are not independent of the primary analysis, as underscored by ODAC statistician Dr. Rubinstein.

In general, any support that can be gleaned from secondary endpoints is contingent upon (1) winning on the primary endpoint and, (2) providing independent substantiation of a treatment effect. These conditions have not been met.

Question 4:
Given that the ODAC panel commented favorably on the overall consistency of all three trial results showing a treatment effect in this fatal medical condition, does the Division agree with the ODAC panel comments that strict adherence to a p value of less than or equal to 0.05 is not appropriate in this case?

FDA response:
No, we do not agree that a clear treatment effect has been demonstrated. Furthermore, we believe that ODAC was divided in their opinions and gave contradictory advice.

When a single trial is submitted for a new indication, the results must be persuasive. This is particularly the case when the two previous trials were considered for their ability to support the indication now requested and the ODAC vote was unanimously negative. The confounding imbalance in patients with favorable histologies on the Gliadel arm that was seen in the previous trial (CL-0190), is seen again in T-301.

Trials can be considered "confirmatory" only after the lead trial is concluded to be positive.

Question 5:
Would the Division reconsider its decision if additional survival data on patients still alive at the end of the study demonstrate a durable survival advantage?

FDA response:
We are not certain of the meaning of a "durable survival advantage". We are interested in overall survival and would take into consideration any imbalances that might affect conclusions. Specifically, it is conceivable that imbalances in favorable histologies could confound interpretation of the tails of the survival curves. We are particularly interested in the histology of GBM, since it represents that majority of patients with malignant glioma, behaves differently than other histologies and it is the subgroup for which an indication was granted in the refractory setting.

We note that the survival data provided in the sNDA was mature (73-76% deaths in the Gliadel and placebo arm, respectively), adhered to the protocol-specified cutoff point (one year after the last patient was entered). Nevertheless we are generally interested in survival updates. In fact, the FDA asked the sponsor at the Division Presentation May 24, 2001 whether additional data were available. The sponsor answered that data was not collected beyond the protocol-specified cutoff point. Please explain.

Given the natural history of this disease and that June, 2000 was the last observation and data cutoff date, death may have occurred in all patients. Credible data on additional deaths could be of interest, but both missing data and the quality of the retrieved data will be issues. Prior to any

submission, an additional meeting with the division would be recommended to discuss added value of this data, as well as additional data on relevant confounders such as additional surgeries and brachytherapies.

The meeting was concluded at 10am.

/S/ /S/

Concurrence:

Paul Zimmerman, Project Manager/5-30-02
Minutes preparer

Alla Shapiro, M.D., Medical Officer/6-3-02

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Alla Shapiro
6/3/02 06:02:09 PM

MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS

DATE: July 20, 2001

SUBJECT: sNDA 20-637/016 Gliadel

BETWEEN: Guilford Pharmaceuticals
Enoch Bortey, Ph.D., Associate Director, Biostatistics
Robin Butler, Senior Clinical Research Associate
Dana C. Hilt, M.D., Vice President, Clinical Research
Louise M. Peltier, Senior Director, Regulatory Affairs
Steve Piantadosi, M.D., Ph.D., Johns Hopkins Oncology Center (Consultant)
Peter Suzdak, Vice President, Research and Development

and FDA

Richard Pazdur, M.D.	--	Division Director
Alison Martin, M.D.	--	Medical Team Leader
Alla Shapiro, MD	--	Medical Reviewer
Ning Li, Ph.D.	--	Biometrics Reviewer
Gang Chen, Ph.D.	--	Biometrics Team Leader
Ann Staten,RD	--	Project Manager
Debra Vause, RN	--	Project Manager
Joanne Minor	--	OSHI

Discussion:

Dr. Pazdur explained to Guilford Pharmaceuticals that the purpose of the phone call was to alert them that the ongoing review had revealed review issues regarding the approvability of the sNDA and that the supplement would be taken to the September ODAC meeting.

In summary, the following review issues were communicated:

- The FDA's analysis showed that the study failed on the primary endpoint. The protocol-defined primary endpoint was overall survival in the ITT population and was not statistically significant (P-value 0.078) in the FDA's analysis (protocol specified non-stratified log-rank test).

- The results of the log-rank test using the covariates (performance score, age, tumor type) were also not statistically significant.

- The only statistically significant p-value is the result of stratifying by country (p-value 0.03). However, in the primary efficacy statistical analysis stratification by country was not pre-specified and is not considered a win here.

Ann Staten for Paul Zimmerman
Regulatory Health Project Manager, HFD-150

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Staten
7/31/01 01:30:53 PM
CSO

INTERNAL TEAM MEETING MINUTES

MEETING DATE: July 17, 2001 **TIME:** 8:30-9:30 a.m. **LOCATION:** cr-B
IND/NDA NDA 20-637
DRUG: Gliadel wafer
SPONSOR/APPLICANT: Guilford Pharmaceuticals

TYPE of MEETING:

1. team meeting
2. **Proposed Indication:** for initial surgery for newly diagnosed malignant glioma..

