CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-637/S-016

Medical Review(s)

NDA # 20,637

GLIADEL® Wafer
(Polifeprosan 20 with Carmustine Implant)

Submission Date: April 6, 2001

ODAC: December 6, 2001

Medical Reviewer: Alla Shapiro, M.D.

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

Applicant: Guilford Pharmaceuticals

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Executive Summary

I. Recommendations

The current sNDA presents the results of a multicenter, randomized, double-blinded, placebo-controlled clinical trial (T-301) in patients with newly diagnosed malignant glioma. The primary medical and statistical reviewers recommend against marketing approval of GLIADEL wafer for the new indication of treatment of newly diagnosed malignant glioma.

A single study (T-301) was submitted in support of marketing approval in this sNDA. A total of 240 patients with newly diagnosed malignant gliomas (120 in each treatment group) were enrolled. The T-301 study demonstrated an increased median survival in the intent to treat (ITT) population in the GLIADEL group of 13.9 months (12.1- 15.3) compared to placebo 11.6 months (10.2 – 12.6). Statistical significance is not reached by the protocol-specified analysis (p=0.08, non-stratified log-rank test). Secondary endpoints for this study, survival in the glioblastoma multiforme (GBM) population, 1-year survival, progression free survival (PFS), time to Karnofsky Performance Status (KPS) and neurological deterioration, and Quality of Life (QoL) were not statistically significant either in the ITT or in the GBM population.

The toxicity profile of the GLIADEL wafer is acceptable in patients with newly diagnosed malignant gliomas. The incidence of intracranial hypertension and CSF leaks was greater in the GLIADEL group. However, the placebo wafer as the control arm does not exclude the possibility of underestimation of the rate of local complications from the wafer implantation.

There are no Phase 4 commitments under consideration.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

GLIADEL® wafer is a biodegradable implant, composed of a copolymer matrix (Polifeprosan 20) with carmustine (BCNU). GLIADEL wafer is designed to deliver carmustine directly into the surgical cavity at the time of tumor resection.

Prior approval for the use of the GLIADEL wafer was based on a survival benefit in a subgroup of patients with recurrent GBM. In a randomized, multicentral, placebo-controlled trial (#8802), 222 patients with recurrent malignant gliomas

(anaplastic astrocytoma, anaplastic oligodendroglioma, and GBM) were treated with GLIADEL or placebo wafer at the time of reoperation for disease progression. The treatment effect on overall survival in all patients with high grade malignant glioma did not reach statistical significance (p=0.29 and p=0.11 by the log-rank and Wilcoxon tests, respectively). The largest treatment differences were noticed at six months (40% mortality rate in the GLIADEL arm vs. 52.7% on placebo) which did not carry over to overall survival.

Sixty five percent of patients in this study carried the diagnosis of GBM. A subgroup analysis showed that in patients with GBM, median survival in the GLIADEL group was statistically significant (p=0.021) compare to the placebo.

Study CL-190, a small (32 patients) study in newly diagnosed malignant gliomas, was also submitted in 1996. A statistically significant treatment effect on survival was seen in the ITT population, however, the treatment arm was imbalanced in that all 5 patients with the more favorable histology (anaplastic astrocytoma, anaplastic oligodendroglioma and ependymoma) were randomized to GLIADEL. The trend for improvement in survival for patients with GBM was not statistically significant.

This sNDA contains data from one randomized, double-blinded, multicenter, placebo-controlled trial in a total of 240 patients with newly diagnosed malignant gliomas (T-301). After maximal resection of the tumor, 120 patients were treated with GLIADEL and 120 received placebo implant. Subsequently, all patients received limited field radiation therapy. The primary endpoint was survival in the intent to treat (ITT) population.

B. Efficacy

Survival in the ITT population was the primary endpoint in this study. Survival in the GBM subgroup, 1-year survival, progression free survival, time to Karnofsky Performance Status (KPS) and time to neurological deterioration along with the Quality of Life (QoL) were secondary endpoints.

Survival in the ITT population did not reach statistical significance (p=0.08) using the non-stratified log-rank test prespecified in the protocol and Statistical Analysis Plan (SAP). Survival did not reach statistical significance (p=0.20) in newly diagnosed GBM, the subgroup of main interest for the treatment effect.

FDA performed an exploratory analysis of survival using the histological diagnoses provided by the central pathologist. In this analysis, the p-value also did not reach statistical significance (P=0.15 and p=0.40 for ITT population and GBM subgroup, respectively).

Other secondary efficacy endpoints (1-year survival, progression free survival, time to KPS and time to neurological deterioration along with QoL), in both the ITT population and GBM subgroup are not significant by non-stratified and stratified log-rank tests. Time to KPS and neurological deterioration reached statistical significance in the sponsor's analysis with death counted as an event. In the analysis performed by the FDA, where death was censored rather than counted as an event, statistical significance was not apparent.

C. Safety

Two hundred forty patients (120 in each treatment group) were exposed to GLIADEL or placebo wafer in T-301. Follow-up ranged from 12 to 30 months. Forty-four patients (36.7%) in the GLIADEL group and 47 patients (39.2%) in the placebo group received the maximum of eight wafers implanted.

The toxicity profile of GLIADEL in patients with newly diagnosed malignant gliomas is consistent with a regional delivery system at the time of operation. The primary toxicities were related to neurologic function. There were numerical differences in incidence of intracranial hypertension (ICH) and cerebrospinal fluid (CSF) leak. Other local complications, such as cerebral edema, brain abscesses, cerebral hemorrhages and brain cyst formation appear to be balanced in both arms. There were 3 deaths from the cerebral hemorrhages within the first 30 days after surgery in the GLIADEL group that could possibly related to therapy.

D. Dosing

The dose and schedule used in T-301 is consistent with the labeled use. 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 and whether the wafers had been broken in more that 2 pieces, in which case they were to be discarded. Each GLIADEL wafer contains 7.7mg of BCNU.

E. 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).. It should be noted that the eligibility criteria had a cut-off age for the patients entering the study of 65 years.

There were no specific studies designed to investigate the efficacy or safety of GLIADEL wafer in **hepatically- or renally-impared** individuals. Carmustine concentrations delivered by GLIADEL in human brain tissue have not been determined. Plasma levels of carmustine after GLIADEL wafer implant were not determined.

The applicant does not seek **pediatric indications** and the 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.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

- Name of drug:

  Established: Polifeprosan 20 with Carmustine Implant
  Proprietary: GLIADEL® Wafer

- Applicant:

  Guilford Pharmaceuticals Inc.
  6611Tributary Street
  Baltimore, MD 21224

- Drug Class: Antineoplastic

- Indication:

Current: "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."

Proposed: "GLIADEL wafer is indicated for use as a treatment to significantly prolong survival and maintain overall function (as measured by preservation of Karnofsky Performance Status) and neurological function in patients with malignant glioma undergoing primary and/or recurrent surgical resection."

- Dosage and Administration

Excerpted from the current label (no changes proposed): "Each GLIADEL wafer contains 7.7 mg of carmustine, resulting in a dose of 61.6 mg when eight wafers are implanted. 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...

Once the tumor is resected, tumor pathology is confirmed, and hemostasis is obtained, up to eight GLIADEL wafers ...may be placed to cover as much of the resection cavity as possible. Slight overlapping of the wafers is acceptable. Wafers broken in half may be used, but wafers broken in more than two pieces should be discarded in a biohazard container. Oxidized

regenerated cellulose (Surgicel®) may be placed over the wafers to secure them against the cavity surface. After placement of the wafers, the resection cavity should be irrigated and the dura closed in a water tight fashion."

- How Supplied

Excerpted from the current label: "GLIADEL is available in a single dose treatment box containing eight individually pouched wafers. Each wafer contains 7.7 mg of carmustine and is packaged in two aluminum foil laminate pouches. The inner pouch is sterile and is designed to maintain product sterility and protect the product from moisture. The outer pouch is a peelable overwrap. The outside surface of the outer pouch is not sterile."

B. State of Armamentarium for Indication(s)

The estimated annual incidence of newly diagnosed primary brain neoplasms in adults is roughly 7 to 17 per 100,000 per year (Smirniotopoulos, 1999). Gliomas are by far the largest category of primary neoplasms: 50% are high grade. Glioblastoma multiforme (GBM) accounts for 80% of adult high grade gliomas and anaplastic astrocytoma for 20% (Davis, 2000).

The revised World Health Organization (WHO) nomenclature classifies low grade histologies as anaplastic oligodendrogliomas (15%), meningiomas (20%), ependymoma (3%), and embryonal tumors, such as medulloblastoma, PNET, and mixed glial tumors (11%) (Cohen. 1999).

The standard treatment of newly diagnosed gliomas consists of surgery followed by cranial radiation and, at times, adjuvant systemic chemotherapy. The median survival after surgery followed by radiation therapy in patients with GBM is about 13 months (Shinoda, 2001).

Randomized trials of radiation therapy have consistently demonstrated statistically significant improvement in survival of about 16 to 18 weeks over surgery alone (Walker, 1980). Randomized controlled trials of systemic chemotherapy have not demonstrated a consistent improvement in survival in GBM. Prospective randomized Brain Tumor Cooperative Group trials comparing patients with high grade gliomas (anaplastic astrocytoma and GBM) who received radiation therapy with and without BCNU have mixed results. A 1993 meta-analysis of the major adjuvant therapy trials showed that there was a 10% increase in survival at 1 year and an 8.6% increase at 2 years for patients treated with both chemotherapy and radiation therapy as opposed to those treated with radiation therapy alone (Fine, 1993). It has been argued that this improvement is confined to the subgroup of patients with anaplastic astrocytoma.

For patients with anaplastic oligodendroglioma, adjuvant therapy with PCV (procarbazine, CCNU, vincristine) may be considered standard adjuvant therapy (Prados, 1999). However, a recent analysis by the Radiation Therapy Oncology Group concluded that for newly diagnosed anaplastic atrocytoma, the PCV regimen does not confer a survival advantage over BCNU (Prados. 1998).

C. Other Relevant Information

GLIADEL has received marketing approval for patients with *recurrent* malignant gliomas or recurrent GBM in the following countries as of December 2000: Canada, France, Argentina, Austria, Brazil, Chile, Columbia, Germany, Greece, Hong Kong, Israel, Ireland, Luxembourg, Malaysia, The Netherlands, New Zealand, Peru, Portugal, Singapore, South Africa, South Korea, Spain, U.K. and Uruguay. The sponsor states that "product is not yet commercially available in all of these countries."

