

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**20-637/S-016**

**Statistical Review(s)**

# Combined Medical-Statistical Review

## BIostatistics REVIEW



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

### STATISTICAL REVIEW AND EVALUATION

**Medical Division:** Oncology Drug Products (HFD-150)

**Biometrics Division:** Division of Biometrics I (HFD-710)

**NDA NUMBER:** 20-637 (S016)  
**DRUG NAME:** Gliadel®  
**INDICATION:** Treatment of Malignant Glioma  
**SPONSOR:** Guilford  
**DOCUMENTS REVIEWED:** Volume 1 of 1  
**STATISTICAL REVIEWERS:** Ning Li, M.D, Ph.D. (HFD-710)  
**STATISTICAL TEAM LEADER:** Gang Chen, Ph.D. (HFD-710)  
**BIOMETRICS DIVISION DIRECTOR:** George Chi, Ph.D. (HFD-710)  
**CLINICAL REVIEWERS:** Alla Shapiro M.D. (HFD-150)  
**PROJECT MANAGER:** Paul Zimmerman (HFD-150)

**Distribution:** NDA 20-637

HFD-150/Zimmerman  
HFD-150/Pazdur  
HFD-710/Li  
HFD-710/Chen  
HFD-710/Mahjoob  
HFD-710/Chi  
HFD-710/Anello

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### Statistical Review and Evaluation Of sNDA

#### BACKGROUND

GLIADEL, a sterile, biodegradable polymer wafer containing 7.7 mg of compressed carmustine powder, is designed to deliver local chemotherapy to the surgical cavity remaining after resection of a malignant glioma. In 1996, GLIADEL was approved for "use as an adjunct to surgery to prolong survival in patients with recurrent glioblastoma multiforme for whom surgical resection is indicated." A sNDA (20-637) submitted on April 6, 2001 requesting extension of the indication to treatment of patients undergoing initial surgery.

The efficacy claims of sNDA 20-637 rest primarily upon data from protocol T-301, a multicenter (38), international (14 countries), randomized, double-blind placebo-controlled trial in 240 patients with newly diagnosed glioma. After maximal resection of tumor, up to eight wafers of either Gliadel or placebo were placed against the resection surfaces. All patients (120 in each treatment group) were to receive standard limited-field radiation therapy and patients with anaplastic oligodendroglioma were also to receive systemic chemotherapy. The primary endpoint was overall survival. This was to be performed 12 months after the last patient was enrolled.

At the protocol-specified cutoff date, (June 30, 2000, one year after enrollment of the last study subject), 88 patients (73.3 %) in the Gliadel group and 93 patients (77.5 %) in the placebo group had died. Median survival for patients treated with GLIADEL was 13.9 months (12.1 – 15.3) and 11.6 months (10.2 – 12.6) for patients receiving placebo.

Statistical significance was not reached by the protocol-specified logrank test ( $p=0.078$ ). Statistical significance was reached by a stratified logrank test ( $p=0.027$ ). The sponsor claimed randomization was stratified by country; therefore, the logrank should be stratified by country. However, the statistical analysis plan for the protocol stated that randomization was stratified by center. A logrank test stratified by center was not significant ( $p=0.07$ ).

Of the 240 patients enrolled, 207 carry the diagnosis of GBM. Overall survival and one year survival in this population demonstrated a non-significant trend for improvement.

On December 6, 2001, Oncology Advisory Committee discussed whether data from trial T-301, which is submitted in sNDA 20-637, in conjunction with data from the prior approval, provided sufficient evidence of clinical benefit in patients

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with newly diagnosed malignant glioma to justify approval. In March 2002, the Division of Oncology Drug Products (DODP) sent a non-approval (NA) letter.

On October 11, 2002, the sponsor and DODP held a conference call to discuss the deficiencies listed in the NA letter. The FDA agreed that the sponsor could submit the results of long-term follow-up, which contained the survival status of patients enrolled in Study T-301 through August 16, 2002.

On October 25, 2002, the sponsor submitted a one volume amendment to sNDA 20-637 to the FDA. The submission contained only the updated survival data for study T-301.

### SUMMARY OF UPDATED EFFICACY RESULTS

This section will summarize the results of intention to treat analysis for study T-301. The intention to treat patient population includes all patients as randomized. All tests used in this review are two-sided unless otherwise stated. The updated results using the long-term follow-up cut off date of August 16, 2002 are reviewed. For comparison, some of the original results using the cut off date June 30, 2002 are also presented.

#### Primary Efficacy Endpoint

The primary efficacy endpoint for this study was 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 the updated long-term study was to determine the survival status of patients enrolled in Study T-301 through August 16, 2002.

The updated long-term follow-up results for the primary endpoint are summarized in Table 1.

**Table 1. FDA's Analysis for Overall Survival (Updated Data: 8/16/2002)**

ITT Population N=240	Median (95%CI) (Month)	Hazard Ratio	95% CI for Hazard Ratio	P-value
Gliadel (111/120)	13.8 (12.1-15.1)	0.73	0.56-0.95	0.02*
Placebo (117/120)	11.6 (10.2-12.7)			0.02**

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

\*\* Wald test for HR.

