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**Clinical Pharmacology and Biopharmaceutics
Review**

GLIADEL[®] WAFER

3.0 SUMMARY

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AGT	Alkylguanine-DNA Alkyltransferase
ALT (SGPT)	Alanine aminotransferase (serum glutamate-pyruvate transaminase)
AST (SCOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BCNU	1,3-bis(2-chloroethyl)-1-nitrosourea
CI	Confidence interval
CNS	Central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPH	Cox Proportional Hazards model
CSF	Cerebrospinal fluid
CT	Computed tomography
dL	Deciliter
EVAC	Ethylene vinyl acetate
F	Female
FDA	Food and Drug Administration
g	Gram
GBM	Glioblastoma multiforme
GEE	General Estimating Equations
IND	Investigational New Drug
ITT	Intent to treat
KPS	Karnofsky Performance Status
L	Liter
LOC	Level of consciousness
LOCF	Last observation carried forward
M	Male
mg	Milligram
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
N or No.	Number
N/A	Not applicable
NDA	New Drug Application
NR	Normal range
OC	Observed cases
ODAC	Oncology Drug Advisory Committee
PCPP:SA	Poly[bis(p-carboxyphenoxypropane):sebacic acid]
QOL	Quality of life
SAE	Serious adverse event

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

SE	Standard error
sNDA	Supplemental New Drug Application
TEAE	Treatment emergent adverse event
U/L	Units per liter
ULN	Upper limit of normal
WBC	White blood cells
WNL	Within normal limits

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3.1 PHARMACOLOGICAL CLASS, SCIENTIFIC RATIONALE, INTENDED USE AND POTENTIAL CLINICAL BENEFITS

3.1.1 Scientific Rationale

BCNU (carmustine), a widely used chemotherapeutic agent approved for use in the treatment of malignant brain tumors in the United States in 1979, has several limitations to its intravenous use in that setting. Although it is lipophilic and crosses the blood-brain barrier, its half-life in the circulation after intravenous administration is approximately 20 minutes. Furthermore, the intravenous dosages used in an attempt to produce a tumoricidal effect on the malignant brain tumor are often associated with systemic toxicity such as delayed myelosuppression and, less frequently, pulmonary fibrosis. Active metabolites may be responsible for the delayed bone-marrow toxicity. The entry of active metabolites into the cerebrospinal fluid (CSF) is rapid, with metabolite concentrations in the CSF of man equal to 50% of the concurrent plasma concentrations.

Because most malignant gliomas recur within two centimeters of their initial boundaries, local (regional) therapy for malignant gliomas is a logical approach to treatment. Local (regional) therapy affords an opportunity to increase the tumor's exposure to a chemotherapeutic agent by increasing the local concentrations or the duration of contact with the tumor, or both of these variables. Local (regional) therapy in the treatment of malignant gliomas has taken several approaches, including targeted intra-arterial infusions, infusion through implanted catheters, reservoirs, or pumps, and targeted disruption of the blood-brain barrier followed by systemic chemotherapy.

A different conceptual approach to local (regional) therapy for malignant gliomas is the use of implanted polymers containing chemotherapeutic agents. Early examples of such polymers included Spongostan sponge, gelatin sponge, or Surgicel. However, none of these agents were conclusively shown to be efficacious. Preclinical data on BCNU released from intracerebrally-implanted polymers composed of _____ or poly[bis(p-carboxyphenoxypropane)-sebacic acid], (PCPP-SA), have shown sustained release of high local BCNU concentrations, and survival has been shown to be extended when compared with controls in a model of established intracranial 9L gliosarcoma. There has been no evidence of systemic toxicity, and only local inflammatory changes around the implant in a primate model.

Polifeprosan 20 with carmustine implant (GLIADEL®) is a biodegradable wafer, composed of a copolymer matrix with carmustine (3.85%). GLIADEL® Wafer is designed to deliver carmustine directly into the surgical cavity created when a brain tumor is resected.

At the present time GLIADEL® Wafer is indicated for the treatment of patients with recurrent glioblastoma multiforme. Implantation of GLIADEL® Wafers after resection of recurrent malignant glioma produced a survival advantage compared to placebo wafer-treated patients. This benefit had a strong trend toward statistical significance in unadjusted analyses and became statistically significant when adjusted for specified prognostic factors. The evidence for GLIADEL®'s effectiveness in patients with the most

common and severe form of malignant glioma, glioblastoma multiforme, was similar to that obtained in the all-patient analyses.