GLIADEL has received marketing approval for the treatment of *newly diagnosed* malignant gliomas in Canada based on the data submitted to the FDA in 1996. See Reviewer Table 1 in Section IVB.

D. Important Issues with Pharmacologically Related Agents

Nitrosourea (BCNU, carmustine), which is the active ingredient of the GLIADEL wafer, has the same features as classic alkylating agents. The major dose-limiting toxicity is pulmonary, predominantly fibrosis (O'Driscol et al., 1990). The most consistently noted toxicity is delayed myelosuppression, which reaches a nadir 4 to 6 weeks after treatment and can prevent subsequent cycles of chemotherapy by 6 to 8 weeks (DeVita, 1993). High dose systemic BCNU is associated with hepatic necrosis, encephalopathy, and cardiac necrosis (Phillips et al., 1983).

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

This document represents a collaborative review by the primary medical and statistical reviewers. Independent medical or statistical reviews of sNDA 20-637 were not produced. New data regarding chemistry, animal pharmacology and toxicology, microbiology or biopharmaceutics were not submitted by the sponsor. For further information, the reader is directed to the label for the marketed product (Appendix III).

III. Human Pharmacokinetics and Pharmacodynamics

The following is excerpted from the current label of the original approval for GLIADEL.

"The absorption, distribution, metabolism and excretion of GLIADEL in humans is unknown. A waiver was granted of the requirements for information under Section 6, Human Pharmacokinetics and Bioavailability in 1996. Classical bioequivalence studies are hampered by assay insensitivity for uM or nM drug concentrations needed for radiolabeling studies. Obtaining tissue (brain) samples for analysis is considered inappropriate. Information on the biodegradability of the wafers in humans is based on patients who have had a reoperation or autopsy. Biodegradability of the wafers appears variable with a spectrum of complete dissolution to remnants or complete wafers recovered months later. In the few instances where

BCNU content of the wafer remnants was analyzed, it has not been found to be present in the wafer remnants.

Pharmacokinetic and/or pharmacodynamic information was not studied in T-301 and no new information has been submitted with this sNDA.

IV. Description of Clinical Data and Sources

A. Overall Data

Supplemental NDA 20-637 (sNDA) contains the primary (raw) data from the trial T-301, conducted in 38 centers in 14 countries including the US.

B. Table of Clinical Trials

Reviewer Table 1 presents the trials of GLIADEL conducted in newly diagnosed patients with malignant glioma. Trial T-301 is new data not previously reviewed by the FDA. Studies 9003 and CL-0190 were submitted and reviewed in 1996 when study 8802 supported approval of GLIADEL for patients with recurrent GBM for whom reoperation is indicated. In 1996, ODAC did not consider the randomized trial CL-0190 sufficient to extend the indication to newly diagnosed patients. Data from study 8802 in patients with recurrent GBM can be found in the label in Appendix III. Excerpts from the 1996 review of CL-0190 and 9003 are located in Appendix IV.

Reviewer Table 1: Clinical Trials in Patients with Newly Diagnosed Malignant Glioma

Protocol	Enrollment Dates	Treatment	Population	#Planned/ Entered	Primary Endpoints
[redacted]					
#T-301	12.19.97 ⇒ 06.30.99	GLIADEL vs. Placebo	Newly-dx Malignant Glioma	240/240	Survival
#CL-0190*	03.23.92 ⇒ 05.14.93	GLIADEL vs. Placebo	Newly-dx Malignant Glioma	100/32	DFS; Survival
[redacted]					
#9003*	07.05.90 ⇒ 08.14.91	GLIADEL	Newly-dx Malignant Glioma	22	Safety Pilot with XRT

*Previously reviewed; see Appendix IV.

C. Postmarketing Experience

Postmarketing data from the FDA's Adverse Event Reporting System (AERS) contains reports of the adverse events from the US as well as foreign reports. The most commonly reported toxicities were neurological complications such as cerebral edema, convulsions, confusion, headache, brain abscess and wound infection. Reported adverse events are consistent with the GLIADEL labeling. The sponsor did not submit postmarketing events as part of the sNDA.

D. Literature Review

Review of the published literature was conducted and did not identify other randomized or single-arm efficacy trials with GLIADEL.

V. Clinical Review Methods

A. How the Review was Conducted

The review centers on the data from the randomized trial T-301, which was the only primary data submitted in this sNDA. Additional data on 32 patients with newly diagnosed malignant glioma treated in trial CL-0190 reviewed in 1996, was not considered sufficient to support an indication in this population (see Reviewer Table 1 and Appendix IV).

B. Overview of Materials Consulted in Review

The following materials were reviewed by the medical and statistical officers:

- The regulatory history of the application;
- The 1996 medical and statistical review of GLIADEL;
- INDs [redacted] and [redacted]
- Electronic submission of the sNDA, including Case Report Forms (CRFs), SAS and ACCESS datasets;
- Relevant published literature.

C. Clinical Inspection Summary

The Division of Scientific Investigations, CDER, FDA conducted an audit of the centers with the largest accrual (two centers in France: 17 and 14 patients).
The detailed report of the inspection was sent on October 15, 2001 and concluded that "data related to the primary endpoint (mortality) for this study are valid." Minor deviations from the protocol were noticed in the methodology of reporting of Serious Adverse Events (SAEs), possibly attributable to differences in practice of reporting SAEs in France.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor states that study T-301 was conducted in accordance with the Declaration of Helsinki and in compliance with local regulations and the International Conference of Harmonization Good Clinical Practice guidelines. The protocol and its amendments were reviewed and approved by Independent Ethics Committees and/or Institutional Review Boards.

Written informed consent was required prior to entering the study.

E. Evaluation of Financial Disclosure

Louise Peltier, Senior Director, Regulatory Affairs, Guilford states, "The sponsor of this clinical study (T-301), performed to support this sNDA filing, was — and was conducted under their IND [redacted] — was responsible for all financial arrangements with all investigators who participated in this study.

Guilford Pharmaceuticals Inc. reacquired the rights to GLIADEL, including — IND and NDA on October 24, 2000. It has not been possible to date to obtain the financial information required to complete item 2 of this Certificate. Guilford has and will continue to make every effort to obtain this information from —.

Reviewer Comment: Despite Guilford Pharmaceuticals due diligence in attempting to obtain the information, applicant was unable to do so.

VI. Review of Efficacy

Phase III Trial T-301: Phase III, Multicenter Randomized Double-Blind, Placebo-Controlled trial of Polifeprosan 20 with Carmustine 3.85% Implant for Patients Undergoing Initial Surgery for Newly Diagnosed Malignant Glioma

A. Protocol Review

Principal Investigator:

Professor M. Westphal
Department of Neurosurgery
University Hospital Eppendorf
Martinistrasse 52, Hamburg, Germany

Reviewer Table 2: Protocol T-301 Milestones

Milestone	Date	[redacted]	[redacted]
Amendment 1	6/10/97	0	Not submitted to FDA. Per sNDA: (1) change in total RT from 56-60 to 55-60 Gy; (2) chemorx regimen for AO determined by investigator; (3) PD defined.
Co-sponsor = RPR	6/20/97	0	
First Pt Entered	12/19/97	1	
Full sponsor = RPR	3/12/99	Close to 200	
Amendment 2	3/18/99	Close to 200	Sample size ↑ from 200 to 240.
Last Pt Entered	6/30/99	240	
Statistical Analysis Plan submitted	11/3/99 revised		
Last Observation	6/30/00	--	Per protocol, all pts followed for a minimum of 1 year or until death.
Data Cutoff Date	6/30/00		
Data Lock	7/17/00		Data unlocks after unblinding on 8/12/00, 1/23/01, and 2/19/01
Guilford "reacquired rights to GLIADEL"	10/24/00		Financial disclosure not available. [redacted] was sponsor of trial; Guildford is applicant.
sNDA submitted	4/6/01		

Study Design/Synopsis:

Protocol T-301 was a multicenter, international, randomized, double-blind, placebo-controlled phase 3 trial of GLIADEL wafer (7.7 mg Carmustine per polifeprosan 20 copolymer implanted wafer) implanted at the time of surgery in the resection cavity of patients with newly diagnosed malignant glioma. After maximal resection, up to eight wafers of either GLIADEL or placebo were placed against the resection surfaces. Between postoperative days 14 and 28, patients on both arms were to receive standard limited field radiation therapy (RT) described as 55-60 Gy delivered in 28 to 30 fractions over six weeks. Patients with anaplastic oligodendroglioma were to receive systemic chemotherapy in addition to GLIADEL and RT.

The primary endpoint was overall survival 12 months after the last patient was enrolled. Secondary endpoints included overall survival in the subgroup of patients with glioblastoma multiforme, progression-free survival, 1-year survival, time to neurological deterioration, change in baseline Karnofsky Performance Status (KPS), and Quality of Life (QoL) measures.

Objective:

"To determine the safety and efficacy of polifeprosan 20 with carmustine 3.85% implant plus surgery and limited field radiation therapy compared to placebo implants plus surgery and limited field radiation therapy for improving the survival in patients undergoing initial surgery for newly-diagnosed malignant glioma."

Eligibility criteria:

- 18 to 65 years old
- Radiographic evidence on cranial magnetic resonance imaging (MRI) of a unilateral, unifocal, supratentorial cerebral tumor at the time of present surgery
- KPS $\geq$ 60
- Intraoperative diagnosis of malignant glioma by frozen or squash preparation prior to wafer implantation (including patients with a prior proven biopsy)
- Adequate organ function as defined by baseline laboratory parameters

Exclusion criteria:

- Prior cytoreductive surgery (excluding diagnostic stereotactic biopsy)
- Previous and/or current use of chemotherapeutic agents
- Prior radiotherapy to the brain
- Concomitant life-threatening diseases with life expectancy less than 12 months
- Known hypersensitivity to nitrosourea
- Pregnancy

Reviewer Comment: In a protocol planning meeting January 30, 1997, the FDA expressed the preference for a trial population limited to GBM, given the information on effect limited to patients with GBM in the recurrent setting. However, it was conceded that definitive histology can only be known after surgery and therefore it was not feasible to enroll only patients with GBM. The FDA recommended that the primary analysis be done in the intent-to-treat population as well as in the GBM subgroup. Therefore, the analysis of the GBM subgroup was prespecified in the protocol and statistical analysis plan. The Statistical Analysis Plan states... "Because of its resistance to chemotherapy, the study interest is mainly on GBM."