FDA PARTICIPANTS:

Richard Pazdur, M.D.	--	Division Director
Alison Martin, M.D.	--	Medical Team Leader
Alla Shapiro, MD	--	Medical Reviewer
Ning Li, Ph.D.	--	Biometrics Reviewer
Gang Chen, Ph.D.	--	Biometrics Team Leader
Ann Staten,RD	--	Project Manager
Debra Vause, RN	--	Project Manager
Joanne Minor	--	OSHI
Jan Buckner, M.D.	--	ODAC consultant

MEETING OBJECTIVES:

To discuss the review issues regarding the approvability of the sNDA.

DISCUSSION and DECISIONS REACHED:

POTENTIAL PROBLEMS:

- The protocol-defined primary endpoint was overall survival in the ITT population and was not statistically significant (P-value 0.078) in the FDA's analysis (protocol specified non-stratified log-rank test).

- The results of the log-rank test using the covariates (performance score, age, tumor type) were also not statistically significant.

- The only statistically significant p-value is the result of stratifying by country (p-value 0.03). However, in the primary efficacy statistical analysis stratification by country was not pre-specified.

Discussion:

- Dr. Buckner speculated that the significant p-value for the stratified analysis by country was possibly due to the tumor type.

- Dr. Buckner recommended that we look at the continuous distribution of age (not only the mean value).
-

- Secondary endpoints are trending in the same positive direction.

ACTION ITEMS

	Who	When
1. Add Howard Fine as a consultant for the review process and for ODAC	Ann	Done E-mail to KSomers and COI E-mail 7-17-01
2. Ask sponsor for the randomization codes	Ann	Pending
3. Look to see if randomization by country is looking correct	Ning Li	Pending
4. Statistical Analysis by age	Ning Li	Pending
5. Notify Karen that the application is going to ODAC in Sept.	Ann	Done 7-17-01
6. Check on the status of the response to Medical reviewer's info. request 7-5-01.	Ann	To be submitted 7-20-01
7. Answer patient consultant's request	Joanne Minor	To be done 7-20-01

Attachment: Draft clinical/Statistical comments/handout

/S/

Ann Staten, Project Manager
Minutes preparer

Draft intialed by AShapiro and AMartin

Attachment:

Primary Efficacy Endpoint: Survival

The primary efficacy endpoint for this study was the overall survival. The survival time defined in the protocol is the time period from the date of randomization to the last day of follow up or the date of death. The primary objective of this trial was to show. The sponsor's results for the primary endpoint are summarized in Table 1.

Table 1. Sponsor's Analysis for Overall Survival (ITT analysis)

ITT Population N=240	Median (95%CI) (Month)	Hazard Ratio	95.6% CI for Hazard Ratio	Log-rank P-value
Gliadel (88/120)	13.9 (12.1-15.3)	0.77	0.574-1.032	
Placebo (93/120)	11.6 (10.2-12.6)			0.027*

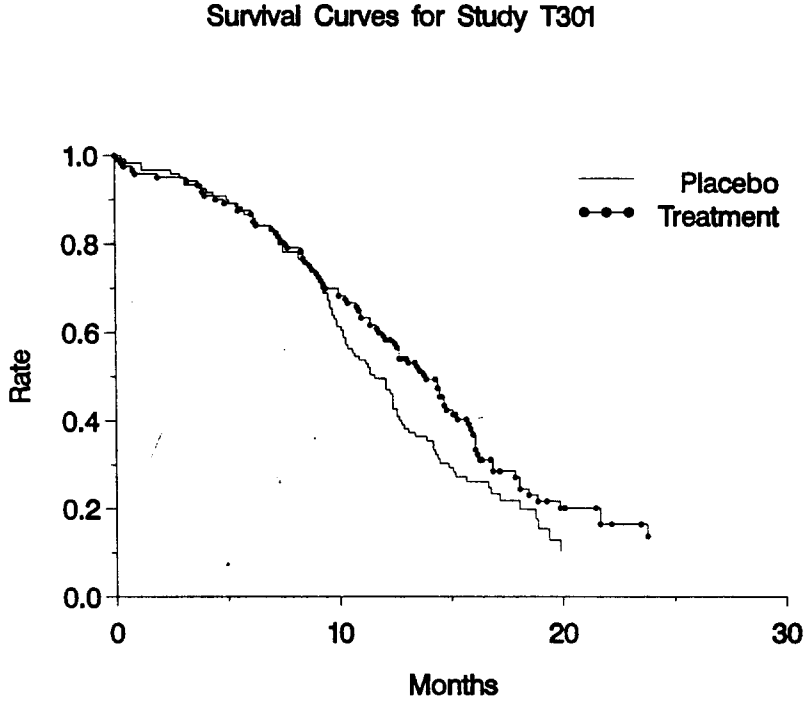
*Based on Sponsor's stratified analysis stratified by country.

Table 2. FDA's Analysis for Overall Survival (ITT analysis)

ITT Population N=240	Median (95%CI) (Month)	Hazard Ratio	95.6% CI for Hazard Ratio	P-value
Gliadel (88/120)	13.9 (12.1-15.3)	0.77	0.574-1.032	0.08**
Placebo (93/120)	11.6 (10.2-12.6)			0.078*

*Based on protocol specified non-stratified log-rank test.
** Wald test for HR.

