Table 46: Treatment-emergent adverse events occurring in ≥5% of patients in either treatment group by body system, COSTART term and treatment group (continued)

Adverse event	GLIADEL® N=120 n (%)	Placebo N=120 n (%)
Nervous system (continued)		
Coma	5 (4.2)	6 (5.0)
Confusion	28 (23.3)	25 (20.8)
Convulsion	40 (33.3)	45 (37.5)
Depression	19 (15.8)	12 (10.0)
Dizziness	6 (5.0)	11 (9.2)
Facial paralysis	8 (6.7)	5 (4.2)
Grand mal convulsion	6 (5.0)	5 (4.2)
Hallucinations	6 (5.0)	4 (3.3)
Hemiplegia	49 (40.8)	53 (44.2)
Hypesthesia	7 (5.8)	6 (5.0)
Hypokinesia	2 (1.7)	8 (6.7)
Incoordination	3 (2.5)	8 (6.7)
Insomnia	6 (5.0)	7 (5.8)
Intracranial hypertension	11 (9.2)	2 (1.7)
Neuropathy	8 (6.7)	12 (10.0)
Paresthesia	7 (5.8)	10 (8.3)
Personality disorder	10 (8.3)	9 (7.5)
Somnolence	13 (10.8)	18 (15.0)
Speech disorder	13 (10.8)	10 (8.3)
Thinking abnormal	7 (5.8)	10 (8.3)
Tremor	6 (5.0)	8 (6.7)
Respiratory system		
Dyspnea	4 (3.3)	8 (6.7)
Pneumonia	10 (8.3)	9 (7.5)
Skin and appendages		
Alopecia	12 (10.0)	14 (11.7)
Rash	14 (11.7)	13 (10.8)
Special senses		
Abnormal vision	7 (5.8)	7 (5.8)
Conjunctival edema	8 (6.7)	8 (6.7)
Diplopia	1 (0.8)	6 (5.0)
Eye disorder	3 (2.5)	6 (5.0)
Visual field defect	6 (5.0)	8 (6.7)
Urogenital system		
Urinary incontinence	9 (7.5)	9 (7.5)
Urinary tract infection	10 (8.3)	13 (10.8)

The most common AEs are related to the nervous system. Hematologic abnormalities, as seen with systemic BCNU, occurred in <5% of patients and therefore are not included. The overall incidence of nausea and vomiting, also seen with systemic BCNU, appear more commonly in patients treated with GLIADEL; however, similar numbers (7 on GLIADEL and 6 on placebo) were considered severe or life-threatening.

- **Serious Adverse Events (SAEs)**

The incidence of common Serious Adverse Events by body system is presented in Sponsor Table 55 (excluding nervous system).

Table 55: Serious adverse events experienced by more than one patient in a treatment group by body system, preferred term and treatment group (excluding nervous system SAEs)

Adverse event	GLIADEL® N=120 n (%)	Placebo N=120 n (%)
Body as a whole		
Abdominal pain	2 (1.7)	0
Abscess	6 (5.0)	3 (2.5)
Accidental injury	4 (3.3)	2 (1.7)
Aggravation reaction	85 (70.8)	83 (69.2)
Asthenia	3 (2.5)	2 (1.7)
Chest pain	2 (1.7)	0
Cyst	2 (1.7)	2 (1.7)
Death	2 (1.7)	3 (2.5)
Fever	7 (5.8)	5 (4.2)
Headache	7 (5.8)	7 (5.8)
Infection	6 (5.0)	3 (2.5)
Neoplasm	2 (1.7)	1 (0.8)
Sepsis	0	2 (1.7)
Suicide attempt	0	2 (1.7)
Cardiovascular system		
Cerebral hemorrhage	3 (2.5)	0
Deep thrombophlebitis	5 (4.2)	7 (5.8)
Heart arrest	2 (1.7)	0
Hemorrhage	4 (3.3)	3 (2.5)
Pulmonary embolus	10 (8.3)	10 (8.3)
Thrombophlebitis	1 (0.8)	2 (1.7)
Digestive system		
Nausea	3 (2.5)	4 (3.3)
Vomiting	4 (3.3)	2 (1.7)
Endocrine system		
Diabetes mellitus	1 (0.8)	2 (1.7)

Table 55: Serious adverse events experienced by more than one patient in a treatment group by body system, preferred term and treatment group (excluding nervous system SAEs) (continued)

Adverse event	GLIADEL® N=120 n (%)	Placebo N=120 n (%)
Hemic and lymphatic system disorders		
Thrombocytopenia	0	2 (1.7)
Metabolic and nutritional disorders		
Healing abnormal	4 (3.3)	1 (0.8)
Musculoskeletal system		
Myasthenia	2 (1.7)	2 (1.7)
Respiratory system		
Lung disorder	1 (0.8)	2 (1.7)
Pneumonia	3 (2.5)	6 (5.0)
Urogenital system		
Urinary tract infection	1 (0.8)	2 (1.7)

Sponsor Table 56 summarizes SAEs involving the nervous system.

Table 56: Serious adverse events involving the nervous system experienced by more than one patient in a treatment group by body system, preferred term and treatment group

Adverse event	GLIADEL® N=120 n (%)	Placebo N=120 n (%)
Nervous System		
Amnesia	0	3 (2.5)
Aphasia	5 (4.2)	6 (5.0)
Brain edema	7 (5.8)	8 (6.7)
Cerebral infarct	2 (1.7)	0
CNS neoplasia	3 (2.5)	2 (1.7)
Coma	4 (3.3)	6 (5.0)
Confusion	8 (6.7)	4 (3.3)
Convulsion	40 (33.3)	44 (36.7)
Facial paralysis	2 (1.7)	1 (0.8)
Grand mal convulsion	6 (5.0)	5 (4.2)
Hemiplegia	19 (15.8)	18 (15.0)
Hypokinesia	1 (0.8)	2 (1.7)
Incoordination	1 (0.8)	2 (1.7)
Intracranial hypertension	7 (5.8)	2 (1.7)
Neuropathy	4 (3.3)	5 (4.2)
Somnolence	3 (2.5)	6 (5.0)
Speech disorder	6 (5.0)	2 (1.7)
Stupor	2 (1.7)	4 (3.3)
Tremor	1 (0.8)	2 (1.7)

The most common serious adverse events noticed by the sponsor were "aggravation reaction" which occurred in 85 patients (70.8%) in the GLIADEL group and in 83 patients (69.2%) in the placebo group. This term, not used in the U.S., is described in Sponsor Table 45.

Table 45: Main adverse event terms coded to "Aggravation reaction"

Verbatim investigator term	Number of patients (%) with AE
Tumor progression	133 (40.1)
Tumour progression	55 (16.6)
Disease progression	30 (9.0)
Tumor recurrence	14 (4.2)
Neurological deterioration	12 (3.6)
Brain tumor evolution	5 (1.5)
Malignant disease progression	5 (1.5)

Reviewer Comment: "Aggravation reaction" is a term, used in collecting data outside the US and is defined by the sponsor as "mainly tumor/disease progression or general deterioration of condition."

Seizures

In this study, seizures were the most common serious treatment-emergent adverse event involving the nervous system. Reviewer Table 21 below presents the incidence of seizures.

Reviewer Table 21: Convulsions in Patients in the ITT population

	Treatment Group	
	GLIADEL N=120 (%)	**Placebo N=120 (%)**
New or worsening Convulsions	40 (33.3)	45 (37.5)
Grand mal	6 (5)	5 (4.2)
TOTAL	46 (38.3)	50 (41.7)

Reviewer Comment: The number of patients cited by the sponsor with seizures (grand mal and convulsions) were confirmed by the reviewer (derived from database UAE – adverse events, variables – D_AESR – onset date, AESERNY – serious, AECOSE – COSTART term). Each patient was counted once.

In 10 patients in the GLIADEL group and 16 patients in the placebo group, convulsions occurred within the first 30 days of randomization (initial surgery).

The incidence and distribution of postoperative seizures in both groups within the first 30 days of the wafer implantation, as well as at the later periods for up to 120 days after the initial surgery is presented in Reviewer Table 22.

Reviewer Table 22: Timeframe of Postoperative Seizures

Seizures	Treatment Group	
	GLIADEL N=120 (%)*	Placebo N=120 (%)*
Reported at Baseline	**30 (25.0)**	**28 (23.3)**
First 30 Days		
Patients	**11 (9.1)**	**16 (13.3)**
Events	**24 (20.0)**	**45 (37.5)**
31-90 Days		
Patients	**12 (10)**	**7 (5.8)**
Events	**15 (12.5)**	**8 (6.6)**
91-120 Days		
Patients	**8 (6.6)**	**8 (6.6)**
Events	**8 (6.6)**	**8 (6.6)**

* Each patient was counted once.

Of the patients who developed seizures within the first 30 days, 6 patients in the GLIADEL group and 11 patients in the placebo group had seizures at baseline. Among the patients who had baseline seizures and postoperative seizures within the first 30 days, 5 of 6 in the GLIADEL group and 6 of 11 in the placebo group had multiple events (from 2 to 10).