3.2 FOREIGN MARKETING HISTORY SALES – SALES AND MARKETING

GLIADEL[®] Wafer received marketing approval in the United States, 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, United Kingdom and Uruguay as of December 2000 although the product is not yet commercially available in all of these countries.

3.3 CHEMISTRY, MANUFACTURING, AND CONTROLS

Please refer to the manufacturing process described in section 2.0 of the NDA.

3.4 NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY

Please refer to the pharmacology and toxicology information provided in section 5.0 of the NDA.

3.5 MICROBIOLOGY SUMMARY

Please refer to the pharmacology and toxicology information provided in section 7.0 of the NDA.

3.6 CLINICAL DATA SUMMARY OF STATISTICAL ANALYSIS

GLIADEL[®] Wafer currently has marketing authorization by the Food and Drug Administration (FDA) in the United States and in Europe (including France, Germany, Austria, Greece, Ireland, Luxembourg, Portugal, Spain and The Netherlands), for the treatment of patients with recurrent glioblastoma multiforme in whom surgical resection is indicated. The local action of GLIADEL[®] Wafer provided a rationale to explore its use as a first line treatment in patients with newly-diagnosed malignant glioma undergoing primary surgical resection. Additional clinical trials were conducted to properly assess the risk-benefit ratio of the GLIADEL[®] Wafer as first line treatment.

To evaluate the safety and effectiveness of GLIADEL[®] Wafer as first-line treatment for malignant glioma, the following three clinical trials were conducted:

- One pivotal, Phase III, multicenter, multinational (United States and 13 other countries), randomized, double-blind, placebo-controlled trial in 240 patients (120 in each treatment group) undergoing initial surgery for newly diagnosed-malignant glioma. The safety and efficacy of the GLIADEL[®] Wafer (polifeprosan 20 with carmustine 3.85%) was compared to placebo implants plus surgery and limited field radiation therapy. Up to eight GLIADEL[®] Wafers or placebo wafers were implanted into the tumor resection cavity after maximal tumor resection. All patients were to undergo a standard course of post-operative limited field radiation therapy between 2 to 4 weeks following wafer implantation.

Patients were periodically evaluated for safety and efficacy for up to 30 months post-implantation of the wafers. The main efficacy assessment was overall survival 12 months after enrollment of the last patient. Secondary efficacy variables included overall survival in a subgroup of patients with GBM, survival to 12 months, progression-free survival, survival censoring patients with reoperation for disease progression, Quality of Life (QOL), Karnofsky Performance Score (KPS), and neurological evaluation. Safety assessments included adverse events and laboratory testing (hematology and serum chemistry).

- One supportive, Phase III, multicenter, international (Finland and Norway), randomized, double-blind, placebo-controlled trial in 32 patients (16 in each treatment group) undergoing initial surgery for newly-diagnosed malignant glioma. The safety and efficacy of the GLIADEL® Wafer (polifeprosan 20 with carmustine 3.85%) was compared to placebo implants plus surgery and limited field radiation therapy. Up to eight GLIADEL® Wafers or placebo wafers were implanted into the tumor resection cavity after maximal tumor resection. About three weeks after surgery, standard radiotherapy was to begin. Patients were periodically evaluated for safety and efficacy for up to two years following wafer implantation. The primary efficacy endpoints included one-year survival rates, median survival duration, and time to treatment failure. Safety assessments included adverse events, laboratory testing (hematology, serum chemistry, and urinalysis), tumor imaging, and neurological examinations.
- One multicenter (United States only), open-label, Phase I/II trial in 22 patients undergoing surgery for initially-diagnosed malignant glioma or high grade glioma. The safety of the GLIADEL® Wafer (polifeprosan 20 with carmustine 3.85%) was studied. Up to eight GLIADEL® Wafers were implanted into the tumor resection cavity after maximal tumor resection. About three weeks after surgery, standard radiotherapy was to begin. Patients were periodically evaluated for safety and efficacy for up to two years following wafer implantation. Evaluations of safety included neurological examinations, level of consciousness (LOC) assessments, KPS evaluations, Mini-Mental State Examinations (MMSE), and computed tomography (CT) or magnetic resonance imaging (MRI) scans. Time to treatment failure (based on tumor imaging scans and KPS Score), QOL, and patient survival were also evaluated.

3.6.1 ADDITIONAL Indication for Which Sponsor is Seeking Approval for the GLIADEL® Wafer

The additional indication for which the Sponsor, Guilford Pharmaceuticals Incorporated, is seeking approval is use of the GLIADEL® Wafer 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 surgical resection.