Figure 1. Kaplan-Meier Survival Curves for Study T301



Reviewer's Comments:

1. The survival curves are presented in Figure 1. The sponsor claimed that the survival of Gliadel is statistically superior to the placebo based upon a stratified log-rank test. This claim is questionable because the stratified analysis was not the pre-specified analysis.

2. According to the sponsor's Statistical Analysis Plan, the primary efficacy analysis should be the log-rank test (without stratification). A log-rank test stratified on each covariate "are considered as supportive and all the statistical tests must be interpreted with caution." (p11 of the "Statistical Analysis Plan".) There are other covariates listed in the protocol (KPS, AGE, and Tumor Type), the result of log-rank tests using KPS, AGE, and Tumor type are shown in

Table 3. It is not convincing that the post-hoc choose of the country as a stratified variable is justified.

Table 3. FDA's Analysis for Overall Survival (ITT analysis) using different stratification variables*

ITT Population N=240	p-value Stratified by Country	p-value Stratified by GBM/Other	p-value Stratified by KPS	p-value Stratified by Age
Gliadel (88/120)	0.03	0.14	0.067	0.103
Placebo (93/120)				

*The p-value for the overall survival without stratification is 0.078

3. Table 3 listed other covariates mentioned in the protocol (country was one among these variables). The only statistically significant p-value is the one stratified by country. As discussed, the primary analysis should the non-stratified log-rank test that was pre-specified in the protocol. The rest of the analyses can only be used for exploratory purpose

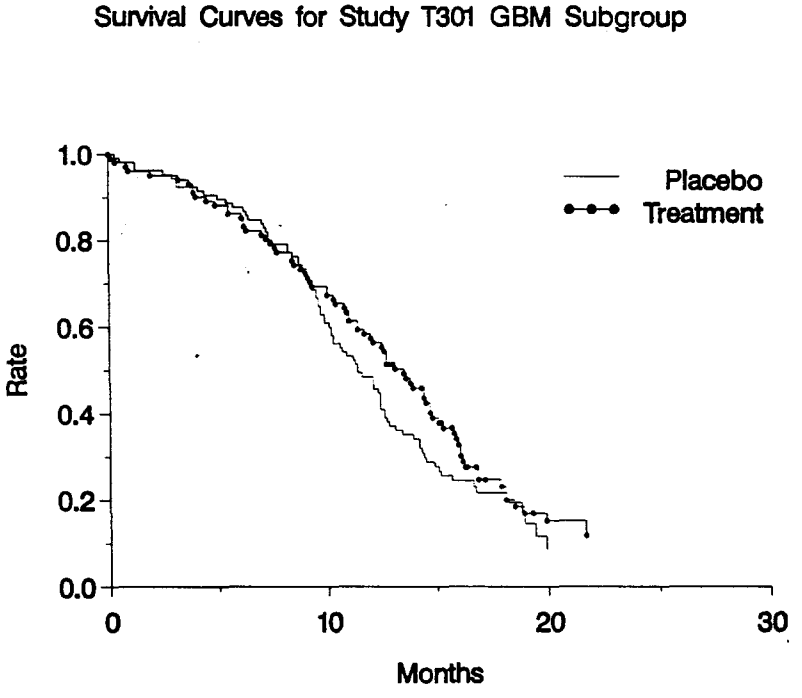
4. Survival for GBM patients only: Table 4 summarized the FDA's analysis for GBM subgroup patients. Figure 2 is the K-M curves for the same subpopulation. The sponsor provided an analysis that was based upon a stratified analysis on country, again this stratified analysis was not a planned analysis.

Table 4. FDA's Analysis for Overall Survival for GBM subgroup*

ITT Population N=207	Median (95%CI) (Month)	Hazard Ratio	95.6% CI for Hazard Ratio	P-value
Gliadel 78% (79/101)	13.5 (11.4-14.8)	0.82	0.601-1.113	
Placebo 80% (85/106)	11.4 (10.2-12.6)			0.20*

*Based on protocol specified non-stratified log-rank test.

Figure 2


Survival Curves for Study T301 GBM Subgroup
Placebo
Treatment
Rate
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
Months

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Staten
7/24/01 09:11:14 AM
CSO

MEETING MINUTES

MEETING DATE: February 23, 2001 **TIME:** 11am **LOCATION:** room 6041 (I)

Drug Name: Gliadel **NDA:** 20,637 **Type of meeting:** pre sNDA

Preparation package: dated February 2, 2001 **Sponsor:** Guilford Pharmaceuticals
(meeting request received December 21, 2000 and January 12, 2001)

FDA Invitees, titles and offices:
Robert Temple, M.D., Director, ODE1
Rachel Behrman, M.D., M.P.H., Deputy Office Director
Richard Pazdur, M.D., Division Director
Alison Martin, M.D., Medical Team Leader
Alla Shapiro, M.D., Medical Officer
Jan Buchner, M.D., ODAC representative (premeeting)
Gang Chen, Ph.D., Statistical Team Leader
Raji Sridhara, Ph.D., Statistical Reviewer
Atiqur Rahman, Ph.D., Biopharmaceutics Team Leader
Lydia Kieffer, Pharm.D., Biopharmaceutics Reviewer
Xiao Chen, Ph.D., Chemistry Reviewer
Eric Duffy, Ph.D., Chemistry Team Leader
JoAnn Minor, Public Health Specialist, OSHI
Jeannine Walston, patient representative (by phone)
Karen Somers, Advisors and Consultants Staff
Paul Zimmerman, R.Ph., Project Manager
(attendees are bolded)