Reviewer Comment: The incidence of seizures within the first month of operation ranged from 9 to 13%. Although the frequency of postoperative seizures is reasonably balanced between the arms, the control arm is a placebo waver and may lead to underestimation of related seizures.

G. Healing Abnormalities Checklist

The adverse events coded as "healing abnormalities" consisted of 4 categories: (1) fluid, CSF or subdural collection, (2) CSF leaks, (3) wound dehiscence, breakdown or poor wound healing, and (4) subgaleal or wound effusion.

Sponsor Table #50 summarizes the patients with healing abnormalities.

Table 50: Healing abnormal checklist results

	GLIADEL® N=120	Placebo N=120
Fluid, CSF or subdural collections		
Number of patients (%)	5 (4.2)	6 (5.0)
Median duration (days)	18.0	9.5
Range for duration (days)	12 - 60	1 - 68
CSF leaks		
Number of patients (%)	6 (5.0)	1 (0.8)
Median duration (days)	14.0	3.0
Range for duration (days)	2 - 211	3
Wound dehiscence, breakdown or poor healing		
Number of patients (%)	6 (5.0)	6 (5.0)
Median duration (days)	9.5	13.0
Range for duration (days)	2 – 261	2 - 172
Subgaleal or wound effusion		
Number of patients (%)	4 (3.3)	5 (4.2)
Median duration (days)	16.5	9.5
Range for duration (days)	3 – 72	2 - 26

A total of 33 patients (18 and 15 in the GLIADEL and placebo group, respectively) had abnormal wound healing recorded on their checklist. sponsor notes that patients treated with GLIADEL have an increased incidence of CSF leaks as well as a greater duration of the complications of fluid collections, CSF leaks and effusion at the wound site.

H. Additional Local Adverse Events.

Additional local adverse events from the database UPAT – Description and Disposition of Patients, UAE – Adverse Events, and USURG – Surgery) are presented in the Reviewer Table 23 below.

Reviewer Table 23: Additional Local Treatment-Emergent Adverse Events

Adverse Event	Treatment Group	
	GLIADEL N=120 (%)	Placebo N=120 (%)
Intracranial hypertension	11 (9)	2 (1.7)
Cerebral hemorrhage	8 (6)	5 (4)
Brain abscess	8(6)	5 (4)
Brain cyst	2 (1.7)	3 (2.5)
Cerebral edema	27 (22.5)	23 (19.2)

Reviewer Comment: We confirmed the number of patients with local complications such as intracranial hypertension, cerebral hemorrhages, and brain edema (by queries to the electronic database UAE – adverse events, variables AESERNY – serious, D_AESR – onset date; USURG – surgery, variables ASURGNY – additional surgical procedure). The number of patients with brain abscess and cysts differs between the sponsor and reviewer.

Brain abscess in 3 patients (2 from the GLIADEL and 1 from the placebo group) were counted by the sponsor as "wound infection". FDA reviewer included these patients in the category "brain abscess" because of the information extracted from CRF's:

One patient, ID 01209 from the placebo group, was included by the sponsor only in the listing of patients who underwent an additional surgical procedure (Table 1.06). However, this patient had additional surgery on day 14 after the initial surgery due to brain cyst formation that caused midline shift, confusion and urinary incontinence. Therefore this patient was included by the reviewer in the category of treatment-emergent AE.

GLIADEL group:

- *Patient ID 01085 – on postoperative day 14, patient developed a complication that was captured as "wound infection". On day 15, patient underwent exploratory craniotomy and was diagnosed with a brain abscess.*
- *Patient ID 02059 – on postoperative day 12, patient developed a complication that was captured as "wound infection". On day 19, patient underwent re-craniotomy and was diagnosed with a brain abscess.*

Placebo group:

- *Patient ID 01036 – on postoperative day 36, the patient showed evidence of clinical deterioration and the next day underwent re-craniotomy with surgical resection of a brain abscess.*

FDA requested information from the sponsor regarding type of pathogens isolated from patients who developed brain abscesses/wound infections. Since the study protocol did not require the collection of information on pathogens from patients with these AEs, this information was collected at the discretion of the investigator and information is not available for all patients. The following is a listing of the available information.

GLIADEL group: Propionobacterium acne was identified in 5 of 8 patients with brain abscesses or wound infection. For 3 patients in this group, no bacterial culture information is available.

Placebo group: Propionobacterium acne was identified in 1 of 8 patients. For the rest of the patients either no bacterial culture information was available or "event was coded Not Serious by the investigator, thus additional information was not collected."

VIII. Dosing, Regimen, and Administration Issues

Patients who met the full inclusion criteria had up to eight wafer implanted into the bed of the tumor resection cavity on the day of randomization (day of surgery). The number of wafers implanted was determined by the size of the tumor resection cavity. Each GLIADEL wafer contains 7.7mg of BCNU. "It is recommended that eight wafers be placed in the resection cavity if the size and shape of it allows. Should the size and shape not accommodate eight wafers, the maximum number of wafers as allowed should be placed. Since there is no clinical experience, no more than eight wafers should be used per surgical procedure" (proposed labeling information).

There are some dosing and administration issues with regard to GLIADEL wafer for newly diagnosed malignant gliomas, such as increased friability of the Gliadel wafer which might cause technical difficulties during the wafer implantation and also influence the amount of BCNU delivered into the surgical cavity.

IX. Use in Special Populations

Overall, there were more male patients than female patients in both treatment groups, with males constituting 63.3% of the GLIADEL group and 70.0% of the placebo group. In the sponsor analysis **gender** was not a predictor of survival. In a log-rank test stratified by gender as a covariate, p-value was not statistically significant (p=0.58) in the ITT population.

The differences in efficacy or safety profile of the GLIADEL wafer were not assessed with regard to **ethnicity.** The majority of patients (96.7%) in each treatment group were Caucasian.

Mean age was comparable for the GLIADEL group (mean 52.6 years, range: 21 to 72 years) and the placebo group (mean 53.6 years, range: 30 to 67 years).

To assess an effect of age as a prognostic factor on survival, FDA analyzed age as a continuous variable. In a non-stratified test, **age** did not reach statistical significance (p=0.20). Furthermore, for the eligibility criteria the cut-off age for the patients entering the study was 65 years. These limitations prevented the enrollment of older patients who have potentially worse prognosis for survival.

The absorption, distribution, metabolism, and excretion of the copolymer in humans is unknown. Carmustine concentration delivered by GLIADEL in human brain tissue is unknown. Plasma levels of carmustine after GLIADEL wafer implantation were not determined.

The applicant does not seek **pediatric indications** and Pediatric rule does not apply to this indication. Newly diagnosed malignant gliomas are exceedingly rare in children (approximately 2,000 children develop a brain tumor each year in the US).

There are no studies assessing the use of Carmustine in **pregnancy**. The active component of GLIADEL is an alkylating agent that can cause fetal harm when administered to pregnant women.

X. Conclusions and Recommendations

A. Conclusions

Study T-301 met most of the criteria for a well controlled study, e.g., statement of objectives, trial design, randomization, and method of assessment of the endpoints. However, it should be noted that primary analysis of the data performed by the sponsor was not prospectively specified in the protocol.

The protocol identified the primary efficacy endpoint as survival in the ITT population assessed by the log-rank test. Median survival in the ITT population 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. Median survival in the GBM subgroup was 13.5 months (11.4-14.8) in the GLIADEl group and 11.4 months (10.2-12.6) in placebo. Although a trend in improvement of survival was shown in the ITT population as well as in the GBM subgroup, we concluded that T-301 trial did not demonstrate a clinically meaningful and statistically persuasive effect on the primary endpoint survival (p-values in the protocol-specified log-rank test 0.08 for the ITT population and 0.2 for the GBM subgroup).

The protocol identified country as one of the potential covariates along with age, histological diagnosis, and KPS, and stated that the treatment effect "will be estimated using a model stratifying for this covariate." This analysis was considered by the sponsor as "supportive." The treatment effect on survival in all patients with newly diagnosed malignant gliomas reached statistical significance only when stratified by country. The other secondary endpoints such as one-year survival, progression-free survival, time to KPS and neutoperformance measures deterioration and QoL did not show significant differences. The meaning for a positive result when country is used as a stratification variable is unknown.

By the study cut-off date, 88 patients (73.3%) in the GLIADEL group and 93 patients (77.5%) in the placebo group died. The primary cause of death was disease progression in both groups. In the first 30 days of randomization 7 patients (5 in the GLIADEl and 2 in placebo group, respectively) died from cerebral hematoma, pulmonary embolism, acute abdominal or coronary event, and sepsis.

The toxicity profile of GLIADEL is consistent with a regional delivery of the drug at the time of operation. The primary toxicities were related to neurologic function (seizures, brain hemorrhages, brain cysts) and wound infection/brain abscesses. Increased incidence of CSF leaks and increased duration of fluid collection were noticed in the GLIADEL and placebo group, respectively.