Randomization:

The protocol states that patients will be randomized to one of two groups: resection and limited field radiation plus either GLIADEL or placebo. "Treatment assignment will be determined by sequential enrollment in ascending order into randomized blocks." The Statistical Analysis Plan states that "the randomization list is equilibrated for each center by blocks."

Reviewer Comment: The sNDA states that randomization was stratified by country (Final Study Report, section 5.3.2). Clarification of the randomization codes and

algorithm requested from the sponsor identify that stratification was by center. Block sizes of four were assigned to a center. Treatment assignment within a center was carried out by sequential enrollment in ascending order. Randomization was 1:1.

Treatment:

Wafer. Following maximal tumor resection and the intraoperative conformation of malignant glioma, up to eight wafers of GLIADEL or placebo were to be positioned to cover the entire resected surface.

Radiation Therapy. Between study day 14 and 30, all patients were to undergo a course of limited field radiation therapy to the tumor site and surrounding margins. Patients would receive fractionated radiation to a total of 55 to 60 Gy in 28 to 30 fractions over a six week period. (For further details of the RT protocol, see Appendix II). Patients with the diagnosis of pure anaplastic oligodendroglioma may have radiation delayed or withdrawn, per investigator.

Chemotherapy. All patients with a pathologic diagnosis of anaplastic oligodendrogloima (AO) as determined by the institution's pathologist were to receive systemic chemotherapy "based on a regimen which will be determined at the investigator's discretion." (Amendment 1)

Reviewer Comment: The original protocol stated that the regimen for patient's with AO should consist of six cycles of PCV (lomustine 110 mg/m^2 d1; procarbazine 60 mg/m^2 d 8-21; vincristine 1.4 mg/m^2 d 8 and 29).

Patients with other histologic diagnoses were not to receive chemotherapy for treatment of their initial tumor. At the time of progressive disease, both systemic chemotherapy and reoperation were allowed.

Concomitant Medications. Supportive medication such as steroids and anti-convulsant drugs were permitted at the investigator's discretion.

Patient Evaluation and Schedule of Tests:

Sponsor's Table 3 (Abridged): Schedule of Tests

	Days					Months						
	Baseline	Surgery										
Visit	1	2	3	4	5	6	7	8	9	10	11	12
Study Day[2]	-14 – 0	1	3	7[3]	14	28	3	6	12	18	24	30
Written informed consent	X											
Medical history	X											
Interim medical history		X	X	X	X	X	X	X	X	X	X	X
Medication review	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X											
Neurological exam	X	X	X	X	X	X	X	X	X	X	X	X
Focused physical exam			X	X	X	X						
KPS	X	X[4]		X	X	X	X	X	X	X	X	X
QoL	X					X	X	X	X	X	X	X
Brain MRI	X	X[5]					X					
Laboratory evaluations	X		X	X	X	X						
Urine pregnancy test[6]	X											
Adverse event Reporting	X[7]	X	X	X	X	X	X	X	X	X	X	X
Begin radiation therapy					X[8]							
Begin systemic chemorx						X[9]						
Survival			X	X	X	X	X	X	X	X	X	X
Wafer implantation		X										

[1] All timing was relative to the Day of Study Surgery, which was defined as Study Day 1
[2] ±3 days for Visits 5-6, ± 15 days for Visits 7-12
[3] Or Day of Discharge (the earlier of these dates was to be Visit 4)
[4] Neurological exam and KPS score were to be performed pre-operatively
[5] Post-operative MRI scan was to be performed within the 48 hours post-operatively
[6] For women of child-bearing potential only
[7] Adverse event reporting started after written informed consent was obtained
[8] Post-operative, limited field radiation therapy was to begin between Study Days 14 and 30
[9] Systemic chemotherapy was only for patients with anaplastic oligodendroglioma

Reviewer Comment: The neurologic examination was designed to rate 11 pre-specified parameters (vital signs, level of consciousness, personality, speech, visual status, fundus, cranial nerves III, IV, VI, cranial nerves other, sensory status, cerebellar status and other).

Definition of Endpoints

- **Survival.** Overall survival was defined "from the date of randomization (study surgery) and the date of death from any cause, or to the date of last contact for censored information."

• **Progression-free survival** was defined as the time between randomization (day of surgery) and the first of two events, progression or death. Progression is defined as clinical or radiologic deterioration. Clinical deterioration is defined as new neurologic signs or a decrease in the KPS of at least 10%. Radiologic progression is defined as a 25% increase in tumor size based on the product of the 2 largest perpendicular diameters or appearance of a new lesion as compared to the last previous post-operative MRI.

• **Quality of Life Measures.** Quality of Life (QoL) Assessments were measured by the EORTC QLQ – C30 quality of life instrument as well as the specially designed questionnaire for Brain Tumors (BCM-20; 20 items). The EORTC QLQ-C30 contains 5 functional scales (physical, role, emotional, cognitive and social functioning), 3 symptom scales (fatigue, nausea and vomiting, pain) 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) and one global health status/QoL scale. The BCM-20 assesses 4 scales (future uncertainty, visual disorder, motor dysfunction, communication deficit) and 7 single symptoms. (See Appendix II for the questionnaires.)

• **Karnofsky Performance Status** was assessed according to the schedule in sponsor's Table 3 above.

Definition of Adverse Events

An adverse event (AE) was defined as any symptom, sign, illness or experience which develops or worsens in severity during the course of the study. Serious AEs were an event that was fatal, life-threatening, requires or prolongs hospitalization, results in persistent or significant disability or incapacity, a congenital anomaly or birth defect or an important medical event.

Statistical Considerations:

The primary endpoint was overall survival as assessed by the Kaplan-Meier curve 12 months after enrollment of the last study patient. The secondary endpoints were progression-free survival, overall survival in a subgroup of patients with GBM, 1-year survival, change in KPS scores, change in neurologic evaluation and Quality of Life.

Statistical Analysis:

The following are excerpts from the protocol:
Sample size. "Sample size estimation, based on the following assumptions using the Log-rank test to compare two survival curves, indicates that 200 patients are required for this study:

1. 50%-70% 12 month survival rates of the placebo and polifeprosan 20 with carmustine implant treatment groups, respectively.
2. 15% patient loss rate.

3. 18 months accrual time.
4. Minimum of 12 months follow-up after last patient is enrolled.
5. Two-sided 5% significance level.
6. 90% power.

Data from prior studies indicate that approximately 70% of patients meeting inclusion and exclusion criteria similar to the ones in this protocol have a final pathological diagnosis of glioblastoma multiforme. Thus, this study can be expected to enroll a total of 140 patients with a final pathological diagnosis of glioblastoma multiforme. Using the same assumptions mentioned above, a sample size of 140 glioblastoma multiforme patients will yield 80% power to detect a difference between the two survival curves using the log-rank test.

The final tumor pathology based on the central neuropathological review of all entered patients will be monitored throughout the study in a blinded fashion. If after 200 patients are enrolled, the total number of enrolled patients with glioblastoma multiforme is less than 140, enrollment will continue until 140 patients with glioblastoma multiforme have been enrolled.

Because the sample size calculations are based on the number of events (deaths) over time, the number of deaths during the study will be monitored in a blinded fashion, and cost free adjustments of the number of patients enrolled and/or the length of follow-up may be made as necessary.

Analyses

- Primary: Survival will be estimated by the Kaplan-Meier method 12 months after enrollment of the last study patient or after a sufficient number of deaths has been observed to reach the predetermined 90% power (estimated for a sample size of a total of 200 patients) whichever occurs first. The curves will be compared using the Wilcoxon test for the primary comparison (log-rank test would be performed as a sensitivity test)."

  Reviewer Comment: FDA review from 8/22/97: (1) sample size may not be sufficient to provide power (falls from 90% to 53%) if the true 12 month survival rate for GLIADEL is actually (not overly optimistic) 62.5% instead of 70%. (2) A log-rank test is suggested as the primary analysis if a Cox regression analysis for covariate adjustment is the supporting analysis. Consistency in the direction of results across analyses is the goal in the regulatory setting. A Wilcoxon test is efficient when more deaths are expected at an early stage of a trial and eventually the total number of deaths will be similar at the end of the study, which would indicate that the proportional hazard assumption does not hold.

Amendment 2 (3/18/99): RPR states that the IDMC had a second meeting 1/28/99 to review the blinded data collected up to 1/15/99. "The hope for surgical benefit of GLIADEL of 20% at one year is probably unrealistic." This amendment will increase accrual from 200 to 240 in order to detect a 1year survival for the GLIADEL group of 68% vs. 50% (from 70% vs. 50%) without changing the accrual period from 18 months. This would be expected to increase the number of patients with GBM from 140 to 168.

- "The effect of center will be examined using a proportional hazards model."
- The effect of strong prognostic factors will be assessed in adjusted analyses using the proportional hazards regression model. Baseline KPS, age, and tumor type may be included depending on the validity of the proportional hazards assumptions.
- All survival analyses and proportional hazards regression analyses will also be performed for the subgroup of GBM patients.
- The SAP states that the Cox model will include country. "Countries with a small number of patients included will be pooled together. If a country effect cannot be tested due to small number of patients in each country, countries will be pooled together in a geographical continent basis (Europe + Israel, USA, Australia...)....These analyses are considered as supportive..."
- Twelve-month survival rate will be estimated.
- PFS will be estimated by Kaplan-Meier and compared by a Wilcoxon test.
- KPS. Change from baseline will be computed for each of the treatment groups at each of the post-surgical timepoints.

QoL. "... summary of the main indicators and comparison of the evolution over time of quality of life between the two treatment groups for each subscale will be performed. Analytical methods will include general linear model (repeated measures and survival techniques, time to QoL deterioration)."

The Statistical Analysis Plan states that the Global Health status/QoL scale based upon questions 29 and 30 of the EORTC QLQ-C30 will be the primary QoL parameter of interest.