Sponsor, titles and offices:
Enoch Bortey, Ph.D., Associate Director, Biostatistics
Robin Butler, Senior Clinical Research Associate
Karen Darcy, M.B.A., Senior Project Manager
Dana C. Hilt, M.D., Vice President, Clinical Research
Louise M. Peltier, Senior Director, Regulatory Affairs
Steve Piantadosi, M.D., Ph.D., Johns Hopkins Oncology Center (Consultant)

Meeting Objective(s):
To discuss the submission of an sNDA for initial surgery for malignant glioma.

Background:

PRODUCT:

- GLIADEL is a biodegradable wafer, composed of a copolymer matrix with Carmustine.
- GLIADEL is designed to deliver Carmustine directly into the surgical cavity created when brain tumor is resected.

APPROVAL FOR 2nd LINE TREATMENT OF GBM:

- GLIADEL was approved by the FDA on June 14, 1996. Indication: GLIADEL is indicated for use as an adjunct to surgery to prolong survival in patients with recurrent glioblastoma multiforme for whom surgical resection is indicated.
- In a randomized, double-blind, placebo-controlled study (Study 8802), 222 patients underwent implantation of either GLIADEL or placebo wafers at surgery for recurrent malignant gliomas.
- Median survival for all the patients in the GLIADEL group was 60%, compared to 47% in the placebo group (7.2 months vs. 5.4 months)

INITIAL TREATMENT FOR MALIGNANT GLIOMAS:

- Current phase III study was to determine the efficacy and safety of GLIADEL compared to placebo wafers in patients undergoing initial surgery for newly-diagnosed malignant gliomas.

- Median survival for the GLIADEL group was 13.9 months vs. 11.6 months in the placebo group.

- Median survival for GBM patients was 13.5 months for GLIADEL group vs. 11.4 months for placebo patients.

SUPPORTIVE TRIALS:

- In randomized, double-blind, placebo-controlled European clinical trial (Study CL-0190), 32 patients underwent Gliadel or placebo wafer implantation at the tine of initial surgery for the newly-diagnosed malignant gliomas.

- Increase in median survival in all patients in all the patients in GLIADEL group was 13.4 months vs. 9.2 months for the placebo group.

- In the subgroup of patients with GBM, median survival for GBM patients was 12.3 months for GLIADEL patients vs. 9.2 months for placebo patients.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Question #1

Is our intention to summarize the safety of each study separately in the sNDA agreeable with the Agency?

FDA response:

- Which studies is the sponsor intending to submit? We assume these studies are (1) RPR 132596/T-103, the first-line study that will serve as the primary study supporting an indication; and (2) Study CL-0190, which was conducted in Scandinavia in patients undergoing initial surgery for malignant glioma and which was closed early for lack of study drug (32 patients entered).
  (The sponsor noted that they will submit both studies above and study 9003.)
- The Agency agrees to presentation of safety data from these two studies separately.
- In the NDA, please list all studies under this IND, related INDs with gliadel and any foreign IND. Our understanding is that the other related US INDs are exploring different concentrations of carmustine in Phase 1 trials and therefore the data is not directly pertinent to the requested indication.

Question #2

Will the Phase III Study results support an approval of the target indication of first line malignant glioma?

FDA response:

- This is a review issue. We will consider approval if the submitted data indicate a clinically and statistically significant survival benefit with acceptable toxicity.

Question # 3
Will this sNDA be subject to priority review at an advisory committee meeting?
FDA response:

- Designation of review status will be determined within 45 days after the filing of NDA. We may also know at that time whether or not the application will be taken to ODAC.

FDA Question:
What is the data cutoff date? Does this conform to the protocol-specified point when the last patient entered is followed for at least 12 months?
(The sponsor noted that the cutoff date is June, 2000 (the last patient was entered June, 1999).

Please address the following in the NDA submission:

- Please provide the checklist for collection of adverse events.

- Please provide an "annotated CRF", i.e., a CRF which maps each blank in the CRF to a corresponding element in the database. The sponsor should write "not entered into database" in all sections where this applies. One useful method for presenting the detailed data definition is to include all such defining elements in one large electronic table so that one can electronically search the data definintion elements.

- Do the analyses based on histopathology use the central pathologist's diagnosis, as stated in the protocol? Please provide a list by patient ID # of all differences in diagnoses between the central pathologist and treating institution.

- Please provide number of patients entered (and patient ID #) by center and country.

- Please provide information on subsequent treatment of patients who progressed. We note data on reoperation has already been included in the meeting package.

- Clarify histopathology of patients listed in the category "other" (Table 4, p.11).

- Please specify the time course of post-operative convulsions.

- Is the number of deaths within 30 days of randomization the same as number of deaths within 30 days after surgery? (The sponsor confirmed that these numbers are the same.)

- Please provide details of all deaths within 30 days, including CRFs and surgical operative reports/summaries.