B. Recommendations

In the absence of demonstrating a significant treatment effect in the primary (survival) and secondary endpoints (survival in the GBM subgroup, 1-year survival, PFS, time to KPS and neurological deterioration, and QoL) in the single, multicenter, randomized, placebo-controlled T-301 trial, the primary reviewers recommend against marketing approval for GLIADEL wafer as proposed in the draft label.

The data for survival from the previously conducted trial, #CL-0190, a small (32 patient) European study in newly diagnosed patients with malignant gliomas, were not convincing due to the imbalance in tumor histology between the treatment arms favoring the GLIADEL group.

Data from the #8802, a randomized, multicenter, placebo-controlled trial entering patients with recurrent malignant gliomas, was the basis for an FDA approval of the GLIADEL wafer in 1996 "to prolong survival in patients with recurrent glioblastoma multiforme (GBM) for whom surgical resection is indicated" also did not provide convincing evidence of a survival effect in the ITT population. Therefore this trial cannot be considered as supportive for the T-301 trial.

2 PAGE(S) REMOVED. SEE THE ADVISORY COMMITTEE MEETING INFORMATION LOCATED ON THE FDA WEBSITE BELOW:

http://www.fda.gov/ohrms/dockets/ac/cder01.htm#Oncologic

pp.
62-63

APPENDIX II: Protocol T-301 Details

Reviewer Table 24: Randomization List for US Sites

Pat ID	Arm	Date	Center	Block#
2005*	Placebo	2/12/98	US3096	2
2006	Gliadel	8/24/98	US3096	2
2013*	Placebo	6/25/98	US4109	4
2014	Gliadel	10/28/98	US4109	4
2021*	Placebo	2/20/98	US4110	6
2022	Gliadel	7/01/98	US4110	6
2023	Placebo	8/25/98	US4110	6
2024*	Gliadel	1/30/98	US4110	6
2026	Placebo	8/13/98	US4288	7
2027	Gliadel	9/17/98	US4288	7
2028	Placebo	12/01/98	US4288	7
2029	Gliadel	2/01/99	US4400	8

Reviewer comment: We reviewed the randomization codes and come to an agreement with the sponsor that the randomization was stratified by center (not country). We can tell this by checking US patients in all 5 US sites. A fixed block size of 4 was used. If the country was the stratification factor, then the patients with similar randomization dates should be clustering together. For example, 4 patients entered the study in January and February: pt #2005, #2013, #2021, and #2024 should share the same block number.

Reviewer Table 22: Tumor Histology by Country

Country	GLIADEL						Placebo					
	Histology*						Histology*					
	AA	AO	AOA	GBM	M/BM	Other	AA	AO	AOA	GBM	M/BM	Other
Austria				3						4		
Australia				7		1			1	7		1
Belgium				7				1		6		
Switzerland		2		3						4		
Germany		3		18	1					22		
Spain				2								
France			2	21		1		2	1	21		
U.K.			1	14				1		15		1
Greece				2					1	1		
Israel		1	2	13	1					15		
Italy				1								
Netherlands	1		1	5			1			7		
N. Zealand				1						1	1	
U.S.			2	4			1	1		3		1
Total	1	6	8	101	2	2	2	5	3	106	1	3

*AA-Anaplastic astrocytoma AO-Anaplastic oligodendroglioma AOA-Anaplastic oligoastrocytoma GBM-Glioblastoma multiforme M/BM-Metastasis/Brain Metastasis

RADIATION THERAPY PROTOCOL

1. General
Patients should be treated with involved/limited field radiotherapy to the planning target volume (PTV) including the tumour [gross tumour volume (GTV), clinical target volume (CTV)] and a defined margin with localized radiotherapy technique.

2. Patient positioning
Patients should be immobilized in an immobilization device in use in the radiation therapy center.

3. Volumes of treatment

3.1 Tumour volumes should be defined on the basis of preoperative imaging.

3.2 GTV should be defined as the region of enhancement presumed to represent tumour (on preoperative imaging –either CT or MRI). In unenhancing tumours GTV should be defined by the region of low density on CT of high signal intensity on T2 weighted MRI.

3.3 The definition of CTV is not mandatory and may include GTV plus 1 – 3 cm margin in 3 dimensions or the region of low signal intensity (CT)/high signal intensity (T2W MRI) in enhancing tumour, or other definition specific to the radiation therapy centre. Exception for the margin definition can be made for bone and meningeal structures which are considered anatomical barriers to tumour spread.

3.4 PTV definition may be related either to GTV or CTV.
Overall it is recommended that PTV is defined as GTV/CTV plus 2 – 5 cm margin in 3 dimensions as used in the radiation therapy center. Exception for the margin definition can be made for bone and meningeal structures which are considered anatomical barriers to tumour spread.

3.5 The radiation therapy may be carried out to a single PTV throughout or by a two phase technique reducing at 40 – 45 Gy to a smaller PTV.

3.6 It is recommended that the planning volumes are defined by each radiation therapy center prior to commencing the study.

4. Treatment planning.

4.1 Treatment planning should be performed on a planning computer and dose homogeneity within and coverage of the PTV should conform to the ICRU 50 criteria.

4.2 The aim of treatment planning is to minimize the amount of normal brain irradiated and minimize the dose to normal brain. Multiple field arrangements are preferred. Parallel opposed lateral field arrangements and whole brain radiotherapy should be avoided. The use of custom blocking is optional.

5. Dose fractionation

5.1 Dose should be prescribed according to the ICRU 50 criteria.

5.2 The total dose to the PTV should be 55 – 60 Gy in 30 – 33 daily fractions. All fields should be treated daily, Monday to Friday.

Clinical Review Section

EORTC QLQ-C30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials : _____

Your birthdate (Day, Month, Year) : _____

Today's date (Day, Month, Year) : _____

		No	Yes
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2
2.	Do you have any trouble taking a long walk?	1	2
3.	Do you have any trouble taking a short walk outside of the house?	1	2
4.	Do you have to stay in a bed or a chair for most of the day?	1	2
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2
6.	Are you limited in any way in doing either your work or doing household jobs?	1	2
7.	Are you completely unable to work at a job or to do household jobs?	1	2

During the past week:

		Not At All	A Little	Quite A Bit	Very Much
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall physical condition during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

FINAL BRAIN CANCER MODULE (BCM 20) FOR USE IN COMBINATION WITH QLQ-C30

Please indicate how much you experienced the following during the past week.

During the past week :	**Not At All**	**A Little A Bit**	**Quite Much**	**Very**
1. Did you feel uncertain about the future?				
2. Did you feel you had setbacks in your condition?				
3. Were you concerned about disruption of family life?				
4. Did you have headaches?				
5. Did your outlook on the future worsen?				
6. Did you have double vision?				
7. Was your vision blurred?				
8. Did you have difficulty reading because of your vision?				
9. Did you have seizures?				
10. Did you have weakness on one side of your body?				
11. Did you have trouble finding the right words to express yourself?				
12. Did you have difficulty speaking?				
13. Did you have trouble communicating your thoughts?				
14. Did you feel drowsy during the daytime?				
15. Did you have trouble with your coordination?				
16. Did hair loss bother you?				
17. Did itching of your skin bother you?				
18. Did you have weakness of both legs?				
19. Did you feel unsteady on your feet?				
20. Did you have trouble controlling your bladder?				

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pp. 71-81

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pp. 83-84

APPENDIX IV: Excerpts from 1996 Review of CL-0190 (Phase 3); #9003 (Phase 1)

Phase 3 Trial #CL-0190: Interstitial Chemotherapy for Malignant Glioma: A Phase 3 Placebo Controlled Study to Examine the Safety and Eficacy of GLIADEL Placed at the Time of First Surgery

Protocol CL-0190 was conducted under a foreign IND and not identified prospectively as a pivotal trial for submission with an NDA in the U.S. The NDA's submitted protocol, statistical section, and amendments as well as decisions made during the trial are not part of the Agency's records and are presented below as per applicant.

9.1 Protocol Review

- *Review of Amendments*

Amendment #1, 11/15/91 -- Sweden withdrew and was replaced with a center in Norway.
-- An upper age limit of 65 years was added.
-- Imaging was rearranged to be on day of discharge.

Amendment #2, 2/5/92 -- Randomization was changed from blocks of 10 patients per center (5 active + 5 placebo in random order) to blocks of 4 patients per center.

Comment: All patients were enrolled after both amendments.

- *Objectives*

"To determine the safety and efficacy of using GLIADEL® as adjunctive treatment with surgery and external beam radiotherapy in newly diagnosed malignant glioma patients."

Primary endpoint (per statistical section): "The primary efficacy analyses will be comparisons of survival and progression free time between the two treatment groups."

- *Study Design/Schema*

CL-0190 was a multicenter, randomized, double blind placebo-controlled phase III trial, designed to compare the safety and efficacy of interstitial BCNU chemotherapy in treatment-naive patients with malignant glioma. Patients were enrolled after malignant glioma was pathologically confirmed during surgery.

After maximal tumor resection, up to eight wafers, GLIADEL® or placebo, were placed against the resection surface.