B. Trial Results

B.1. Conduct of the Study

- **Informed Consent**

The study was conducted in accordance with the Declaration of Helsinki; patients gave written informed consent.

- **Randomization**

The sNDA provides the details of the randomization process. Randomization was stratified by center.

- **Blinding**

Placebo. The placebo wafer was manufactured and packaged by Guilford. The placebo was identical in composition to GLIADEL except that the placebo did not contain the drug substance (BCNU). The physical characteristics of the wafer differed in several regards from GLIADEL. A chemistry amendment dated August 1, 1997 describes GLIADEL as off-white to yellow and placebo as off-white to white.

Unblinding. The study was to be unblinded after the last patient enrolled was followed for 12 months. An individual investigator could decide to unblind treatment for a patient after discussion with the Clinical Project Director if this information was considered to be important for management of an adverse event. The sNDA describes, "The code information was part of the tear-off portion of the medication that was attached to the randomization page of the CRF, once the implants were used. The non-transparent layer covering the medication code on the label could be erased to reveal the medication allocated to the patient."

Reviewer Comment: Theoretically, blinding could have been compromised in two ways:

1. *Physical characteristics. Color was not identical, per chemistry amendment August 1, 1997 and confirmed upon inspection by reviewers at the FDA. Reviewers also noted increased friability of the Gliadel wafer. Sponsor Table 42 below on page 33 presents frequency of broken wafers by treatment arm and confirms the greater friability of Gliadel compared to placebo.*
2. *Treatment code could be broken locally.*

In the protocol planning stage, the value of blinding was considered important to control for supportive or treatment interventions. Balance between the arms with regard to RT, reoperation and chemotherapy will be addressed in this section (see Sponsor Tables #20 and 24, and Reviewer Table #22).

- **Central and Referee Pathologists**

All diagnoses were to be reviewed locally by the institutional pathologist and centrally by an independent neuropathologist blinded to treatment. The initial histological diagnosis was determined by the institutional (local) neuropathologist. The final histopathological diagnosis was determined by a centralized neuropathological assessment. The central neuropathologist was Differences between the local and central pathologists were sent to a referee neuropathologist whose interpretation was final. The referee neuropathologist was .

Reviewer Comment: In the communication with the sponsor it was confirmed that only "pathology slides from patients with divergent GBM and non-GBM diagnoses were sent to a referee pathologist for review". Cases classified by both local and central pathologists as "non-GBM" were not forwarded to the referee, even if there were discordant diagnoses, eg, astrocytoma vs. ependymoma. In these instances, the central diagnosis was final.

- **Protocol Violations**

Sponsor Table 5 presents the number and type of protocol violation per arm.

Sponsor Table 5: Recorded Protocol Deviations (All Patients)

Protocol Deviation	GLIADEL N = 120	Placebo N = 120
RT outside schedule	35	27
Required RT not done	11	9
Anaplastic oligodendroglioma and no CT	11	10
RT outside schedule/CT for reason other than progression	0	2
CT for reason other than progression	1	1
Required RT not done/RT outside schedule	0	1

RT = radiotherapy; CT = chemotherapy
Data extracted from Appendix II.F, Listing 1.03
Sponsor Table 5, Study Summary, p. 53

Reviewer Comment: The most frequently occurring deviations were RT outside of schedule, required radiotherapy not done, and a diagnosis of anaplastic oligodendroglioma and no chemotherapy. We disagree with the sponsor's data on the number of patients listed as "Required RT not done". We identified 15 patients in the GLIADEL group and 11 patients in the placebo group who did not receive radiation

therapy by query of the electronic database. Communication dated August 27, 2001 with sponsor indicates their agreement with FDA numbers.

Eligibility violations are shown in Reviewer Table 3. There were 5 violations in the GLIADEL group and 6 in the placebo group.

Reviewer Table 3: Eligibility Violations

Protocol Deviation	GLIADEL N = 120	Placebo N = 120
Age > 65	2	1
Non-enhancing tumors	1	2
Not supratentorial	0	1
Multiple foci of tumor	0	2
Tumor crossing midline	2	0

Ref: Final Study Report, p. 56 and 57

- **Audits**

Site audits by the FDA's Division of Scientific Investigations were conducted for the 2 largest accruing centers in France. Summary of the results is presented on p. 14, Clinical Review Methods (Section V).

B.2. Enrollment, Demographics, Baseline Characteristics

- **Enrollment by Study Center**

A total of 240 patients were enrolled at 38 centers in 14 countries. The largest number of patients were accrued in two countries: a total of 48 patients were accrued in 7 centers in France; 44 patients were accrued in 5 centers in Germany. Only 12 patients were accrued in 5 centers in the U.S. Equal numbers of patients, 120, were randomized to the two treatment arms.

Enrollment per country and center is displayed in Sponsor Table 1.02. on the following page.

Sponsor Table 1.02: Randomized Patients by Country and Center by Treatment Group

INVESTIGATOR NAME BY COUNTRY	Treatment Group		
	Polifeprosan / Carmustine (N=120)	Placebo (N=120)	ALL (N=240)
Austria			
KOSTRON HERWIG	3 (2.5%)	4 (3.3%)	7 (2.9%)
Australia			
BESSER MICHAEL	2 (1.7%)	2 (1.7%)	4 (1.7%)
FARINYI GAVIN	4 (3.3%)	4 (3.3%)	8 (3.3%)
KAYE ANDREW	2 (1.7%)	3 (2.5%)	5 (2.1%)
Belgium			
DE WITTE OLIVIER	3 (2.5%)	3 (2.5%)	6 (2.5%)
PLETS CHRISTIAN	4 (3.3%)	4 (3.3%)	8 (3.3%)
Switzerland			
BARCETTI MARIO	3 (2.5%)	2 (1.7%)	5 (2.1%)
REMELLA REZIO RAFFAELE	2 (1.7%)	2 (1.7%)	4 (1.7%)
Germany			
ARNOLD D	0 (0.0%)	1 (0.8%)	1 (0.4%)
MENDORN MAXIMILLIAN	4 (3.3%)	4 (3.3%)	8 (3.3%)
STOLKE DIETMAR	2 (1.7%)	1 (0.8%)	3 (1.3%)
TERZIS JORGE	2 (1.7%)	3 (2.5%)	5 (2.1%)
TOHN JOERG CHRISTIAN	6 (5.0%)	5 (4.2%)	11 (4.6%)
WESTPHAL MANFRED	8 (6.7%)	8 (6.7%)	16 (6.7%)
Spain			
BINI WALTER	1 (0.8%)	0 (0.0%)	1 (0.4%)
CORDOBA	1 (0.8%)	0 (0.0%)	1 (0.4%)

INVESTIGATOR NAME BY COUNTRY	Treatment Group		
	Polifeprosan / Carmustine (N=120)	Placebo (N=120)	ALL (N=240)
France			
BRET PHILLIPE	8 (6.7%)	9 (7.5%)	17 (7.1%)
CORNU PHILLIPE	5 (4.2%)	8 (6.7%)	13 (5.4%)
GRISOLI FRANCOIS	1 (0.8%)	0 (0.0%)	1 (0.4%)
MENEGALLI DOMINIQUE	3 (2.5%)	1 (0.8%)	4 (1.7%)
STILHART BERNADETTE	4 (3.3%)	4 (3.3%)	8 (3.3%)
TADIE MARC	3 (2.5%)	2 (1.7%)	5 (2.1%)
UK			
BYRNE PAUL	3 (2.5%)	2 (1.7%)	5 (2.1%)
MENDELOW ALEXANDER DAVID	4 (3.3%)	7 (5.8%)	11 (4.6%)
PAPANASTASSIOU VARIS	2 (1.7%)	2 (1.7%)	4 (1.7%)
WHITTLE IAN	6 (5.0%)	6 (5.0%)	12 (5.0%)
Greece			
FOROGLOU GEORGE P.	2 (1.7%)	2 (1.7%)	4 (1.7%)
Israel			
ISRAEL Z	1 (0.8%)	2 (1.7%)	3 (1.3%)
RAM ZVI	11 (9.2%)	11 (9.2%)	22 (9.2%)
RAPPAPORT Z H	5 (4.2%)	2 (1.7%)	7 (2.9%)
Italy			
VILLANI ROBERTO	1 (0.8%)	0 (0.0%)	1 (0.4%)
Netherlands			
BOSCH DIRK ANDRIES	6 (5.0%)	6 (5.0%)	12 (5.0%)
WOLBERS JOHN G	1 (0.8%)	2 (1.7%)	3 (1.3%)

INVESTIGATOR NAME BY COUNTRY	Treatment Group		
	Polifeprosan / Carmustine (N=120)	Placebo (N=120)	ALL (N=240)
New Zealand			
MEE EDWARD	1 (0.8%)	2 (1.7%)	3 (1.3%)
US			
BLACK KEITH	1 (0.8%)	2 (1.7%)	3 (1.3%)
BOATTI JOHN	1 (0.8%)	0 (0.0%)	1 (0.4%)
HAMILTON ALLAN	1 (0.8%)	1 (0.8%)	2 (0.8%)
PALEOLOGOS NINA A	2 (1.7%)	2 (1.7%)	4 (1.7%)
THORON LOUISA	1 (0.8%)	1 (0.8%)	2 (0.8%)

Ref: Appendix II.F

- **Baseline Demographics:**

Sponsor Table 6 presents demographics by study arm. The majority of patients were male, ranging from 63% to 70% in the ITT population and 64% to 69% in the GBM subgroup. All but 8 patients in the ITT and 6 in the GBM population were caucasian. Age ranged from 21 to 72, with a mean of 53 in the ITT population in the GLIADEL group and of 54 years in the placebo group. In the GBM subgroup a mean age for both treatment group was 54 years.