- Please provide details of the definition of the preferred term "aggravating reaction" which is the most frequently reported severe or life-threatening adverse event.

- Please resolve the apparent inconsistency regarding occurrence of intracranial hypertension. On p.32 the incidence of intracranial hypertension is estimated as 5.8% in the Gliadel group, compared to 1.2% in the placebo group. On p.38, 11 patients (9.2%) in Gliadel group developed intracranial hypertension vs. 2 patients (1.7%) in the placebo group.

- Financial disclosure for all participating investigators should be summarized. Individuals who have not submitted appropriate forms should be identified by institution.

- Results should be compiled for special populations (race, women, geriatric, impaired renal or hepatic function) if applicable or explain why these results were not complied.

- Please provide randomization dates by treatment arm.

- Please provide all available data regarding the extent of tumor resection in the gliadel and placebo group.

- Any interim analysis conducted should be reported in the NDA. (The sponsor noted that no interim analysis were done.)

The sponsor agreed in general to provide the requests listed above.

The meeting was concluded at 12:05PM.

/S/ /S/

Paul Zimmerman, Project Manager/date
Minutes preparer

Concurrence:

Alla Shapiro, M.D., Medical Officer/date

/s/

Paul Zimmerman
2/26/01 01:11:30 PM

Alla Shapiro
2/27/01 10:41:46 AM

Div.

INDUSTRY MEETING MEMO

MEETING DATE: January 30, 1997 / 12-1:30 pm / WOC II -G

IND # [redacted] **(N-128) 12/23/96**
Gliadel (polifeprosan 20 w/ carmustine implant)

EXTERNAL PARTICIPANT: Guilford Pharmaceuticals Inc.
Rhone-Poulenc Rorer Pharmaceuticals Inc.

TYPE OF MEETING: Phase 3 Clinical Development

MEETING CHAIR: Alison Martin, M.D.

MEETING RECORDER: Maureen A. Pelosi, PM, for Paul Zimmerman

ATTENDEES:

FDA: Robert Temple, M.D. , HFD-100
Robert Justice, M.D., Deputy Dir., HFD-150
Julie Beitz, M.D., Med. Team Leader, HFD-150
Alison Martin, M.D., Med Reviewer, HFD-150
Judy Chiao, M.D., Med Reviewer, HFD-150
Joe Aquilina, Ph.D., Clin. Pharm. Fellow
Clare Gnecco, Ph.D., Biometrics Team Leader
Masahiro Takeuchi, Sc.D., Biometrics Reviewer
Maureen Pelosi, R.Ph., Project Manager

GUILFORD: Gerald Pan, M.D., A. Dir, Clin Research
Earl Henry, VP, Clin Research
Eugenia Henry, Sr. Dir, Biomedical Oper
Ross Laderman, VP, Reg Affairs
Louise Peltier, Dir, Reg Affairs
Craig Smith, M.D., Pres & CEO
Susan Smith, Dir, Proj Planning & Mgt.

RHONE-POULENC RORER: Phillip Chaiken, M.D., VP WW Clin Dev
Anne-Margaret Martin, A. Dir, WW Reg Affairs

MEETING OBJECTIVES:

To discuss the adequacy of the proposed Phase 3 clinical study for expanding the Gliadel labeling to include front-line therapy for malignant glioma.

BACKGROUND:

The one placebo-controlled first surgery trial included in the NDA was judged too small to support an indication in this population. A larger randomized, multi center, double-blind, placebo-controlled trial is planned for this new indication.

OPENING REMARKS:

The sponsor explained the planned sequence regarding the proposed Phase 3 trial. After discussion with the FDA, they will finalize the protocol with their European colleagues and then submit it to the FDA. They anticipate beginning a multinational trial in June.

The study will enroll patients with unifocal initially-diagnosed and previously-untreated malignant glioma (glioblastoma multi forme plus others). The primary endpoint will be survival over a period of time - 12 months after last enrollment. Duration could extend up to 36 months from initial surgery, with 12 month primary data. Kaplan-Meier survival curves will be prepared and compared by log rank test. Median survival time is estimated to be one year. The sponsor changed the statistical plan for the meeting package - full details will be submitted with the protocol.

DISCUSSION POINTS: Clinical Issues

- The FDA accepted a single trial, given the additional data included in the NDA and that it would be multi center. A placebo control was accepted.

- Further define "malignant glioma" since there is a survival difference between glioblastoma multi forme (GBM) and others. FDA would prefer GBM only; however, the sponsor thought this was not feasible in initially diagnosed patients at the time of surgery. Central pathology will be obtained.

- The FDA recommends controlling the use of systemic chemotherapy. This could be done by tumor type, center, or age cut off. If treatment is needed for progressive disease, the choice would not matter at that point. Uncontrolled chemotherapy could affect efficacy and toxicity, especially the latter if a QOL instrument is to be used.

- If a major advance in therapy were to occur, the sponsor could change the standard chemotherapy during the study.

DISCUSSION POINTS: Clinical Issues, Continued

- The FDA recommended standardization of radiation therapy in the protocol. Limited field radiation appears to be the current trend versus whole brain radiation as the standard. The FDA asked for control for brachytherapy or gamma knife. The sponsor will limit these to patients with progressive disease. The FDA also asked about QA for radiation therapy.