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Eligibility Criteria:

- -- 18 to 65 years of age
- -- KPS > 60
- -- Witnessed informed consent
- -- Unilateral, unifocal tumor of > 1 cm diameter, by brain imaging. Tumor must not cross midline
- -- Confirmation of high grade glioma by frozen or squash preparation surgery

Comment: High grade glioma was defined as a grade III glioma (anaplastic astrocytoma) or IV glioma (glioblastoma multiforme) in the CRF.

Exclusion Criteria:

- -- Significant renal or hepatic disease, as determined by BUN, creatinine, SGOT, SGPT, LDH or bilirubin levels exceeding 2 X ULN of the center's normal range
- -- Concomitant life-threatening disease that would limit lifespan to within 6 months of study entry
- -- Platelets < 100,000/ml or leukocytes < 4,000/ml
- -- Pregnancy
- -- Hypersensitivity to contrast material to the extent that contrast-enhanced CT or MRI would not be obtained

- *Procedure, Treatment, and Schedule of Tests*

Randomization. Study centers received one block of 4 numbers (per amendment #2) to start and further blocks depending on accrual. When drug and placebo wafers were received from the U.S., Orion-Farmos placed a non-peelable label over the Nova Pharmaceutical label to blind the content. The labels were site-specific, and included the patient number (randomization number) and principal investigator's name.

Treatment. Following maximal tumor resection, up to eight wafers (GLIADEL® vs. polymer placebo) were to be placed in the cavity. Once adequate hemostasis was obtained, the wafers were placed to cover the entire resection surface, with overlapping permitted. Avitene, gelfoam, or surgicel could be left along the brain surface. The decompressed area could be filled with irrigation fluid prior to tight closure of the dura. "Standard methods and schedules (of radiotherapy) will be used." No systemic chemotherapy was allowed.

Schedule of Tests.

Visit # Study Day	# 0 Baseline=B	#1 D1	#2 D3	#3 Discharge=D[1]	#4 RT	#5, etc. D90, etc. q 3 mo.[2]
History/ P.E.	X					
Karnofsky PS	X			X	X	X
Neurological Exam/ MMSE	X			X	X	X
CT or MRI (w & w/o contrast)	X (within 2 wks)	X			X	X
CBC, SMA, U/A	X		X	X	X	X
Surgery/Implantation		X				
Radiation Therapy					X	

[1]Visit # is the date of discharge or day 10, whichever comes first.
[2]Followup in #8802 is q 2 months.

- *Endpoints and Statistical Analysis*

Definitions of Endpoints:

Treatment failure was defined identically to #8802, by changes on contrast-enhanced CT or MRI scan and/or the Karnofsky performance status, see pages 6-7.

(Survival was not specifically defined.)

Statistical Analysis:

The protocol states..."The maximum number of 100 patients with histologically verified malignant, primary, supratentorial Grade III-IV glioma without any previous chemotherapeutic treatment will be enrolled in the study.

The expected median survival time is 12 months after the first surgery and radiotherapy. GLIADEL is considered an effective treatment, if we shall obtain a 33% (4 months) longer median survival in comparison with placebo.

Monitoring of the results is done after every tenth event using a sequential restricted triangular stopping rule. This rule will terminate the study early, with 80% power and 5% one-sided type error rate, if we find a 33% difference in the survival time.

Primary analyses divide into three parts: assessment of demographics, efficacy and safety data. Evaluations on safety and efficacy will be based on neurological, Karnofsky, MMSE, medical events, concomitant medications, imaging results, time to treatment failure and survival data. **The primary efficacy analyses will be comparisons of survival and progression free time between the two treatment groups.**

If there is no difference between the two treatment arms after the first 100 patients, the trial will be stopped due to ethical reasons and the analysis will be done with conventional survival analysis techniques. On the other hand, if the study stops because mortalities are different, sequential analysis of survivorship will be applied."

Comment: Further details of the statistical analysis plan are not prespecified.

9.2 Results

9.2.1 Conduct of the Study

- *Early Termination.*

Patient accrual was terminated early by the sponsor, Orion-Farmos, after enrollment of 32 patients due to inadequate drug supply. The applicant, Guilford, references internal memoranda from Orion-Farmos and Nova Pharmaceutical Corp. identifying two reasons. First, Orion-Farmos, after noting three cases of infection, was concerned about the lack of documentation that wafers from lot SR042-49-7 had not been retested at intervals for sterility (subsequent testing by Orion-Farmos confirmed sterility and the incidences of

wound infection/meningitis were attributed to a single center mistakenly placing the unsterile packet in the sterile surgical field). The second reason is that lot SR042-49-10 did not pass a 6-month retest because of a "slightly low BCNU content". There was no other drug supply; the last patient treated on CL-0190 was the last patient treated with GLIADEL® on any trial until Guilford assumed manufacture, opening a Treatment IND in the U.S. in November 1995. An interim analysis of CL-0190 was performed in the Spring of 1994 after data was collected on 16 patients (analysis not provided with the NDA). On March 9, l994, Orion-Farmos notified the Finnish regulatory authorities that the study was completed December 22, l993.

- *Randomization.*

Subject ID numbers (randomization numbers) were ranked from a low of "1" to a maximum of "12" at any one center. Review of the order of these numbers showed correlation with date of surgery/wafer implantation with one exception. The Tondheim, Norway center entered the first patient with a number of "12", although drug was shipped either in a block of 10 (pre-amendment) or a block of four for the initial shipment (2 blocks of 4 for subsequent shipments). Thereafter, the numbers were consecutive and correlated in order with the date of surgery. Information on patients registered but not entered is not available (not collected).

- *Eligibility.*

All patients were considered evaluable and are included in the final analyses of safety and efficacy. The following were the protocol eligibility violations:

Reviewer Table 9

Eligibility Criterion	GLIADEL®	Placebo
Age 18 to 65	1 pt age 67	–
KPS ≥ 60	–	1 pt with KPS 40
LFTs < 2X ULN	2 pts without baseline LFTs	1 pt without baseline LFTs

- *Referee Neuropathologist.*

By protocol direction, samples of the tumors were sent to the sponsor, and then forwarded to Dr. Hannu Kalimo at the University of Turku, Finland. The referee pathologist was blinded to treatment. The local pathologist and Dr. Kalimo agreed on the diagnoses in all but one case in which an astrocytoma grade III was upgraded to GBM.

- *Quality Assurance.*

Although CL-0190 was conducted by Orion-Farmos, Guilford "has independently assessed the integrity and accuracy of the clinical data...to assure their adequacy...Audits have been conducted, including comparison of case report forms to source documents, to assess the validity of selected key data variables...In addition, quality assurance audits have been conducted at a number of participating clinical sites...to evaluate the conduct of the studies and the content of the data at these sites."

9.2.2 Enrollment, Demographics, Baseline Characteristics

- *Study Dates:*

First Patient Randomized: 3/23/92
Last Patient Randomized: 5/14/93
Date of Last Observation: 5/14/95

- *Study Centers:*

Enrollment and assignment to treatment arm per center is displayed in Reviewer Table 10, derived from Applicant's Table 4.1.

Reviewer Table 10

SITE	GLIADEL® N = 16	PLACEBO N = 16
#1 Turku, Finland	4	5
#2 Tampere, Finland	3	2
#3 Helsinki, Finland	4	5
#4 Tondheim, Norway	5	4

- *Baseline Demographics and Clinical Characteristics*

Reviewer Table 11 is a composite of Applicant's Tables 4.2, 4.5, 4.6, 4.8, 4.11, and 4.12. The only statistically significant difference between the treatment arms was tumor type. All patients randomized to placebo carried the diagnosis of GBM; however, 11/16 (69%) treated with GLIADEL® had GBM.

Reviewer Table 11: Baseline Demographics and Clinical Characteristics

	GLIADEL® (n = 16)	Placebo (n = 16)	P-value
AGE (years)			
mean (S.D.)	53.5 (9.5)	53.9 (8.0)	0.905[1]
median	56	54	
range	37-68	36-65	
GENDER			
male	88	106	0.722[1]
female			
RACE*			
KARNOFSKY PS			
40	0	1	
60	3	1	
70	5	1	
80	1	4	
90	5	7	
100	2	2	
Mean (S.D.)	78.75 (14.08)	81.94 (15.10)	0.542[2]
Median (range)	75 (60-100)	90 (40-100)	0.402[3]
HISTOLOGY (referee pathology)			0.043[1]
GBM	11 (69)	16 (100)	
AA	2 (13)	0	
Oligodendroglioma, gr-3	2 (13)	0	
Ependymoma, gr 3	1 (6)	0	
MMSE (total score)			
Mean (S.D.)	23.19 (4.59)	22.88 (4.03)	0.839[2]
Median	24.5	24.5	0.732[3]
NEURO EXAM (total score)			
Mean (S.D.)	4.31 (3.48)	3.94 (3.45)	0.762[2]
Median	4.00	4.00	0.675[3]

*Not collected on the CRF in this study
[1]Fisher's Exact Test for discrete variables; F-test from ANOVA for the continuous variables
[2]Two sample t-test for comparing means between treatment groups
[3]Wilcoxon Rank Sum test for comparing means between two treatment groups

- *Tumor Size*

The mean tumor area was 22.4 (+ 8.6) cm^2 in the GLIADEL® arm vs. 19.2 (+6.1) cm^2 in the placebo group. Median tumor areas were 20 cm^2 in both arms. Tumor volume estimates were not provided for this study because data was not available for one patient.