Sponsor Table 6: Summary of Demography

Characteristic	Overall (N = 240)		GBM Subgroup (N = 207)	
	GLIADEL (N = 120)	Placebo (N = 120)	GLIADEL (N = 101)	Placebo (N = 106)
Sex				
Male N (%)	76 (63.3)	84 (70.0)	65 (64.4)	73 (68.9)
Female N (%)	44 (36.7)	36 (30.0)	36 (35.6)	33 (31.1)
Race				
Caucasian N (%)	116 (96.7)	116 (96.7)	97 (96.0)	103 (97.2)
Black N (%)	1 (0.8)	1 (0.8)	1 (1.0)	0
Oriental N (%)	1 (0.8)	1 (0.8)	1 (1.0)	1 (0.9)
Hispanic N (%)	1 (0.8)	0	1 (1.0)	0
Other N (%)	1 (0.8)	2 (1.7)	1 (1.0)	1 (1.9)
Age (years)				
Mean (SEM)*	52.6 (0.8)	53.6 (0.8)	53.5 (0.84)	54.2 (0.78)
Range	21–72	30-67	28-72	30-65

Ref: Final Study Report, p. 53

*SEM – standard error of the mean

Age is also displayed by decade in Reviewer Table 4. No significant imbalances between the treatment arms are noted in either the ITT population or the GBM subgroup.

Reviewer Table 4: Age Distribution by Decades and Treatment Group

	Overall Population		GBM Population	
Age Groups	GLIADEL N=120 (%)	Placebo N=120 (%)	GLIADEL N=101(%)	Placebo N=106
21-39	12 (10)	8 (7)	7 (7)	5 (5)
40-49	25 (21)	27 (22)	23 (23)	23 (22)
50-59	49 (41)	49 (41)	40 (40)	43 (41)
60-65	32 (27)	35 (29)	29 (29)	35 (33)
>65	2 (2)	1 (1)	2 (2)	0

Reviewer Comment: Protocol eligibility criteria limit the age to 65 years old. This exclusion would limit the generalizability of the data for the overall population of patients with malignant gliomas.

- **KPS:**

Sponsor Table 17 presents baseline KPS scores in the ITT population and GBM subgroup by treatment arm. The KPS score was comparable between the two treatment groups at baseline for the ITT. In the GBM subgroup, slightly more patients in the placebo group (57 patients) compared to the GLIADEL group (46 patients) had a KPS score of 90 or more.

Table 17: KPS Scores at baseline

Karnofsky Performance Status Score	Overall (N=240)		GBM subgroup (N=207)	
	GLIADEL® n=120 n (%)	Placebo n=120 n (%)	GLIADEL® n=101 n (%)	Placebo n=106 n (%)
60	16 (13.3)	16 (13.3)	13 (12.9)	15 (14.2)
70	21 (17.5)	17 (14.2)	20 (19.8)	14 (13.2)
80	25 (20.8)	24 (20.0)	21 (20.8)	20 (18.9)
85	2 (1.7)	0	1 (1.0)	0
90	31 (25.8)	40 (33.3)	29 (28.7)	36 (34.0)
95	0	1 (0.8)	0	1 (0.9)
100	25 (20.8)	22 (18.3)	17 (16.8)	20 (18.9)

Ref: Table 2.01, Appendix II.F

- **Tumor Size and Extent of Resection:**

Assessment of baseline tumor size is presented in two ways: (a) pre-operative imaging studies (length and width; planar volume is not presented because of 77% and 73% missing data on GLIADEL and placebo, respectively); and (b) assessment at time of surgery. Extent of resection is also presented in two ways: (a) type of surgery; and (b) percent of tumor resected.

Reviewer Table 5: Tumor Size and Extent of Resection

	Overall Population		GBM Subgroup	
	GLIADEL N=120	Placebo N=120	GLIADEL N=101	Placebo N=106
IMAGING DATA				
Planar Size (Length)				
N	114	111	97	97
Missing	6	9	4	9
Mean	4.73	4.47	4.68	4.42
SEM	0.126	0.143	0.136	0.152
Median	4.70	4.00	4.70	4.00
Range	[redacted]			
Planar Size (Width)				
N	114	111	97	97
Missing	6	9	4	9
Mean	4.12	4.04	4.14	4.00
SEM	0.109	0.121	0.117	0.124
Median	4.00	4.00	4.00	4.00
Range	[redacted]			
SURGICAL DATA				
Surgical Estimate of Tumor Volume (cm^3)				
Mean (SEM)	66.8 (5.9)	50.8 (5.3)	67.2 (6.5)	53.4 (5.9)
Range	0.1-250.0	0.6-240.0	0.1-250.0	0.6-240.0
Type Resection				
Subtotal	62 (51.7)	66 (55.0)	51 (50.5)	56 (52.8)
Total	56 (46.7)	49 (40.8)	48 (47.5)	46 (43.4)
Total + Lobectomy	2 (1.7)	4 (3.3)	2 (2.0)	4 (3.8)
Missing	0	1 (0.8)	0	0
% Resected				
Mean (SEM)	89.9 (1.3)	88.3 (1.6)	90.1 (1.5)	89.5 (1.5)
Range	[redacted]			
Missing	5 (4.2)	11 (9.2)	4 (4.0)	9 (8.5)

Ref: Sponsor Tables 9, 12 and 2.05

Reviewer Comment: If complete resection is redefined by pairing two datasets, i.e., requiring extent of resection as total or total + lobectomy and 100% resection, the absolute number of patients with a complete resection falls to 45 (37.5%) on GLIADEL and 38 (31.6%) on placebo. The relative difference between the arms, however, remains the same with an approximate 4-6% advantage to the GLIADEL arm.

- **Tumor Histology:**

Institutional diagnoses were reviewed by a central pathologist blinded to treatment. Disagreements were forwarded to a referee neuropathologist only in "cases where patients were classified as GBM by local histology and non-GBM by central histology or vice versa. In all other cases, the central histopathological diagnosis was used as final". Patients with a diagnosis of giant cell glioblastoma and gliosarcoma were included in the GBM subgroup per protocol. The most common tumor type was GBM: 101 (84.2%) patients in the GLIADEL arm and 106 (88.3%) patients in the placebo group.

Reviewer Table 6: Tumor Characteristics – Histological Type

(Including Referee Diagnoses)

	Treatment group	
	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
Astroblastoma	0	1
Astrocytoma, gemistocytic	0	1
Metastasis/Brain Metastasis	2	1
TOTAL	120	120

Reviewer Comment: Histology was verified by review of electronic database UPAT – description and disposition of patients, variables L_DIAGH – local histological diagnosis, C_DIAGN – central histological diagnosis, R_DIAGH – referee histological diagnosis as well as histopathological reports from the central and referee pathologists submitted by the sponsor. This table differs from Sponsor Table 11 in the sponsor's Briefing Document in one respect – sponsor agrees with FDA that one patient previously categorized as" other" should be reclassified as anaplastic oligoastrocytoma.

Reviewer Table 7 displays the diagnoses from the central pathologist (derived from electronic data as well as histopathological report forms from the central pathologist).

Reviewer Table 7: Tumor Characteristics – Histological Type (Central Diagnoses)

	GLIADEL® N=120	Placebo N=120
Glioblastoma multiforme	**81**	**93**
giant cell glioblastoma	**5**	**5**
gliosarcoma	**2**	**1**
GBM group (TOTAL)	**88**	**99**
Non-GBM (TOTAL)	**24**	**15**
Anaplastic astrocytoma	**1**	**1**
Anaplastic oligodendroglioma	**6**	**7**
Anaplastic oligoastrocytoma	**17**	**7**
Other (TOTAL)	**4**	**5**
oligodendroglioma	**1**	**1**
oligoástrocytoma	**1**	**0**
anaplastic ganglioglioma	**0**	**1**
astroblastoma	**0**	**1**
pleomorphic xanhoastrocytoma	**1**	**1**
gemestocytic astrocytoma	**0**	**1**
PNET	**1**	**0**
Metastasis	**4**	**1**
TOTAL	**120**	**120**

Reviewer Comment: The number of patients with GBM by either central or final diagnoses favors the GLIADEL arm. As GBM is a prognostic factor for survival, this imbalance may have an effect on survival analysis. Survival analyses were performed using central and referee assignments (see Reviewer Tables #12 and #13).

B.3. Protocol Treatment

- **Wafer Implantation**

Patients could receive up to eight wafers following maximal resection of tumor. Sponsor Table 41 presents the number of wafers implanted in the ITT population and the GBM subgroup. Approximately a third of patients received the maximum number of wafers.

Sponsor Table 41: Number of Wafers Implanted

Number of wafers Implanted	Overall (N=240)		GBM subgroup (N=207)	
	GLIADEL® n=120 n (%)	Placebo n=120 n (%)	GLIADEL® n=101 n (%)	Placebo n=106 n (%)
8	44 (36.7)	47 (39.2)	35 (34.7)	42 (39.6)
7.5	2 (1.7)	0	1 (1.0)	0
7	21 (17.5)	28 (23.3)	18 (17.8)	25 (23.6)
6.5	1 (0.8)	1 (0.8)	1 (1.0)	1 (0.9)
6	26 (21.7)	16 (13.3)	24 (23.8)	14 (13.2)
<6	26 (21.7)	28 (23.3)	22 (21.8)	24 (22.6)

The protocol permitted the use of wafers that had broken in half (either on opening the treatment box or during surgery), while those broken in more than 2 pieces were to be discarded in a biohazard container. As seen in Sponsor Table 42, GLIADEL wafers were broken at time of surgery for 56 patients (46.6%). For 19.2% of patients, the wafers were broken into more than 2 pieces and were to be discarded.

Table 42: Broken wafer details

Broken wafers		Overall (N=240)		GBM subgroup (N=207)	
		GLIADEL® n=120 n (%)	Placebo n=120 n (%)	GLIADEL® n=101 n (%)	Placebo n=106 n (%)
During opening (number of pieces)	2	27 (22.5)	14 (11.7)	22 (21.8)	14 (13.2)
	>2	22 (18.3)	18 (15.0)	20 (19.8)	14 (13.2)
	Missing	1 (0.8)	2 (1.7)	1 (1.0)	2 (1.9)
During surgery (number of pieces)	2	24 (20.0)	17 (14.2)	19 (18.8)	14 (13.2)
	>2	2 (1.7)	2 (1.7)	2 (2.0)	2 (1.9)
	Missing	7 (5.8)	3 (2.5)	7 (6.9)	3 (2.8)
During opening or surgery (number of pieces)	2	33 (27.5)	21 (17.5)	27 (26.7)	21 (19.8)
	>2	23 (19.2)	19 (15.8)	21 (20.8)	15 (14.2)
	Missing	8 (6.7)	5 (4.2)	8 (7.9)	5 (4.7)

Reviewer Comment: At the time of opening of the treatment boxes or during the surgical implantation, there were more broken Gliadel than placebo wafers (33 and 21, respectively). Number of pieces greater than two was not significantly different in both groups (23 and 19 for the Gliadel and placebo, respectively).