- Standardize re-operation and retreatment definitions/data since survival time is the end point.

- The sponsor should prospectively collect and define terms for ADRs already seen in previous studies, to insure accurate toxicity reporting..

- Identify areas considered to be ongoing problems.

DISCUSSION POINTS: Clinical Pharmacology

- FDA is satisfied with the pharmacokinetics proposals.

DISCUSSION POINTS: Biometrics

- Please include the proposed analysis plan and specify the quality of life instrument in your protocol.

- Specify prognostic factors for adjusted analysis in the protocol. It was suggested that a stratified logrank test be provided as well as the cox model.

- Explain how randomization will take place. FDA suggested central randomization rather than blocking by sites.

- Primary analysis - do intent to treat as well as GBM subgroup analysis and consider a longitudinal analysis for QOL.

- Consider stratifying by performance status and age.

- No interim analysis is planned by the sponsor due to rapid accrual, but should be included in the protocol if early application submission is anticipated.

- FDA suggested monitoring proportions of each histologic type and re-estimation of sample size if needed. It was agreed that no statistical penalty would be imposed for this type of monitoring.

ACTION ITEMS:

1. Minutes will be exchanged within a month.

2. Sponsor will include a copy of the overheads with their minutes.

/S/ 2/4/97
Maureen A. Pelosi, PM
Recorder

/S/
Alison Martin, M.D.
Medical Reviewer

CC: Original IND [redacted]
HFD-150/Division File
/DeLap
/Justice
/Gnecco
/Takeuchi
/Beitz
/Martin
/Zimmerman
/Pease

R/D by Pelosi, CSO/1-31-96
initialed by Gnecco/1-31-97

F/T by Pelosi, 2-4-97

WP60 30237_01.97

Meeting Memo

USER FEE VALIDATION SHEET

NDA # 20-637 Supp. Type & # SE1-016 UFID # 2833
(e.g., N000, SLR001, SE1001, etc.)

1. (YES) NO **User Fee Cover Sheet Validated?** **MIS_Elements Screen Change(s):**

User Fee paid UFID# 2833

2. (YES) NO **APPLICATION CONTAINS CLINICAL DATA?**
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.**

3. YES (NO) **SMALL BUSINESS EXEMPTION**

4. YES (NO) **WAIVER GRANTED**

5. YES (NO) **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).**
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO **BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required**
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. (P) S **PRIORITY or STANDARD APPLICATION?**

/S/ 5/31/1 /S/ 5-31-01

PM Signature / Date CPMS Concurrence Signature / Date

2/14/00

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-637	Efficacy Supplement Type SE-1	Supplement Number 016 Resubmission after NA
Drug: Gliadel Wafer	Applicant: Guilford Pharmaceuticals, Inc.	
RPM: Paul Zimmerman	HFD-150	Phone # 301-594-5775
Application Type: (✓) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (✓) Priority
• Chem class (NDAs only)	5010110
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	~~10-6-01/12-6-01~~ 4-28-03
❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✓) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No
• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	( ) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	✓
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

❖ Actions	
• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA 3-19-2003
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(✓) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	✓ **(agreed upon text)**
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	January 30, 1997
• Pre-NDA meeting (indicate date)	February 23, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other - End of review meetings	5-29-2002, 8-7-2002
❖ Advisory Committee Meeting	
• Date of Meeting	December 6, 2001
• 48-hour alert	
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	✓ 2-11-03
❖ Clinical review(s) *(indicate date for each review)*	
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	✓
❖ Statistical review(s) *(indicate date for each review)*	
❖ Biopharmaceutical review(s) *(indicate date for each review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	July 6, 2001
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC ECAC report	

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 20

Date: February 14, 2003

COMMENTS: As discussed, the following concern NDA 20-637/S-016.

19 pages redacted from this section of the approval package consisted of draft labeling

Redacted 14

pages of trade

secret and/or

confidential

commercial

information

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 20

Date: February 14, 2003

COMMENTS: As discussed, the following concern NDA 20-637/S-016.

TRANSMISSION OK

TX/RX NO	0254
CONNECTION TEL	914106316884
SUBADDRESS	
CONNECTION ID	GUILFORD PHARM.
ST. TIME	02/14 12:47
USAGE T	02'25
PGS. SENT	20
RESULT	OK

****
*** TX REPORT ***
****

23 pages redacted from this section of the approval package consisted of draft labeling

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6338

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 2

Date: February 23, 2001

COMMENTS: The following concern NDA 20-637.

Regarding our February 23, 2001 meeting please also note the following.

Pediatric Exclusivity:

Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if this drug is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Requirement (PPSR), should be submitted so that we can consider issuing a Written Request.

Please refer to the "Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act" at Drug Information Branch (301) 827-4573 or http://www.fda.gov/cder/guidance/index.htm. You should also refer to our division's specific guidance on pediatric oncology Written Requests which is at http://www.fda.gov/cder/guidance/3756dft.htm.

Pediatric Final Rule:

Please note that you will need to address the December 2, 1998 Pediatric Rule (63 FR 66632) when you submit your NDA unless your product/indication has been designated an Orphan Drug. You may be eligible for a waiver under 21 CFR 314.55(c). Please refer to http://www.fda.gov/ohrms/dockets/98fr/120298c.txt.