- *Characteristics of Surgery*

In the GLIADEL® arm, 13 patients (81%) had eight wafers implanted; in the placebo group, 10 patients (63%) received eight wafers. The least number of wafers implanted was 5 in the GLIADEL® arm and 4 in the placebo arm (Applicant's Table 4.15 which follows).

Applicant's Table 4.15: GLIADEL Dosage

Parameter	GLIADEL 3.85% [N = 16]	PLACEBO [N = 16]	P-value[a]
Number of Wafers Implanted			
Mean (S.D.)	7.6 (1.0)	6.9 (1.5)	0.176
Median	8	8	
Range	4-8	4-8	
Number of Wafers Implanted			
4 wafers	0 (0)	2 (13)	
5 wafers	1 (6)	1 (6)	
6 wafers	2 (13)	3 (19)	
7 wafers	0 (0)	0 (0)	
8 wafers	13 (81)	10 (63)	
Amount of BCNU (mg)			
Mean (S.D.)	58.23 (7.42)	N/A	
Median	61.6		
Range	38.5 - 61.6		

[a] Fisher's Exact test

Excerpts from Applicant's Table 4 below comparing additional characteristics of surgery are shown below. There were no statistically significant differences between the arms.

Applicant's Table 4.12: Characteristics of Wafer Implantation Surgery

	GLIADEL 3.85% [N = 16]	PLACEBO [N = 16]	P-value[a]
Hemisphere			1.000
Left	6 (38)	6 (38)	
Right	10 (63)	10 (63)	
Tumor Location by Lobe			0.752
Frontal	6 (38)	6 (38)	
Temporal	7 (44)	5 (31)	
Parietal	2 (13)	1 (6)	
Occipital	1 (6)	3 (19)	
Temporal / Occipital	0 (0)	1 (6)	
Duration of Anesthesia (Hours)			0.675
Mean (S.D.)	4.4 (1.3)	4.2 (1.1)	
Median	4.6	4.2	
Range	2.7 - 6.5	2.2 - 5.7	
Surgical Resection			1.000
Subtotal	14 (88)	15 (94)	
Total	1 (6)	1 (6)	
Total with Lobectomy	1 (6)	0 (0)	
Tumor Volume (cm^3)			0.640
N	15	16	
Mean (S.D.)	103.9 (92.7)	91.5 (47.8)	
Median	80	82	
Range	1.5 - 336	18.8 - 181	
% of Resection			0.756
Mean (S.D.)	79.3 (16.3)	77.4 (18.6)	
Median	80	85	
Range	40 - 100	40 - 98	

[a] P-value from Fisher's Exact Test for categorical variables, F-test for continuous variables

- *Treatment After Wafer Implantation Surgery*

Radiation Therapy. All but one patient, who died on study day 35 of a rapidly growing tumor, received post-operative radiation therapy. Applicant's Table 4 presents the mean and median doses of radiation delivered.

Applicant's Table 4.14: Radiotherapy Treatment Regimen Summary

	GLIADEL 3.85% [N = 16]	PLACEBO [N = 16]	P-value[a]
	Number (Percentage) of Patients		
Cumulative Radiotherapy (cGy)			
N	15	16	
Mean (SD)	5649.5 (333.0)	5362.9 (878.1)	0.2454
Median	5575	5403	
Range	5040 - 6000	2895 - 6400	

[a] Fisher's Exact Test

Systemic Chemotherapy. Only one patient on the placebo arm received systemic chemotherapy, two courses of procarbazine, lomustine, and vincristine.

- *Concomitant Medications*

Dexamethasone was the most commonly prescribed medication after wafer implantation. All patients received dexamethasone, methylprednisolone or betamethasone. There were no statistically significant differences between the treatment arms with respect to mean daily dose and total dose per patients for each medication.
Anticonvulsants were not commonly prescribed; 3 patients on GLIADEL® and 1 on placebo were prescribed carbamazepine.

9.2.3 Efficacy Results

Orion-Farmos, the sponsor, performed an interim analysis after the first 16 patients, the results of which have not been provided. The NDA states that..."the analysis was blinded and consisted of a few tabulations and a non-parametric analysis of survival. The treatment code for the study was unblinded on June 28, 1995."

Comment: The p-values provided by Guilford for the final reported survival analysis are unadjusted for this first look. However, since the p values are not borderline, this should not have a significant impact on the results

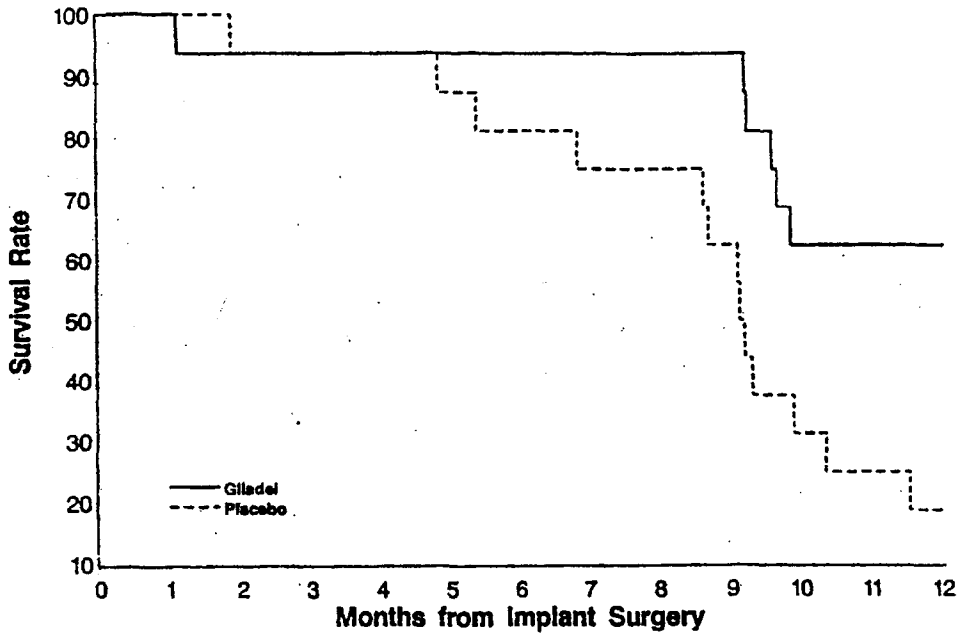
Guilford has assessed the primary endpoint of survival by survival rate at 12 months as well as Kaplan-Meier techniques at two timepoints, 12 and 24 months post wafer implantation. Guilford states, "The 12-month timepoint for the analyses was chosen because 12 months was given in the protocol as the expected median survival in the placebo treatment group, and was used as the basis for the protocol's power calculation....The 24-month timepoint for the analyses was chosen because the maximum duration of follow-up for all patients was 24 months." In addition to survival, the protocol identified a second primary endpoint as the progression-free interval.

- *Twelve-Month Outcomes*

Mortality Rate. Six patients on GLIADEL® and 13 on placebo died by 12 months after wafer implantation (p = 0.029, Fisher's exact test), leaving 10 alive on GLIADEL® and 3 alive on placebo.

Survival. The twelve-month Kaplan-Meier survival curve by treatment arm is shown in Applicant's Figure 2.

FIGURE 2: 12-Month Kaplan-Meier Survival Curves -- All Patients



Cumulative mortality through 12 months shows a highly significantly difference between the arms, with a lower mortality for the GLIADEL® arm with a log-rank p = 0.0087 and a Gehan's generalized Wilcoxon p = 0.0105.

Twelve-Month Survival Adjusted for Prognostic Factors. Eight variables were selected as being of potential clinical importance. Of the eight factors evaluated by univariate regression, three were identified as statistically significant as defined by a P < 0.15 (Applicant's Table 4.20, p.34).