- **Concomitant Medications**

Corticosteroids and anticonvulants were the most commonly prescribed medication after wafer implantation. Sponsor Table 1.09 provides data on the use of concomitant medications during the study.

Sponsor Table 1.09: Summary of Patients with Concomittant Corticosteroids or Anticonvulsants Overall and by Histological Subtype and Treatment Group

	Overall		GBM	
	GLIADEL N=120	**Placebo N=120**	**GLIADEL N=101**	**Placebo N=106**
No. of Patients				
Without Concomitant Rx	71 (59.2%)	70 (58.3%)	59 (58.4%)	60 (56.6%)
With Concomitant Rx	49 (40.8%)	50 (41.7%)	42 (41.6%)	46 (43.4%)
Concomitant Medication				
Corticosteroid	29 (59.2%)	30 (60.0%)	26 (61.9%)	26 (56.5%)
Anticonvulsant	12 (24.5%)	5 (10.0%)	9 (21.4%)	5 (10.9%)

There were no differences between the treatment arms with respect to number of patients who received corticosteroids (59.2% in the GLIADEL group and 58.3% in the placebo group); however more patients in the GLIADEL group were treated with anticonvulsants than patients from the placebo group (24.5% and 10.0%, respectively).

- **Radiation Therapy**

Per protocol, patients were to receive limited field radiation therapy (RT) between postsurgical day 14 and 30 to a total dose between 55 and 60 Gy to the tumor site and surrounding margins. See Appendix 1I for details of the radiation protocol. Sponsor Table 20 presents actual radiotherapy delivered.

Sponsor Table 20: Summary of Patients Receiving Radiotherapy During the Study

Radiotherapy Received	Overall (N=240)		GBM (N=207)	
	GLIADEL (N=120) n (%)	Placebo (N=120) n (%)	GLIADEL (N=101) n (%)	Placebo (N=106) n (%)
No Radiotherapy	11 (9.2)	9 (7.5)	10 (9.9)	7 (6.6)
Standard Course of Radiotherapy	93 (77.5)	98 (81.7)	80 (79.2)	88 (83.0)
Non-standard Radiotherapy	13 (10.8)	8 (6.7)	8 (7.9)	6 (5.7)
Standard and Non-standard Radiotherapy	3 (2.5)	5 (4.2)	3 (3.0)	5 (4.7)
TOTAL	120	120	101	106

Non-standard radiotherapy is defined by the sponsor as therapy given outside the protocol-specified timeframe (eg., due to deterioration of patient's condition, lack of specialized equipment that required transfer to other institution, after chemotherapy or diagnoses other than malignant glioma eg., brain metastasis). Standard RT was delivered to 78% of patients on the GLIADEL group and 80% on placebo. The remaining patients received either "non-standard" or no "radiation". The category defined by the sponsor as "Standard and Non-standard" reflects the error in the data entry.

Reviewer Comment: Review of the electronic database confirms the number of patients who received standard RT. The sponsor has counted 6 patients (4 in the GLIADEL and 2 in placebo group) who did not receive RT in the category of "non-standard radiotherapy." The total FDA count of patients who did not receive RT in the ITT population is 15 (12.5%) treated with GLIADEL and 11(9.2%) treated with placebo. Conversely, the number of patients who received "non-standard" radiotherapy by reviewer count is 9 and 6 patients for the GLIADEL and placebo respectively, which differs from the sponsor's data (13 and 8). Sponsor agreed with FDA count.

B.4. Additional Treatment

- **Reoperation**

Post-study treatments that could potentially confound results were examined. Treatment modalities for the patients in this study include: reoperation, with or without GLIADEL re-implantation, radiation or some combination of them.

Sponsor's Table 23 shows a summary of patients who had additional surgical procedures for disease progression as well as for the postsurgical complications after initial wafer implantation.

Table 23: Summary of patients having additional surgical procedures for malignant glioma

Additional surgical procedures	Overall (N=240)		GBM subgroup (N=207)	
	GLIADEL® n=120 n (%)	Placebo n=120 n (%)	GLIADEL® n=101 n (%)	Placebo n=106 n (%)
Missing (no data)	7 (5.8)	6 (5.0)	5 (5.0)	4 (3.8)
No	65 (54.2)	77 (64.2)	58 (57.4)	68 (64.2)
Yes	48 (40.0)	37 (30.8)	38 (37.6)	34 (32.1)
GBM = Glioblastoma multiforme				

Reviewer Comment: The number of patients who underwent additional surgery for disease progression, as well as for the postsurgical complication, was confirmed by analysis of the electronic database USURG – surgery, variable ASURGY – additional surgery, CM_SURG – reason.

- **Chemotherapy**

The protocol states that patients with the pathological diagnosis of anaplastic oligodendroglioma will receive chemotherapy after initial surgery while others may receive chemotherapy at time of disease progression. Sponsor Table 22 summarizes the number of patients who received chemotherapy in the ITT population and GBM subgroup by treatment arm.

Sponsor Table 22: Summary of Patients Receiving Systemic Chemotherapy for Malignant Glioma

Systemic Chemorx	Overall (N=240)		GBM subgroup (N=207)	
	GLIADEL N=120 N(%)	Placebo N=120 N(%)	GLIADEL N=101 N(%)	Placebo N=106 N(%)
No	103 (85.8)	108 (90.0)	91 (90.1)	99 (93.4)
Yes	17 (14.2)	12 (10.0)	10 (9.9)	7 (6.6)

Reviewer Comment: Analysis of the electronic database UMND – medication and non-drug therapy, variables – DRUGSY – medication, CHEMO – chemotherapy, as well as CRF's reveal that equal number of patients (14 in each group) were treated with chemotherapy at the time of the disease progression. The majority of patients with recurrent disease in both groups had GBM (10 and 11 patients in the Gliadel and placebo, respectively). Sponsor agreed with FDA count.

Review of the electronic database UMND – medication and non-drug therapy, variables – DRUGSY – medication, CHEMO – chemotherapy, as well as CRF's, reveal patients who received chemotherapy within 30 days of randomization. Details are presented in reviewer Table 8 below.

Reviewer Table 8: Chemotherapy within 30 days of randomization.

	Treatment group	
	GLIADEL	PLACEBO
Anaplastic oligodendroglioma	1/6	1/5
Anaplastic oligoastrocytoma	2/8	2/3

Reviewer Comment: Study protocol specifies that only patients with a pathological diagnosis of AOD will receive systemic chemotherapy. No systemic chemotherapy was permitted for treatment for patients with other histopathological diagnoses. It was noted that of the 6 patients in the Gliadel group with the final histological diagnosis of AOD, only 1 patient received chemotherapy, and in the placebo group, only 1 of 5 patients was treated with chemotherapy. However, 4 patients (2 in the Gliadel and 2 in placebo) with pathological diagnosis of AOA received systemic chemotherapy after wafer implantation.

- **Other Treatments**

At the time of the disease progression, four patients, all in the GLIADEL group, received treatments other than systemic chemotherapy. They included tumor resection with GLIADEL wafer reimplantation in 2 patients, brachytherapy in 1 patient and stereotactic radiosurgery in 1 patient.

C. Efficacy Results

- **Primary Efficacy Endpoint: Overall Survival (unadjusted) in the ITT Population.**

The primary efficacy endpoint for this study was overall survival. Survival time is defined in the protocol as time from the date of randomization to the last day of follow up or the date of death. Per protocol and SAP, "The survival curve will be estimated for each treatment group using the Kaplan-Meier method." The survival curves were to be compared by the log-rank test. The sponsor's results are summarized in Reviewer Table 9. The log-rank analysis is stratified by country, which was not a pre-specified analysis.

Reviewer Table 9: Sponsor's Analysis for Overall Survival (ITT analysis)

ITT Population N=240	Median (95%CI) (Month)	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value*
GLIADEL (88/120)	13.9 (12.1-15.3)	0.71	0.53-0.96	
Placebo (93/120)	11.6 (10.2-12.6)			0.027*

*Based on sponsor's log-rank test stratified by country.

Reviewer Comment: FDA requested and reviewed randomization codes for Study T-301. The FDA and the sponsor reached an agreement that the randomization was stratified by center.

Reviewer Table 10 presents the results of the protocol-specified analysis.

Reviewer Table 10: FDA Analysis for Overall Survival (ITT analysis)

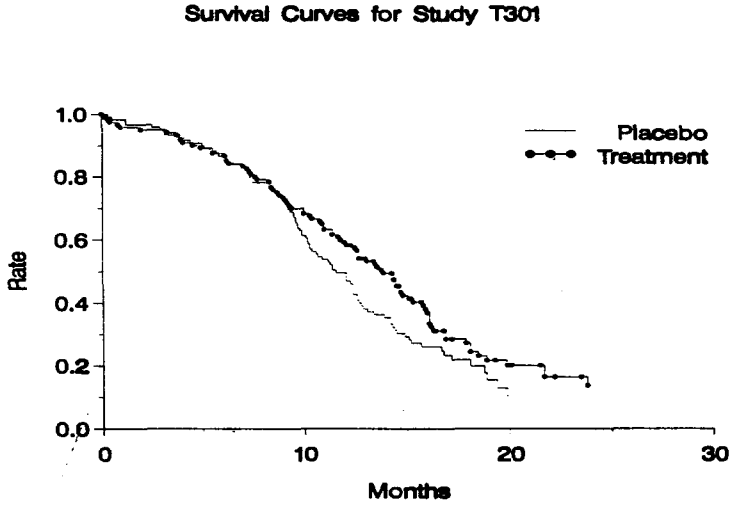
ITT Population N=240	Median (95%CI) (Month)	Hazard Ratio	95% CI for Hazard Ratio	P-value*
GLIADEL (88/120)	13.9 (12.1-15.3)	0.77	0.57-1.03	0.08
Placebo (93/120)	11.6 (10.2-12.6)			

*Based on non-stratified log-rank test.