3.6.2 Overview of Clinical Pharmacokinetics and Pharmacology of the GLIADEL® Wafer

A waiver was granted of the requirements for information under Section 6, Human Pharmacokinetics and Bioavailability. Please refer to Guilford Pharmaceuticals Inc. "Request for Waiver" submitted to the NDA on March 13, 1996.

3.6.3 Controlled and Uncontrolled Clinical Trials Conducted Within and Outside of the United States

3.6.3.1 CONTROLLED CLINICAL TRIALS

The following table displays all controlled clinical trials conducted within and outside the United States to support the indication of GLIADEL® Wafer 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 surgery.

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Table 1: Controlled Clinical Studies Showing That GLIADEL[®] Wafer Is Effective As Treatment For Patients With Newly-diagnosed Malignant Glioma

Study # Publication Information	Completion Status (Start date, Completion date) Investigative Study Sites	Study Design	Treatment Formulation and Dose, Duration of Treatment	Number Entered Each Treatment Number of Dropouts due to AE	Mean Age (years) Gender Race	Results and Conclusions
T-301 No publications	Complete (First patient enrolled December 1, 1997; last patient observed June 30, 2000) 38 sites: Australia, Austria, Belgium, France, Germany, Greece, Israel, Italy, The Netherlands, New Zealand, Spain, Switzerland, UK, US	Pivotal Study Multicenter, randomized, double-blind, placebo-controlled Phase III safety and efficacy study in patients with newly-diagnosed malignant glioma undergoing initial surgery (tumor resection)	GLIADEL [®] Wafer: Up to eight 200-mg polymer wafers each containing 7.7 mg BCNU, surgically implanted once Placebo: Up to eight 200-mg polymer wafers, surgically implanted once	GLIADEL [®] : 120 patients Placebo: 120 patients Dropouts due to AEs: GLIADEL [®] : 1 PLACEBO: 0	GLIADEL [®] : N=120 Mean Age: 52.6 Gender: M: 76 (63.3%) F: 44 (36.7%) Race: White: 116 (96.7%) Black: 1 (0.8%) Oriental: 1 (0.8%) Hispanic: 1 (0.8%) Other: 1 (0.8%) Placebo N=120 Mean Age: 53.6 (0.8) Gender: M: 84 (70.0%) F: 36 (30.0%) Race: White: 116 (96.7%) Black: 1 (0.8%) Oriental: 1 (0.8%) Hispanic: 0 Other: 2 (1.7%)	Efficacy: GLIADEL [®] increased the median survival from 11.6 months to 13.9 months, a 20% improvement (p=0.027). GLIADEL [®] increased the one-year survival rate from 49.6% to 59.2%. GLIADEL [®] also increased overall survival in patients with the tumor type glioblastoma multiforme; the treatment effect was statistically significant when the results were adjusted for prognostic factors (p=0.050). Median survival in this subgroup of patients was 13.5 months in the GLIADEL [®] group and 11.4 months in the placebo group, and one year survival was 57.4% in the GLIADEL [®] group and 48.6% in the placebo group. Safety: Safety results were comparable between the treatment groups. GLIADEL [®] : 1244 AEs in 119 patients; 374 SAEs in 112 patients. Placebo: 1224 AEs in 120 placebo patients and 370 SAEs in 110 placebo patients). Deaths: 88 (73.3%) GLIADEL [®] and 93 (77.5%) placebo patients died before study cut-off date. Most patients died of malignant disease [GLIADEL [®] 75 (62.5%); placebo 84 (70.0%)]. Most common AEs: aggravation reaction [85 GLIADEL [®] patients (70.8%); 83 placebo patients (69.2%)] Most common SAEs: nervous system [76 GLIADEL [®] patients (63.3%); 77 placebo patients (64.2%)], particularly convulsion and

Table 1: Controlled Clinical Studies Showing That GLIADEL® Wafer Is Effective As Treatment For Patients With Newly-diagnosed Malignant Glioma