Applicant's Table 4.19: Potential Prognostic Factors for Overall Patient Survival (Univariate Cox Regression) -- All Patients

Prognostic Factor	Risk Ratio	95% Confidence Limits Lower	Upper	P-value*
GBM Patients vs. Non-GBM Patients	4.715	1.092	20.35	**0.0377**
Karnofsky Score->70 vs. 70	0.723	0.327	1.597	0.4226
75% Resection vs. <75% Resection	0.941	0.419	2.113	0.8824
Age (per Decade)	1.826	1.131	2.950	**0.0138**
Male vs. Female Patients	1.370	0.629	2.987	0.4280
MMSE Scores Median	0.377	0.170	0.833	**0.0159**
Prior Seizures vs. None	0.774	0.309	1.938	0.5845
Number of Wafers 6 vs. >6	1.037	0.449	2.395	0.9328

*Wald Chi-Square test; P-values 0.15 appear in bold-face type

Comment: The NDA lacks a discussion of choice of 8 factors for the Finnish study vs. 15 for the North American Study or for 8 vs. generally accepted prognostic factors in newly diagnosed patients. No new factors are added; some deletions apply to the relapsed setting only, e.g., radiation, prior chemotherapy, years from first surgery, resection vs. biopsy at first surgery, and prior brachytherapy vs. none; information on race was not collected; the remaining two deletions were prior convulsions vs. none and prior steroid use vs. none. KPS, generally accepted as an important prognostic factor in newly diagnoses patients, was not seen to be statistically significant in the applicant's analysis. However, it was found to be significant in analyses performed by the FDA's Statistical Reviewer.

After adjustment for prognostic factors, GLIADEL® produced a statistically significant reduction in mortality compared to placebo. For all patients, the risk ratio was 0.154 (p=0.0010) and 0.179 for all patients stratified by tumor type (p=0.0038). See Applicant's Table 4.20.

Applicant Table 4.20: 12-Month Treatment Effect Adjusted for Prognostic Factors -- All Patients

Prognostic Factor	Risk Ratio	95% Confidence Limits Lower	Upper	P-value[a]
All Patients				
GLIADEL 3.85% vs. PLACEBO	0.154	0.051	0.467	0.0010
Age (per decade)	2.302	1.089	4.864	0.0290
Mini-Mental Scores Median	0.207	0.070	0.613	0.0044
All Patients Stratified by Tumor Type				
GLIADEL 3.85% vs. PLACEBO	0.179	0.056	0.574	0.0038
Age (per decade)	2.266	1.075	4.777	0.0315
Mini-Mental Scores Median	0.218	0.074	0.645	0.0059

[a] Wald Chi-Square test

• *Overall Survival*

As of the data cutoff date of 5/14/95 (observation period up to 24 months), six patients were alive: 5 of 16 (31%) who had received GLIADEL® and 1 of 16 (6%) who had received placebo (p = 0.172, Fisher's exact test). The median duration of survival was 13.37 months (95% CI: 9.66 - inestimable maximum) and 9.17 months (95% CI: 8.64 - 10.33) in the GLIADEL® and placebo groups, respectively.

The Kaplan-Meier curve for 24 months is shown below in Applicant's Fig. 3.

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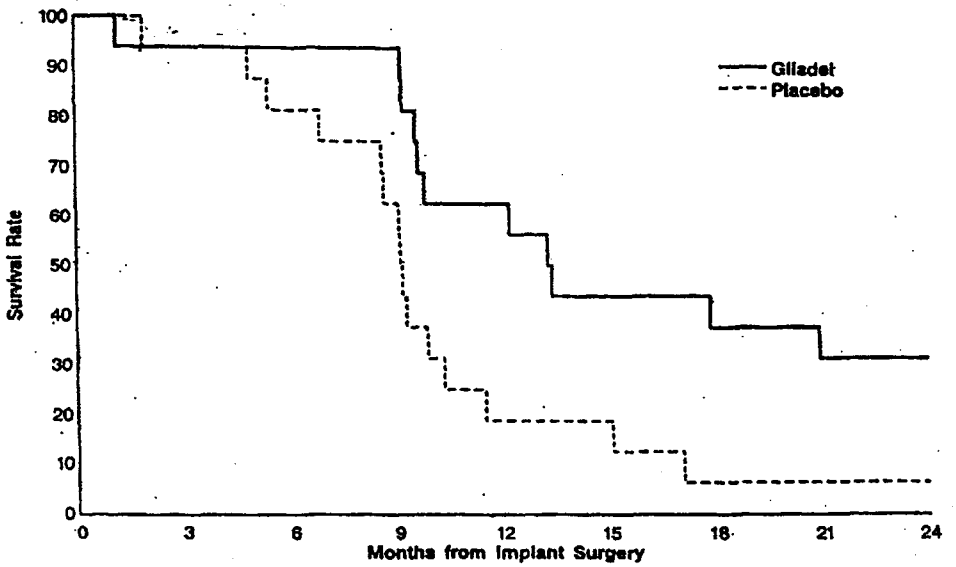
Overall K-M Survival Curves for All Patients
by Treatment Group (n = 32)



Unadjusted		Adjusted	Unadjusted		Adjusted
logrank	GW**	Cox	logrank	GW*	Cox
p=.0087	p=.0105	p=.0010	p=.012	p=.011	p=.0005

*Only four patients (1 Gliadel, 3 Placebo) had died by 6 months.
**Gehan's generalized Wilcoxon test

Overall Survival Adjusted for Prognostic Factors. After adjustment for prognostic factors, GLIADEL® produced significant reductions in overall survival. The risk ratios were 0.177 for all patients (p=0.0005) and 0.214 for all patients stratified by tumor type (p=0.0029), as shown in Applicant's Table 4.21.

Applicant Table 4.21: Overall Treatment Effect Adjusted for Prognostic Factors -- All Patients All Patients

Prognostic Factor	Risk Ratio	95% Confidence Limits		
		Lower	Upper	P-value[a]
GLIADEL 3.85% vs. PLACEBO	0.177	0.067	0.468	0.0005
Age (per decade)	2.248	1.208	4.182	0.0106
Mini-Mental Scores Median	0.250	0.100	0.626	0.0031
All Patients Stratified by Tumor Type				
GLIADEL 3.85% vs. PLACEBO	0.214	0.078	0.590	0.0029
Age (per decade)	2.219	1.193	4.131	0.0119
Mini-Mental Scores Median	0.241	0.094	0.619	0.0031

[a] Wald Chi-square test

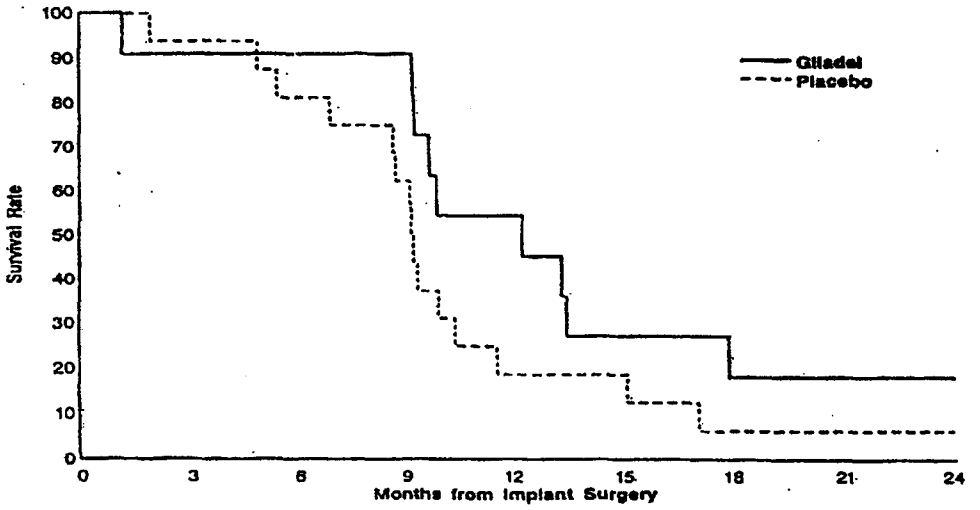
- *Subgroup Analysis: GBM Patients*

Twenty-seven of 32 patients carried the diagnosis of GBM: 11/16 (69%) in the GLIADEL® arm and 16/16 (100%) in the placebo arm. Twelve and 24-month survival for all patients and for GBM vs. non-GBM patients is shown in Reviewer Table 12.

Reviewer Table 12: Survival Rates for All Patients and by Tumor Type

	12-Month		Overall (upto 24months)	
	GLIADEL®	Placebo	GLIADEL®	Placebo
All Patients (n = 32)	n = 16	n = 16	n = 16	n = 16
Dead	6	13	11	15
Alive	10	3	5	1
Fisher's Exact Test	p = 0.029		p = 0.172	
GBM (n = 27)	n = 11	n = 16	n = 11	n = 16
Dead	5	13	9	15
Alive	6	3	2	1
Fisher's Exact Test	p = 0.097		p = 0.5487	
Non-GBM (n = 5)	n = 5	n = 0	n = 5	n = 0
Dead	1		2	
Alive	4		3	

Applicant's Fig. 5 shows an overall Kaplan-Meier survival curve for GBM patients only. The median survival duration was 12.3 months (95% CI: 9.23 - 17.87 mo.) for patients treated with GLIADEL® and 9.2 months (95% CI: 8.64 - 10.35 mo.) for patients on placebo. The difference in 12-month and 24-month survival is shown in below.