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Figure 1. Overall Survival Curves Using Updated Data

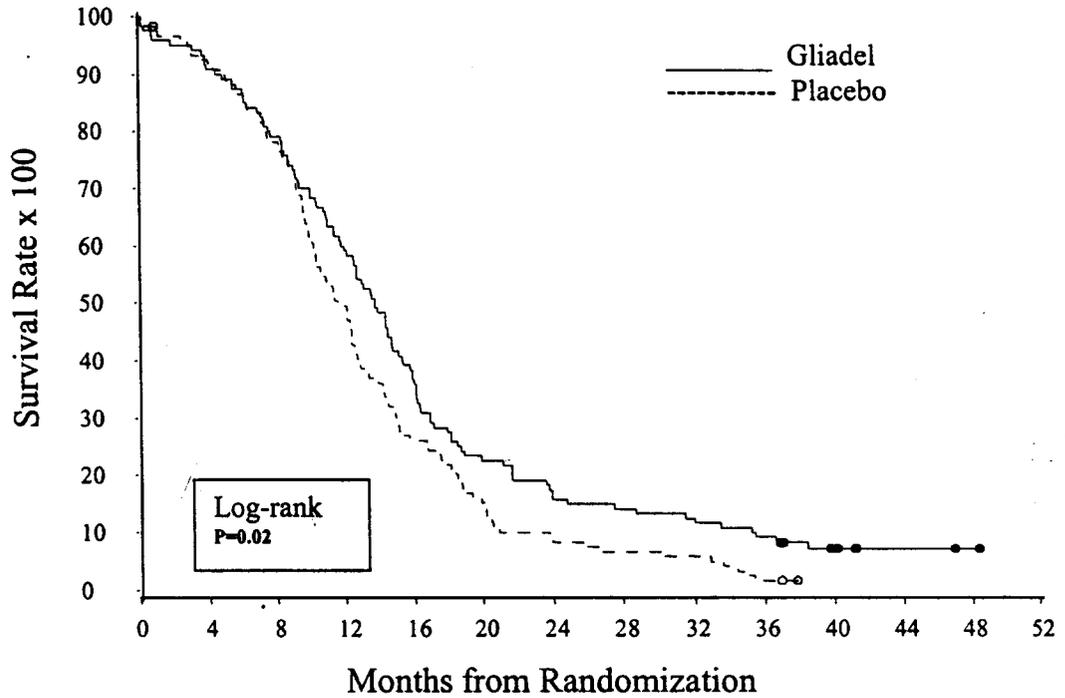


Table 2. FDA's Analysis for Overall Survival (Cut off date: 6/30/2000)

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.

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### Reviewer's Comments:

1. The survival curves using the updated data are presented in Figure 1. The survival of Gliadel arm is statistically superior to the placebo based upon a log-rank test ( $p=0.02$ ).
2. According to the sponsor's Statistical Analysis Plan, the primary efficacy analysis should be the log-rank test (without stratification). By using the updated data, the primary objective of the study is met.
3. Table 2 summarized the overall survival results using the protocol specified cut-off date, June 30, 2000. There is no statistically significant difference by using this data.
4. Multiple analyses are a concern because of two separate analyses of the data. The sponsor used all alpha as specified in the protocol though the updated analysis represents the more mature data (>95% of the events).
5. During the review of the original submission, the FDA found that there was an imbalance in the AOA subgroup (7 patients in the Gliadel group versus 3 in the placebo group). A sensitivity analysis was performed to determine the effect of this imbalance by excluding these 10 patients from the ITT population using the updated analysis. The results are summarized in Table 3. The result showed the consistent benefit of the Gliadel arm in the sensitivity analysis ( $p=0.03$ ).

**Table 3. Analysis for Overall Survival (excluding 10 AOA subjects)**

ITT Population - N=230	Median (95%CI) (Month)	Hazard Ratio	95% CI for Hazard Ratio	P-value
Gliadel	13.6 (12.0-14.8)	0.74	0.57-0.97	0.027*
Placebo	11.6 (10.2-12.6)			

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

6. Survival for GBM patients only: Table 4 summarized the FDA's analysis for GBM subgroup patients. There is no statistically significant difference between the two treatment groups. The sponsor provided a similar analysis.

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**Table 4. Analysis for Overall Survival for GBM subgroup\***

ITT Population N=207	Median (95%CI) (Month)	Hazard Ratio	95% CI for Hazard Ratio	P-value
Gliadel	13.1 (11.4-14.7)	0.78	0.59-1.03	0.08*
Placebo	11.4 (10.2-12.6)			

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

### Statistical Evaluation of Collective Evidence

Study T301 was a multicenter, double-blind, randomized, controlled, Phase III parallel comparative trial of Gliadel versus placebo in a total of 240 patients with Malignant Glioma. Study T-301 demonstrated superiority with respect to survival of Gliadel arm when compared with the control in a long-term follow-up study. The survival of Gliadel arm is statistically superior to the placebo based upon a log-rank test ( $p=0.02$ ). Multivariate analyses adjusted for known prognostic factors such as age, KPS and tumor type also showed statistically significant difference between the treatment groups ( $p=0.045$ ).

In this statistical reviewer's opinion, the study results appear to support efficacy of Gliadel versus placebo in patients with newly diagnosed malignant Glioma using the updated survival data.

APPEARS THIS WAY  
ON ORIGINAL

## BIOSTATISTICS REVIEW

Ning Li, M.D. Ph.D.  
Statistical Reviewer

Date:

Concur: Dr. Chen  
Team Leader

Dr. Chi  
Division Director, DBI

Cc:

HFD-710/ Dr. Li  
HFD-710/ Dr. Chen  
HFD-710/ Dr. Mahjoob  
HFD-710/ Dr. Chi  
HFD-700/ Dr. Anello

This review consists of 7 pages of text  
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/s/

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Alla Shapiro  
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MEDICAL OFFICER

Ann Farrell  
2/20/03 12:31:09 PM  
MEDICAL OFFICER

Gang Chen  
2/24/03 11:32:16 AM  
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Ning Li  
2/24/03 11:34:02 AM  
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George Chi  
2/24/03 12:39:39 PM  
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