A total of 88 patients (73.3%) in the GLIADEL group and 93 patients (77.5%) in the placebo group died before the study cut-off date. Median survival and hazard ratios favored the GLIADEL arm, but did not reach significance in the protocol-specified analysis.

Reviewer Figure 1 displays the Kaplan-Meier survival curves by treatment arm.

Reviewer Figure 1: Kaplan-Meier Survival Curves for Study T-301



Reviewer Table 11 shows effect of stratification for pre-specified prognostic factors and a sensitivity test stratifying for center (not-prespecified but invoking the true stratification factor). P-values became larger when stratified by accepted prognostic factors.
The p-value reaches statistical significance only when stratified by country. The clinical significance of this is unknown.

Reviewer Table 11: FDA Log-rank Test of Overall Survival (ITT analysis) using different stratification variables

ITT Population N=240	p-value Stratified by Country	p-value Stratified by Center	p-value Stratified by GBM/Other	p-value Stratified by KPS	p-value Stratified by Age
GLIADEL (88/120)	**0.03**	**0.07**	**0.14**	**0.07**	**0.103**
Placebo (93/120)					

*The p-value for the overall survival without stratification is 0.08

Reviewer Comment: The sample size was based upon a projected 68% one-year survival in the treatment group. However, the observed one-year survival for the treatment group is 59.2%. The current power is only about 46%. Even if the data provides 100% events, the power would increase only to 57%.

- **Subgroup Analysis: Survival in the GBM Group**

In the SAP, the GBM subgroup was chosen as the population of main interest for the treatment effect. Although median survival was longer in the GLIADEL group (13.5 months) than in placebo group (11.4 months), the survival difference using a non-stratified log-rank test did not reach statistical significance (p=0.20).

Reviewer Table 12 summarizes the FDA's survival analysis for the subgroup of patients with GBM.

Reviewer Table 12: FDA Analysis for Overall Survival for GBM subgroup

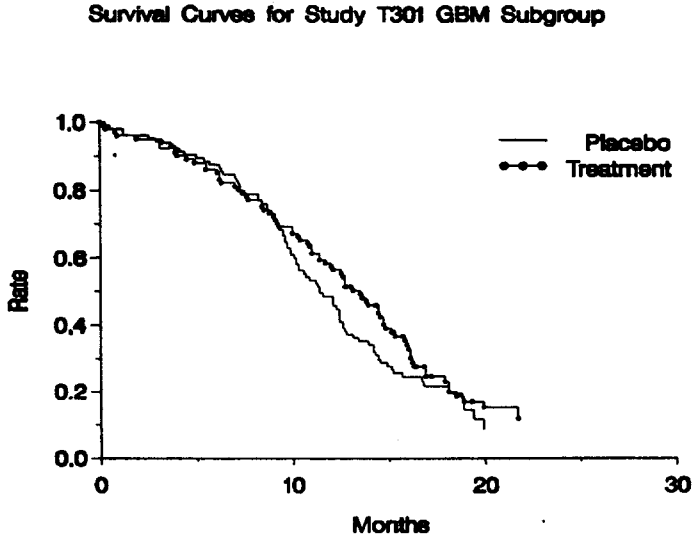
ITT Population N=207	Median (95%CI) (Month)	Hazard Ratio	95.6% CI for Hazard Ratio	P-value*
GLIADEL 78% (79/101)	13.5 (11.4-14.8)	0.82	0.601-1.113	0.20
Placebo 80% (85/106)	11.4 (10.2-12.6)			

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

Reviewer Comment: The sponsor provided an analysis for the GBM population that was based upon an analysis stratified by country, which also did not reach statistical significance with a p-value of 0.10. Other secondary endpoints such as 1-year survival, progression-free survival, time to KPS and neurological deterioration, and QoL were not ranked in the protocol or SAP.

Figure 2 presents the K-M curves for the same subpopulation.

Figure 2. Kaplan-Meier Survival Curves for Study T-301 GBM Subgroup



The next two tables (Table # 13 and Table #14) show an exploratory analysis performed by the FDA for survival in the ITT population as well as in the GBM subgroup using the histological diagnoses provided by the central pathologist.

Reviewer Table 13: FDA Analysis for Overall Survival in the ITT Population Adjusted for GBM (based on Central Diagnoses)

(88 vs. 99 GBMs)

Covariates	Non-stratified test p-value*
Trt + GBM	0.15

*p-value for treatment effect based on Cox regression analysis

Reviewer Table 14: FDA Analysis for Overall Survival for GBM Subgroup (based on Central Diagnoses)

N = 187	Median (95% CI) (Months)	Hazard Ratio	95% CI for Hazard Ratio	p-value
GLIADEL	12.7 (11.4-14.5)	0.86	0.63-1.2	
Placebo	11.6 (10.2-12.6)			0.40

Reviewer Comment: An exploratory analysis for overall survival in the ITT population adjusted for GBM as a covariate based on central pathologist diagnoses, as well as for overall survival for GBM subgroup, showed that the p-value for the treatment effect is not statistically significant (p=0.15, Table #13, and p=0.40, Table #14) with a hazard ratio 0.86 (95% CI: 0.63-1.20).

- **Exploratory Analysis Adjusting for Prognostic Factors**

The accepted prognostic factors in this disease, age, KPS and histology, were prespecified, along with country, as being of interest in exploratory analyses. Reviewer Table 15 presents the p-values for testing the treatment effect on overall survival in the ITT population after adjusting for these prognostic factors. Analyses are performed for the factors individually and together. Age is analyzed as a continuous variable; KPS as ≤ 70 vs. > 70; histology as GBM vs. other. KPS exerts the strongest effect. In a non-stratified test, none of the factors individually or together reach statistical significance.

Reviewer Table 15: ITT Analyses for Survival Adjusting for Prognostic Factors Using Cox Model

Covariates	Non-stratified test p- value*
Treatment only	0.08
Trt+Age	0.20
Trt+KPS	0.06
Trt+GBM	0.12
Trt+Age+KPS	0.15
Trt+Age+GBM	0.23
Trt+PSK+GBM	0.08
Trt+Age+KPS+GBM	0.16

*p-values for the treatment effect.

Reviewer Table 16 presents p-values for testing the treatment effect on overall survival in the GBM population after adjusting the prognostic factors. Again KPS exerts the strongest influence ($\leq$ 70% vs. >70%) but does not reach significance in the non-stratified log-rank test. Using baseline KPS of 70 as cut-off was proposed by the sponsor.

Reviewer Table 16: GBM Subgroup Analyses for Survival Adjusting for Prognostic Factors Using Cox Model

Covariates	Non-stratified test
Treatment only	0.20
Trt +Age	0.32
Trt+KPS	0.12
Trt+Age+KPS	0.22

*p-values for the treatment effect.

- **One-Year Survival**

One-year survival was pre-specified as a secondary endpoint for both the ITT and GBM populations. A 10% difference in one-year survival is noted in both populations; however, confidence limits overlap. The difference in 1 year survival between the treatment groups in the ITT population as well as in the GBM subgroup does not show statistically significance even using the sponsor's preferred analysis stratified of a log-rank test stratified by country (p= 0.11 and p=0.26) for the ITT and GBM population, respectively.

Reviewer Table 17: One Year Survival

One Year Survival	ITT		GBM	
	GLIADEL	Placebo	GLIADEL	Placebo
%	59.2%	49.6%	57.4%	48.6%
95% CI	50.4%, 68.0%	40.6%, 58.6%	47.8%, 67.1%	39.0%, 58.1%

Ref: Sponsor Table 27 and 30

- **Progression-free survival**

Progression-free survival was one of the protocol-prespecified secondary endpoints. Sponsor's analysis does not show a difference between the two treatment groups in progression-free survival (p=0.90) in the stratified log-rank test.

Reviewer Comment: Further analysis of this endpoint by the FDA was not undertaken. The difficulty in assessing tumor size, and therefore progression, in the setting of post-operative and post-radiation changes, further confounded by edema and treatment with steroids, is recognized.

- **Karnofsky Performance Status**

Karnofsky Performance Status was also pre-specified by the sponsor in the protocol as a secondary endpoint. The KPS score was comparable between the two treatment groups at baseline for the ITT population (see Sponsor Table 17). In the GBM subgroup, slightly more patients in the placebo group (57 patients – 53.8%) compared to the GLIADEL group (46 patients – 45.5%) had a KPS score of 90 or more.

The sponsor states that the median time to performance status deterioration in the ITT population was slightly longer in the GLIADEL group compared to placebo: 11.9 months (95% CI 10.4-13.7) in the GLIADEL group and 10.4 months (95% CI 9.5-11.9) in the placebo, (p=0.05) by the sponsor's log-rank stratified by country.

The sponsor states that median time to performance status deterioration between the treatment arms in the GBM subgroup was not statistically significant (p=0.19, log-rank test stratified by country).

Reviewer Comment: In assessing time to KPS deterioration, the sponsor counted death as an event. When only KPS deterioration and not death is used as an event, the time to deterioration did not reach statistical significance in the non-stratified log-rank test (p=0.61).

- **Quality of Life Assessment.**

QoL was assessed by the sponsor by EORTC and QoL Questionnaire-30 and Brain Cancer Module, a validated 24-questions QoL instrument designed to be used with QoL-30. The primary QoL parameter prespecified in the protocol was the Global Health Status/QoL based upon Questions #29 and #30.

The results of the analysis provided by the sponsor did not show significant differences between the two treatment groups.

Reviewer Comment: In the FDA analysis, no significant differences were shown between the two treatment groups in this secondary endpoint, by the unadjusted log-rank test, as well as when stratified by country or by center.

- **Neurological Evaluation**

Neurological evaluation was a protocol-prespecified secondary endpoint. The sponsor defined the time to neuroperfomance deterioration as time from the date of randomization to the date of first neuroperfomance measures. Sponsor's Table 37 below presents a summary of data collected for the eleven pre-specified neuroperformance measures.