12 Months			Overall (up to 24 months) Gliadel 12.3 mo. Placebo 9.2 mo.		
Unadjusted		Adjusted	Unadjusted		Adjusted
logrank	GW*	Cox	logrank	GW*	Cox
p=.059	p=.070	p=.0072	p=.126	p=.093	p=.0035

*Gehan's generalized Wilcoxon test

- *Time to Treatment Failure (All Patients)*

Time to treatment failure was measured from the time of wafer implantation surgery to the earliest point that treatment failure was declared, using protocol specified criteria. Twelve patients (75%) in the GLIADEL® arm and 14 (88%) in the placebo arm were considered to have failure of treatment. The median time to treatment failure for patients on GLIADEL® was 7.79 months (95% CI: 3.22 - 9.66 mo.) vs. 6.67 months (95% CI: 3.02 - 9.86 mo.), p = 0.4668 (log-rank) or p = 0.9635 (Wilcoxon).

- *Secondary Efficacy Analyses*

The applicant found no significant differences between the treatment arms with regard to change in mean KPS or mini-mental status exam from baseline. See Statistical Review for further details.

- *Drug-Demographic Interactions*

The applicant did not provide analyses for a significant treatment by age or gender interaction for this study. Information on race was not collected on the CRF. See the Statistical Review for these analyses; an interaction with gender is seen, with survival in women greater than in men; however, these data should be interpreted cautiously given the small numbers of patients available for analysis.

9.2.4 Safety Results

Adverse events were collected on the CRF by asking the investigator to (1) list the AE; (2) judge severity on a four point scale of mild, moderate, severe, life-threatening; (3) judge its relationship to treatment as not assessable, none, remote, possible, or probable (i.e., no "definite" category); (4) provide start and end dates; and (5) describe outcome. Specific A.E.s were not solicited.

The NDA states..."Pre-existing medical conditions that did not worsen in severity during the study period were not considered treatment-emergent adverse events. Multiple events with the same term, reported by one patient during the study period but having different severities, were treated as a single event of the worst recorded severity..."

- *Deaths*

Applicant Table 4.34: Summary of Cause of Death and Relationship of Death to Study Medication

	GLIADEL 3.85% [N = 11]	PLACEBO [N = 15]	P-value
	Number (Percentage) of Patients		
Cause of Death			0.213
Brain Tumor	10 (91)	13 (87)	
Other	0 (0)	1 (7)*	
Not Assessable	1 (9)	1 (7)	
Relationship of Death to Study Medication[a]			0.083
Probable	0 (0)	0 (0)	
Possible	0 (0)	0 (0)	
Remote	0 (0)	1 (7)	
None	10 (91)	14 (93)	

*Death due to pulmonary embolus

Comment: Deaths were not clustered in the perioperative period, see K-M curves above.

- *Treatment Withdrawal Due to Toxicity*

There were no reports of wafer removal in this study.

- *All Treatment-Emergent A.E.s by Body System*

Due to the limited number of patients on this trial, all treatment-emergent A.E.s (rather than A.E.s with > 5% incidence) are presented (Applicant's Table 4.35 on the following page). Twice as many events (31 vs. 16) were reported in the GLIADEL® arm compared to the placebo arm. The body system that had the most number of A.E.s was the nervous system, with 19 reported in patients treated with GLIADEL® and 9 in patients who received placebo. The difference in the number of patients with A.E.s (vs. number of A.E.s) between the arms was not statistically significant.

Applicant Table 4.35: All Treatment-Emergent Adverse Events Summarized by Body System

	GLIADEL 3.85% [N = 16]		PLACEBO [N = 16]		P-value[a]
Body System[b]	Number of Occurrences	Number (Percentage) of Patients	Number of Occurrences	Number (Percentage) of Patients	
Body as a Whole	2	2 (13)	2	2 (13)	1.000
Cardiovascular	4	3 (19)	2	1 (6)	0.600
Endocrine	1	1 (6)	0	0 (0)	1.000
Hemic and Lymphatic	0	0 (0)	2	2 (13)	0.484
Metabolic and Nutritional	1	1 (6)	0	0 (0)	1.000
Musculoskeletal	1	1 (6)	0	0 (0)	1.000
Nervous	19	10 (63)	9	6 (38)	0.289
Respiratory	0	0 (0)	1	1 (6)	1.000
Special Senses	2	2 (13)	0	0 (0)	0.484
Uncertain	1	1 (6)	0	0 (0)	1.000
Total	31 events were reported by 12 patients		16 events were reported by 9 patients		0.458

[a] Fisher Exact test

[b] The investigator verbatim term* was used in place of a COSTART preferred term when the verbatim term was judged to be so nonspecific that assignment to an appropriate COSTART preferred term could not be made unambiguously, or when the most appropriate COSTART preferred term was either misleading, so general as to be uninformative, or too specific to be accurate. If a patient had more than one instance within a category, only the instance with the greatest severity is listed.

- *Frequently Reported Treatment-Emergent A.E.s*

A.E.s reported in > 2 patients are displayed in Applicant Table 4.36 below.

Applicant Table 4.36: Treatment-Emergent Adverse Events Occurring in Two or More Patients in Either Treatment Group by Body System and COSTART Term

Body System/Adverse Event[b]	GLIADEL 3.85% [N = 16]	PLACEBO [N = 16]	P-value[a]
	Number (Percentage) of Patients		
Nervous			
Aphasia	2 (13)	1 (6)	1.000
Convulsion	3 (19)	2 (13)	1.000
Hemiplegia	6 (38)	4 (25)	0.704
Special Senses			
Visual Field Defect	2 (13)	0 (0)	0.484

[a] Fisher's Exact
[b] The investigator verbatim term* was used in place of a COSTART preferred term when the verbatim term was judged to be so nonspecific that assignment to an appropriate COSTART preferred term could not be made unambiguously, or when the most appropriate COSTART preferred term was either misleading, so general as to be uninformative, or too specific to be accurate.

- *Severity of Treatment-Emergent A.E.s*

In the GLIADEL® arm, 2 A.E.s (P.E. and stupor) were rated by the investigator as life-threatening and 17 severe compared to no life-threatening and 7 severe A.E.s in the placebo arm. Applicant's Table 4.38 tabulates these A.E.s by patient.

Applicant Table 4.38: Life-threatening and Severe Treatment Emergent Adverse Events by Treatment Group and by Body System and COSTART Term

Body System/ Adverse Event[a]	GLIADEL 3.85% [N = 16]	PLACEBO [N = 16]
	Number (Percentage) of Patients	
Cardiovascular		
Pulmonary Embolus	1[b]	1
Thrombophlebitis	1	1[c]
Metabolic and Nutritional		
Diabetes Mellitus	1	0
Musculoskeletal		
Spondylitis VIII-IX*	1	0
Nervous		
Aphasia	2	0
Brain Edema	1	0
Convulsion	1	0
Depression	1	0
Hemiplegia	5	4
Hydrocephalus	1	0
Meningitis	1	1
Stupor	1[b]	0
Special Senses		
Visual Field Defect	1	0
Uncertain		
Rapid Deterioration*	1	0

[a] The investigator verbatim term* was used in place of a COSTART preferred term when the verbatim term was judged to be so nonspecific that assignment to an appropriate COSTART preferred term could not be made unambiguously, or when the most appropriate COSTART preferred term was either misleading, so general as to be uninformative, or too specific to be accurate. If a patient had more than 1 instance within a category, only the instance with the greatest severity is listed.
[b] Life-threatening treatment-emergent adverse event; all other events were severe.
[c] FDA reviewer addition to applicant table to correct typographical error

- *Treatment-Related, Treatment-Emergent A.E.s*

There were no A.E.s that the investigator rated as definitely (not listed as an option on the CRF) or probably related to treatment. The four that were listed as possibly related were infection, fever and headache in 3 patients on GLIADEL® and infection in one patient who received placebo wafer.

- *Clinically Significant A.E.s with Possible Causal Relationship*

Convulsion. There were no statistically signiciant differences in convulsions between the treatment arms. Three patients in the GLIADEL® arm and 2 patients who received placebo had treatment-emergent convulsions. The median time to onset of treatment-emergent convulsions was 207 days in the GLIADEL® group and 61 days in the placebo group.

Healing Abnormality. One patient who received placebo wafer had a CSF leak from the nose, judged to be of mild severity by the investigator.

Infection. Four serious infections occurred, 2 on GLIADEL® (wound infection and meningitis) and 2 on placebo (wound infection and CSF leak/meningitis).

Hydrocephalus/cerebral edema. One patient treated with GLIADEL® had meningitis diagnosed on day 6 and subsequently developed hydrocephalus by day 36. Another patient who received GLIADEL® experienced severe postoperative cerebral edema on day 1.

10.2 #9003: Interstitial Chemotherapy for Malignant Glioma: A Pilot Study to Examine the Safety of GLIADEL® Placed at the Time of First Surgery

#9003 was a multicenter, open-label safety pilot in a maximum of 30 patients in whom GLIADEL® would be implanted during initial resection, followed by standard external beam radiation therapy.

10.2.1 Protocol Review

Objective: "To determine the safety of GLIADEL® as an adjunctive treatment with surgery and external beam radiotherapy in newly diagnosed malignant glioma patients."