/s/

Paul Zimmerman
2/23/01 02:43:46 PM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6338

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: June 26, 2001

COMMENTS: The following concern NDA 20-637/S-016.

As discussed with Dr. Shapiro on June 21, please provide information that explains reasons for wafers removal in both treatment groups. The following related questions also would be of interest: timing of wafers removal, subsequent treatment for those patients, and how they were included in the survival analysis.

Electronic Mail Message

Date: 5/25/01 1:14:30 PM
From: Paul Zimmerman
To: peltierl@guilfordpharm.com
Subject: NDA 20637/S-016

Regarding the statistical analysis plan, please provide the SOP for data analysis.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Zimmerman
5/25/01 01:20:04 PM
CSO

Electronic Mail Message

Date: 7/5/01 1:57:33 PM
From: Paul Zimmerman (ZIMMERMANP)
To: peltierl@guilfordpharm.com
Subject: sNDA 20-637/S-016

Please provide the referee pathologist's diagnoses for patients listed in the category "other" in the database UPAT, variable R_DIAGH, codes "6" - other.
The following patient's ID numbers are extracted from the same database, variable ZPATCODE.
Also, specify the location of these information in the database. If this information is not available from the database, please send us the report from the referee listing the specific diagnoses included in "other".

For the placebo group:	For the Gliadel group:
01055	01129
01092	01007
01229	01020
01261	01082
01283	01129
01309	01266
02026	02022
02028	02027
02048	02029
02057	02046
	02049
	02054

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Zimmerman
7/5/01 01:56:32 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Louise Peltier, Guilford	**From:** Ann Staten, Project Manager for Paul Zimmerman
Fax: 410-631-6884	**Fax:** 301-827-4590
Phone: 410-631-6356	**Phone:** 301-594-5770
Pages: 1	**Date: July 11, 2001**

Re: NDA 20-637/S-016 Gliadel

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

- **Comments:**

Dear Ms. Peltier:

The medical reviewer has the following information request:

1. Please clarify why two different tables have the same title "Summary of patients with additional surgical procedures for the malignant glioma overall and by treatment groups", and both have same number 1.06 in the database (see Appendix II.F). The data in the tables is not identical.

2. Do the numbers in the mentioned tables represent number of patients who underwent additional surgical procedures or number of events that patients experienced.

Sincerely,

Ann Staten, Project Manager for Paul Zimmerman

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Staten
7/11/01 09:19:30 AM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Louise Peltier, Guilford	**From:** Ann Staten, Project Manager for Paul Zimmerman
Fax: 410-631-6884	**Fax:** 301-827-4590
Phone: 410-631-6356	**Phone:** 301-594-5770
Pages: 1	**Date: July 12, 2001**
Re: NDA 20-637/S-016 Gliadel	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Ms. Peltier:

The medical reviewer has the following information request:

> Please clarify whether patients were counted more than once if they received multiple chemotherapy regimens.

Sincerely,

Ann Staten, Project Manager for Paul Zimmerman

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Louise Peltier, Guilford	**From:** Ann Staten, Project Manager for Paul Zimmerman
Fax: 410-631-6884	**Fax:** 301-827-4590
Phone: 410-631-6356	**Phone:** 301-594-5770
Pages: 2	**Date: July 19, 2001**
Re: NDA 20-637/S-016 Gliadel	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Ms. Peltier:

Attached is a copy of the information request sent to you via E-mail from Paul Zimmerman on 7-5-01.

Please let me know if you have any questions.

Sincerely,

Ann Staten, Project Manager for Paul Zimmerman

Electronic Mail Message

Date: 7/5/01 1:57:33 PM
From: Paul Zimmerman (ZIMMERMANP)
To: peltierl@guilfordpharm.com
Subject: sNDA 20-637/S-016

Please provide the referee pathologist's diagnoses for patients listed in the category "other" in the database UPAT, variable R_DIAGH, codes "6" - other.
The following patient's ID numbers are extracted from the same database, variable ZPATCODE.
Also, specify the location of these information in the database. If this information is not available from the database, please send us the report from the referee listing the specific diagnoses included in "other".

For the placebo group:	For the Gliadel group:
01055	01129
01092	01007
01229	01020
01261	01082
01283	01129
01309	01266
02026	02022
02028	02027
02048	02029
02057	02046
	02049
	02054

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Zimmerman
7/5/01 01:56:32 PM
CSO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Staten
7/19/01 09:23:14 AM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6338

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: July 26, 2001

COMMENTS: The following concern NDA 20-637/S-016.

Please provide the exact cause of death for the following patients who died within the first 30 days of randomization: ID 01121; ID 01293, and ID 02063. All patients are in the Gliadel group.

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: August 1, 2001

COMMENTS: The following concern NDA 20-637/S-016.

Please provide the details regarding randomization algorithm and randomization codes.

...please mail the forms to us at the above address by mail. Thank you.

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: August 1, 2001

COMMENTS: The following concern NDA 20-637/S-016.

Please provide the details regarding randomization algorithm and randomization codes.