Sponsor Table 37: Time to Neuroperformance Measures Deterioration, in Weeks (ITT population)

	Median time to deterioration (weeks)		p-value*
	GLIADEL N=120	Placebo N=120	
Vital signs	54.9	49.1	0.010
Level of consciousness	52.1	45.4	0.016
Personality	51.7	40.0	0.008
Speech	49.6	36.7	0.003
Visual status	44.0	42.4	0.087
Fundus	55.1	46.3	0.007
Cranial nerves II, IV, VI	54.9	49.1	0.016
Cranial nerves, other	54.3	46.3	0.003
Motor status	45.4	31.4	0.013
Sensory status	51.6	44.1	0.024
Cerebellar status	54.1	46.7	0.011

*p-values are based on analysis stratified by country

Reviewer Comment: The sponsor claims that in the ITT population the time to neuroperformance deterioration in the GLIADEL group was longer and reached statistical significance ($p<0.05$, stratified log-rank test). The exception was visual status.

Reviewer Table 18 shows the results of the analysis performed by the FDA where death was not counted as an event.

Reviewer Table 18: Time to Neuroperformance Status Deterioration

(death not count as an event).

	sponsor's P – value*	FDA's P – value**
Vital signs	0.010	0.59
Level of consciousness	0.016	0.60
Personality	0.008	0.73
Speech	0.003	0.01
Visual status	0.087	0.32
Fundus	0.007	0.89
Cranial nerves II, IV, VI	0.016	0.84
Cranial nerves, other	0.003	0.94
Motor status	0.013	0.21
Sensory status	0.024	0.75
Cerebellar status	0.011	0.34

** p-value based on sponsor's log-rank test stratified by country*

***p-value based on the FDA non-stratified log-rank analysis*

Reviewer Comment: In the FDA analysis where death is censored rather than counted as an event, the statistical significance is lost.

VII. Review of Safety

A. Extent of Exposure

All 240 patients from T-301 are evaluable for safety, 120 patients in each treatment group. Patients were evaluated on day 3, 7, and then weekly for 1 month, and at 3, 6, 12, 18 and 24 months from the day of randomization (initial surgery). Follow-up ranged from 12 months to 30 months. Forty-four patients (36.7%) in the GLIADEL group and 47 patients (39.2%) in the placebo group received the maximum of eight wafers implanted.

B. Deaths.

By the study cut-off date, 88 patients (73.3%) in the GLIADEL group and 93 patients (77.5%) in the placebo group died.

Sponsor Table #52 presents a summary of reasons for death.

Table 52: Summary of reasons for death

Reason for death	GLIADEL® (N=120) n (%)	Placebo N=120 n (%)
All deaths		
Malignant disease	75 (62.5)	84 (70.0)
Complication of initial surgical procedure	2 (1.7)	0
Complication of surgical procedure (recurrence)	1 (0.8)	0
Other	10 (8.3)	9 (7.5)
Deaths within 30 days of randomization		
Malignant disease	0	1 (0.8)
Complication of initial surgical procedure	2 (1.7)	0
Complication of surgical procedure (recurrence)	1 (0.8)	0
Other	2 (1.7)	1 (0.8)
Deaths at least 30 days after randomization		
Malignant disease	75 (62.5)	83 (69.2)
Complication of initial surgical procedure	0	0
Complication of surgical procedure (recurrence)	0	0
Other	8 (6.7)	8 (6.7)

The primary cause of death was disease progression in both groups. Ten and 9 patients in the GLIADEL and placebo group, respectively, died of causes listed by the investigator as "other". A detailed analysis of this category is as follows. The most frequent cause of death was pulmonary events: 5 patients in the GLIADEL group and 2 in the placebo group died from pulmonary embolism, 2 patients in each group died from pneumonia,

and 1 patient in the GLIADEL group died of pneumothorax. Acute cardiac events caused death in one patient from each group. In the placebo group 2 patients died from the neurological complications (one patient was listed as having "progressive neurological deficit" and the other died of seizures). One patient in the placebo group committed suicide and one died of sepsis. One patient in the GLIADEL group died of tumor progression (listed under "other", per investigator).

Reviewer Comment: All causes of death listed as "other" were verified by review of the CRFs.

C. Deaths in the First 30 Days of Randomization

Five patients (4.2%) in the GLIADEL group and two patients (1.7%) in the placebo group died within 30 days of randomization.

Reviewer Comment: Review of database UPAT – Description and Disposition of Patients confirms the total number of deaths as well as the number of patients of the listing who died in the first 30 days of initial surgery (randomization).

Reviewer Table 19: Reasons for Death in the First 30 days of Randomization

Cause of deaths	Total number of patients	
	GLIADEL (N=120)	Placebo (N=120)
Cerebral hematoma+/- edema	3	0
Pulmonary embolism	1	0
Acute abdominal or coron. Event	1	0
Sepsis	0	1
Malignant disease	0	1
TOTAL	**5**	**2**

Ref: "Death Report Form" of CRF.

D. Discontinuation due to Adverse Events.

One patient (ID 01056) was discontinued from the study due to an adverse event, brain edema, on postoperative Day 5. Her condition improved on Day 6, but subsequently the patient deteriorated, and was discontinued from the study on Day 22 due to the severe confusion and aphasia.

E. Wafer Removal

In the study design section of the protocol, the sponsor states that "the wafers begin to degrade following intracerebral implantation." The clinical pharmacology section of the GLIADEL label states that "although the rate of biodegradation varies from patient to patient, more than 70% of the copolymer degrades by three weeks." Data obtained at the re-operations and autopsies from the randomized trial supporting approval in recurrent GBM patients showed wafer remnants up to 232 days after GLIADEL implantation.

Reviewer Table 20: Indication for Additional Surgeries

During which Wafers were Detected and Removed.

	GLIADEL (N=120)	**Placebo (N=120)**
Complications		
first 30 days	4	3
30 – 80 days	2	1
Tumor progression	11	11
TOTAL	**17 (14.4%)**	**15 (12.5%)**

A total of 32 patients (17 in the GLIADEL arm and 15 in the placebo arm) had wafer removed at the time of additional surgery. The majority of patients (23 patients from both groups) underwent total wafer removal while 9 patients had partial wafer removal.

Reviewer Comment: The list of patients who underwent wafer removal due to an early adverse event is presented below.

GLIADEL group:

- *Patients 01293 – on post-operative Day 0, developed hematoma and underwent craniotomy with subsequent wafer removal.*
- *Patient 02059 – on post-operative Day 19, developed a brain abscess, had craniotomy and wafer removal.*
- *Patient 01056 (the one patient –listed by the sponsor) – had reoperation on Day 4 due to the brain edema.*
- *Patient 01138 – underwent recraniotomy with wafer removal on Day 22 for cyst formation.*

Placebo group:

- *Patients 01081 – developed brain edema on Day 22 after the initial surgery, underwent reoperation and wafers were removed.*
- *Patient 01137 – on postoperative Day 13, developed abscess, underwent reoperation with wafer removal.*
- *Patient 01153 – on the postoperative Day 4, underwent reoperation with wafer removal because of ventricular obstruction by a cyst.*

Wafer remnants were present up to 392 days in the GLIADEL group (derived from data base USURG –Surgery, variables ASURGNY – additional surgery, USMA – Study Medication Administration, variable WAFREM – wafer removal, and NBD_WREM – number of days from randomization to wafer removal).

F. Treatment-emergent adverse events (AE)

Treatment-emergent adverse events were identified by the sponsor as "signs and symptoms that were not present at baseline, or that were present at baseline but increased in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events." In addition to an open ended form by any AE, specific AEs, as described below, were also collected.

AE form AE7-12 requested details about the following 20 events: fever in the absence of infection, pain body whole, infection, thrombophlebitis deep, pulmonary embolus, nausea, vomiting, healing abnormality, aphasia, edema brain, confusion, convulsions, headache, hemiplegia, meningitis, intracranial abscess, hydrocephalus, anemia, leucopenia and thrombocytopenia.

If "healing abnormality" was checked on form AE7-12, another checklist was to be completed identifying type of abnormality: (a) fluid, CSF or subdural collections; (b) CSF leaks; (c) wound dehiscence, breakdown or poor healing; and (d) subgaleal or wound effusions.

Events defined as serious (fatal, life-threatening, requiring prolongation of hospitalization or resulting in persistent or significant disability) were reported on the Serious AE Query Form. All convulsions were to be reported as serious events.

The incidence of common AEs defined as occurring in >5% and irrespective of causality is shown in Sponsor Table 46.

Table 48: Treatment-emergent adverse events occurring in ≥5% of patients in either treatment gro by body system, COSTART term and treatment group

Adverse event	GLIADEL® N=120 n (%)	Placebo N=120 n (%)
Body as a whole		
Abdominal pain	10 (8.3)	2 (1.7)
Abscess	6 (5.0)	3 (2.5)
Accidental injury	6 (5.0)	8 (6.7)
Aggravation reaction	98 (81.7)	95 (79.2)
Allergic reaction	2 (1.7)	6 (5.0)
Asthenia	26 (21.7)	18 (15.0)
Back pain	8 (6.7)	4 (3.3)
Chest pain	6 (5.0)	0
Face edema	7 (5.8)	6 (5.0)
Fever	21 (17.5)	21 (17.5)
Headache	33 (27.5)	44 (36.7)
Infection	22 (18.3)	24 (20.0)
Pain	16 (13.3)	18 (15.0)
Cardiovascular system		
Deep thrombophlebitis	12 (10.0)	11 (9.2)
Hemorrhage	8 (6.7)	7 (5.8)
Pulmonary embolus	10 (8.3)	10 (8.3)
Digestive system		
Constipation	23 (19.2)	14 (11.7)
Diarrhea	6 (5.0)	5 (4.2)
Liver function tests abnormal	1 (0.8)	6 (5.0)
Nausea	26 (21.7)	20 (16.7)
Vomiting	25 (20.8)	19 (15.8)
Endocrine system		
Cushings syndrome	4 (3.3)	6 (5.0)
Diabetes mellitus	6 (5.0)	5 (4.2)
Metabolic and nutritional disorders		
Healing Abnormal	19 (15.8)	14 (11.7)
Peripheral edema	11 (9.2)	11 (9.2)
Musculoskeletal system		
Myasthenia	5 (4.2)	6 (5.0)
Nervous system		
Abnormal gait	6 (5.0)	6 (5.0)
Amnesia	11 (9.2)	12 (10.0)
Anxiety	8 (6.7)	5 (4.2)
Aphasia	21 (17.5)	22 (18.3)
Ataxia	7 (5.8)	5 (4.2)
Brain edema	27 (22.5)	23 (19.2)