Eligibility/Exclusion Criteria: Patients with unifocal, unilateral malignant glioma at least 1.0 cm diameter, at least 18 years of age and with a KPS of > 60. *(Criteria matched the other study enrolling initially diagnosed patients, #CL-0190, with the exception that #9003 did not have an upper age limit.)*

Procedure: Up to eight wafers of GLIADEL® were to be placed in the resection cavity. Sample slides were to be sent to the referee pathologist, Dr. Peter Burger at Duke University. XRT was required to be consistent with "standard methods and schedules," starting three weeks post surgery.

Baseline and Followup Examinations: Physical examination and KPS, MMSE, CT or MRI, and laboratory tests. *(This matched #CL-0190 with the exception that followup was every 2 months starting with the date of surgery.)*

Statistical section: The protocol states that "in order to have a sufficient number of evaluable patients entered to make reasonable conclusions regarding safety, the study will be initiated at three centers. Each center will have the potential to enroll ten patients; however, when any one center reaches ten patients, study entry will be terminated at the remaining centers." All patients were to be evaluated for safety 6 months after radiation therapy for a final study evaluation but followed for a maximum of 2 years postop. Time to treatment failure was defined identically to the controlled studies although this was not a protocol objective. Adverse events were described by severity (mild, moderate or severe), relation to GLIADEL®, whether intervention was required, and information on the outcome (recovered, ongoing, died, lost to followup).

Amendments: **Amendment #1** dated August 6, 1990 prohibited adjuvant systemic BCNU and provided criteria for early cessation of the study based on toxicity. Entry onto the study would cease until a thorough investigation had been completed in the following circumstances: (1) if two patients exhibit a decrement in the neurological examination score of > 2 points (scale 0-4) in > 5 of the 11 categories within two weeks of initiation of XRT that is not attributable to tumor progression; or, (2) death of two patients within one month of initiation of XRT not attributable to progressive disease. **Amendment #2** dated October 3, l990 expanded the critical timeframe for noting changes in the neurological evaluation from within two weeks of XRT initiation to during XRT and within two weeks from the conclusion of XRT.

10.2.2 Results

Twenty two patients were enrolled at three institutions (JHOC 10, Columbia Presbyterian Medical Center 6, Charlotte Memorial Hospital 6) from July 5, l990 to August 14, l991. Seven patients were female (32%) and 15 male (68%) with a median age of 60 (range 40-86). Referee and institutional pathologists agreed that 20 patients had a glioblastoma multiforme and one had anaplastic astrocytoma (the diagnosis of one patient is missing). The median KPS was 85 (range 40-100).Eighteen patients had 8 wafers implanted; four had 7. Three patients (14%) had total resections, 5 patients (23%) had total resection by lobectomy, and 14 patients (64%) had subtotal resections. Twenty-one of the 22

patients received XRT (median dose 5816 cGy, range 4500-8280); followup on the remaining patient is unclear.

- *Deaths.* As of last followup November 10, 1995, 19/22 (86%) of patients had died, with a median survival of 41.7 weeks (95% CI 31.9 to 54.0 weeks). The earliest death occurred 132 days after surgery. The 6-, 12-, and 24-month survival rates were 82%, 36% and 14%, respectively. Deaths were secondary to brain tumor recurrence with the exception of one patient who died of a concurrent intra-abdominal malignant lymphoma, for which treatment was refused. None of the deaths occurred within 2 weeks of the conclusion of XRT.

- *Adverse Events.* Treatment emergent A.E.s experienced by > 2 patients were convulsion, penumonia, necrosis, and UTI; see Reviewer Table 15 derived from the data listings. The most frequent and serious treatment-emergent A.E.s were related to the nervous system. Sixteen patients (73%) experienced one or more A.E.s related to the nervous system and 7 (32%) experienced one or more events elsewhere in the body. Seventeen patients (29%) had an A.E. rated as severe; however, only the events in the central nervous system had more than one patient with a severe A.E. There were no A.E.s considered by the investigator to be definitely-related to study drug.

Reviewer Table 15

Body System	# Patients (%). with A.E.	# Patients (%) with Severe A.D.	Treatment-Related		
			Probable	Possible	Unrelated
Nervous					
Convulsion	12 (54)	3 (14)	0 (0)	2 (9)	9 (41)
Necrosis	3 (14)	1 (5)	1 (5)	2 (9)	0 (0)
Edema	2 (9)	1 (5)	0 (0)	2 (9)	0 (0)
Confusion, Coma,	4 (18)	4 (18)	0 (0)	1 (5)	3 (14)
Neuro	1 (4)	0 (0)	0 (0)	1 (5)	0 (0)
Infection					
Pneumonia	4 (18)	1 (5)			4 (18)
UTI	3 (14)	0 (0)	-	-	3 (14)
Sepsis	1 (5)	1 (5)			1 (5)
Healing Abnormality	1 (5)				1 (5)
DVT	2 (9)	1 (5)	-	-	2 (9)
Metabolic					
Dehydration	1 (5)	1 (5)	-	-	1 (5)
Digestive					
GI hemorrhage	1 (5)	1 (5)	-	-	1 (5)
Vomiting	1 (5)	1 (5)			1 (5)
Other					
Dilantin Toxicity	2 (9)	1 (5)	-	-	2 (9)
2nd malignancy	1 (5)	1 (5)			1 (5)

Of the 11 patients with convulsions, the outcomes of six were considered "recovered" and of 5 to be "ongoing." Two patients had convulsion within the first month of surgery; one had a convulsion 10 days postop requiring intubation. The average time from surgery to convulsion was 2.7 months. Two of the 11 patients had convulsion listed as a baseline medical condition.

- *Reoperation.* Nine of 19 patients underwent reoperation. All patients had completed a course of EBRT.

Comment: In study CL-0190 in which initially diagnosed patients underwent wafer plus XRT, no patient underwent second operation, perhaps due to patterns of practice between the countries.

10.2.3 Conclusion

Toxicity was considered acceptable in this patient population. No dose-limiting toxicities as defined in the protocol were seen.

Reviewer Summary from 1996 NDA 20,637 (Gliadel)

Trial 8802 appears to be an adequate and well-controlled study. The treatment effect on overall survival for patients with high grade gliomas does not reach statistical significance. The largest treatment difference is seen at six months, which does not appear to be a surrogate for overall survival in a population with a median survival of less than a year. The robustness of such a six-month endpoint is weakened by lack of a correlation with improvement in QoL parameters, e.g., KPS, MMSE, and wide variability of results depending on adjustment for prognostic factors, which are not generally accepted in this recurrent patient population. However, the robustness improves for the subgroup of patients with glioblastoma multiforme, where the survival advantage for patients treated with Gliadel® is seen not only at six-months, but is reflected in overall survival in an unadjusted analysis (Gehan's generalized Wilcoxon test), both specified in the protocol.

Study CL-0190, which had not been discussed with the FDA prior to NDA submission, meets many of the criteria for an adequate and well-controlled study; however, the early closure of the trial and limited patient numbers are serious flaws. Even accepting the early closure as unbiased, i.e., no further study drug, only 32 patients were entered thereby possibly inflating any proposed treatment effect. Although a statistically significant treatment effect on survival is seen when all patients are analyzed, clinical trials in malignant glioma are typically conducted separately for AA vs GBM or the trial provides for stratification on the basis of histology due to inherent differences in outcomes. In CL-0190, the 5 patients with the more favorable histology all randomized to Gliadel®. When these patients are excluded in a subgroup analysis for GBM, the statistically significant difference between the treatment groups is lost.

An argument could be made that it would be biologically plausable for a treatment effect in relapsed patients to convey to newly diagnosed patients. However, the results from #8802 might not be considered robust, with variable results depending on the type of analysis and the statistical signficance depending on conducting subgroup analysis or a Cox Regression based on prognostic factors not accepted in the relapsed population. Furthermore, it is not certain that relapsed GBM is more resistant than newly diagnosed GBM, i.e., since the tumor presents as resistant initially, results may not be more dramatic in patients who have not yet received chemotherapy. Other concerns raised at the ODAC meeting were lack of knowledge of chronic toxicity, e.g., dementia which has resulted from other local treatment such as intraarterial chemotherapy to the brain or any effect related to nonbiodegradable wafers, both of which may be more relevant issues for the newly diagnosed patient. Lastly, intravenous BCNU is an available alternative while definitive trials with Gliadel® in the newly diagnosed patient are being conducted.

The toxicity profile of Gliadel® in relapsed patients is consistent with a regional delivery system at the time of operation. The primary toxicities in relapsed patients were related to neurologic function and wound healing/infection. The toxicities could be considered acceptable given the clinical setting; however, it should be noted that the incidence may

be underestimated since the control arm was a foreign body. The biodegradability of the wafers appears to be variable, the clinical significance of which is not yet known.

1 PAGE(S) REMOVED. SEE THE ADVISORY COMMITTEE MEETING INFORMATION LOCATED ON THE FDA WEBSITE BELOW:

http://www.fda.gov/ohrms/dockets/ac/cder01.htm#Oncologic

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