08/01/01 14:49 FDA-DDDP → 9141063168884 NO.028 D01

MESSAGE CONFIRMATION

08/01/01 14:50
ID=FDA-DDDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
08/01	00'27"	410 631 6884	CALLING	01	OK 0000

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 9

Date: August 3, 2001

COMMENTS: The following concern NDA 20-637/S-016.

Please address the attached regarding Adverse Events.

PHONE: (301) 594-5775 FAX: (301) 827-4590

TO: Louise Peltier
(410) 631-6884

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 9

Date: August 3, 2001

COMMENTS: The following concern NDA 20-637/S-016.

Please address the attached regarding Adverse Events.

08/03/01 10:06 FDA-DODP → 9141063168884 NO.028 D01

MESSAGE CONFIRMATION

08/03/01 10:10
ID=FDA-DODP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
08/03	02'09"	410 631 6884	CALLING	09	OK 0000

Please explain the differences in numbers of patients in Gliadel and placebo groups who developed Adverse Events involving nervous system. Each patient was counted once.

Patients ID as follows:

Brain Hemorrhages.

Gliadel group:

01213 – subgaleal hematoma
02047 – subgaleal hematoma
01236 – subgaleal hematoma
02046 – intracerebral hemorrhage
01028 – cerebral infarct
01093 – brain hematoma
01170 – intracerebral hemorrhage
01121 – R. temporal hematoma

01272 – subdural hematoma
02054 – acute intracerebral bleed
01293 – tumor-bed hemorrhage
02063 – intracerebral hemorrhage

TOTAL 12 patients

Placebo group:

01193 - subgaleal hematoma
01067 – extradural hematoma
01006 – L. hemisphere lematoma
01027 – extradural bleeding
01132 – intratumoral bleeding
02048 – intracerebral hematoma
01213 - subgaleal hematoma
TOTAL 6 patients

Sponsor data: In Table 1.06 only one patient from each group is listed with the diagnosis "brain bleeding". Table 1.06 (continued) shows zero and 1 patients, respectively in the Gliadel and placebo group as "subdural hematoma".
Table 55 shows adverse event "cerebral hemorrhage" in 3 patients in the Gliadel group and none in the placebo group.

Brain Abscess/Wound Infection.

Gliadel Group:

01005 – brain abscess, meningitis (d. 84)
01020 – intracranial abscess (d. 22)
01063 - intracranial abscess (d. 118)
01085 – brain abscess (d.14)
01201 – intracranial abscess (d. 39)
01275 – wound infection (d. 29)
02024 - intracranial abscess (d.88)
02059 - intracranial abscess (d. 12)
TOTAl 8 patients

Placebo Group:

01137 – brain abscess (d. 17)
01036 – brain abscess (d. 37)
01077 – wound infection (d. 35)
01083 – wound infection (d. 187)
01137 – brain abscess (d. 17)
01149 – intracranial abscess (d.49)
01177 – abscess (d. 183)
02021 – wound infection (d. 6)
02023 – swelling surgical site
Total 9 patients

(Sponsor data: 6 patients in Gliadel and 3 patients in the placebo group are listed in Table 55 under the category "abscess").

Brain Cyst Formation.

Gliadel group:	**Placebo group:**
01138 – d.22	01209 – d. 14
01110 – d.126	01153 – d. 4
TOTAL 2 patients	01233 – d. 78
	TOTAL 3 patients

Sponsor data: Table 1.06 "Cyst formation – 2 and 0 patients in the Gliadel and placebo group, respectively and Table 1.06 (continued) "Post-operative cyst" – numbers reversed. Table 55 shows similar numbers for patients (2) with cyst in both groups.

Attachment.
Listing of patients from both groups who had convulsions and brain edema.

All reviewer's data derived from the dataset UPAT, UAE, USURG, and USMA.

ZPATC	TRTG
01274	1
01275	1
02006	1
02014	1
02027	1
02029	1
02046	1
02047	1
02059	1
02061	1

Gradel Group.

Total 58 pts (sp.-46)

ZPATC	TRTG
01009	1
01010	1
01020	1
01022	1
01030	1
01032	1
01034	1
01050	1
01051	1
01054	1
01057	1
01059	1
01063	1
01065	1
01069	1
01085	1
01087	1
01091	1
01093	1
01107	1
01110	1
01111	1
01116	1
01122	1
01131	1
01139	1
01141	1
01144	1
01148	1
01167	1
01170	1
01173	1
01190	1
01191	1
01196	1
01201	1
01205	1
01207	1
01211	1
01213	1
01217	1
01218	1
01236	1
01259	1
01262	1
01266	1
01271	1
01272	1

total: 58 patients
sponsor data – 46 patients

Brain Edema

Hladel Group. Sponsor: 27

ZPATC	TRTG
01005	1
01007	1
01009	1
01010	1
01014	1
01020	1
01028	1
01032	1
01033	1
01050	1
01056	1
01061	1
01063	1
01069	1
01070	1
01087	1
01093	1
01107	1
01111	1
01116	1
01122	1
01133	1
01138	1
01141	1
01144	1
01151	1
01152	1
01205	1
01268	1
01271	1
01272	1
01297	1
02006	1
02014	1
02054	1
02059	1

Total: 36 pts

Sponsor data – 27 patients