Study # Publication Information	Completion Status (Start date, Completion date) Investigative Study Sites	Study Design	Treatment Formulation and Dose, Duration of Treatment	Number Entered Each Treatment Number of Dropouts due to AE	Mean Age (years) Gender Race	Results and Conclusions
						hemiplegia. More GLIADEL® patients had intracranial hypertension (11 GLIADEL®; 2 placebo [p=0.019]). More GLIADEL® patients [6, (5.0%)] compared to placebo [1, (0.8%)] had CSF leaks. Fewer than 10% of all AEs and fewer than 20% of all SAEs were considered treatment-related; treatment-related AEs/SAEs were comparable between groups. D/C AE: One GLIADEL® patient discontinued due to AE. Labs: Lab abnormalities and mean lab values during the study were similar between groups; there were no clinically significant patterns of lab abnormalities associated with study drug.
F-GLI-CL-0190 Valtonen S, Timonen U, Tolvanen P, Kalimo H, Kivipelto L, Heiskanen O, Unsgaard G, Kuurne T.	Complete (First patient enrolled March 23, 1992; last patient observed May 14, 1995) 4 sites: Norway, Finland	Supportive Study Multicenter, randomized, double-blind, placebo-controlled Phase III	GLIADEL® Wafer: Up to eight 200-mg polymer wafers each containing 7.7 mg BCNU, surgically implanted once Placebo: Up to eight 200-mg	GLIADEL® : 16 patients Placebo: 16 patients Dropouts due to AEs: GLIADEL® : 0	GLIADEL® : N=16 Mean Age: 53.5 Gender: M: 8 (50%) F: 8 (50%) Race: N/A	Efficacy: GLIADEL® increased one-year survival rates by approximately 230% (63% of GLIADEL® patients were alive compared to 19% of placebo patients; P = 0.029). GLIADEL® treatment produced statistically significant reductions in mortality relative to placebo treatment over both the 12-month period (relative risk 0.154 [95% CI: 0.051 to 0.467; P = 0.0010) and the 24-month period (relative risk 0.177 [95% CI: 0.067 to 0.468]; P = 0.0010).

Table 1: Controlled Clinical Studies Showing That GLIADEL[®] Wafer Is Effective As Treatment For Patients With Newly-diagnosed Malignant Glioma

Study # Publication Information	Completion Status (Start date, Completion date) Investigative Study Sites	Study Design	Treatment Formulation and Dose, Duration of Treatment	Number Entered Each Treatment Number of Dropouts due to AE	Mean Age (years) Gender Race	Results and Conclusions
Interstitial Chemotherapy with Carmustine-Loaded Polymers for High Grade Gliomas--A Randomized, Double-Blind Study. Neurosurg, 1997; 41:44-9.		safety and efficacy study in patients with newly-diagnosed malignant glioma undergoing initial surgery (tumor resection)	eight 200-mg polymer wafers, surgically implanted once	Placebo: 0	Placebo: N=16 Mean Age: 53.9 Gender: M: 10 (62%) F: 6 (38%) Race: N/A	(relative risk 0.177 [95% CI: 0.067 to 0.468]; P = 0.0005) after wafer implantation surgery. GLIADEL [®] treatment increased median overall patient survival by more than 18 weeks (58.1 weeks vs. 39.9 weeks; P = 0.011). Safety TEAEs: 12 (75%) GLIADEL [®] patients and 9 (56%) placebo patients experienced at least 1 TEAE. SAEs: 10 SAEs in 5 GLIADEL [®] patients; 5 SAEs in 4 placebo patients. Deaths: 11 (69%) GLIADEL [®] and 15 (94%) placebo patients died during the study. Most frequent TEAEs: GLIADEL [®] - hemiplegia (38%), convulsion (19%), aphasia (13%), and visual field defect (13%). Placebo - hemiplegia (25%) and convulsions (13%). The investigator did not consider any event to be probably-related to study drug. In the GLIADEL [®] group, 3 (10%) patients had possibly-related TEAEs; one (6%) placebo patient had a possibly-related TEAE.

3.6.3.2 UNCONTROLLED CLINICAL TRIALS

The following table displays all uncontrolled clinical trials conducted within and outside the United States to support the indication of GLIADEL® Wafer 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 surgery.

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Table 2: Uncontrolled Clinical Studies of GLIADEL[®] Wafer Used as Treatment For Patients With Newly-diagnosed Malignant Glioma

Study # Publication Information	Completion Status (Start date, Completion date) Investigative Study Sites	Study Design	Treatment Formulation and Dose, Duration of Treatment	Number Entered Each Treatment Number of Dropouts due to AE	Median Age (years) Gender Race	Results and Conclusions
9003 Brem H, Ewend MG, Piantadosi S, Greenhoot J, Burger PC, Sisti M. The Safety of Interstitial Chemotherapy with BCNU-Loaded Polymer Followed by Radiation Therapy in the Treatment of Newly Diagnosed Malignant Gliomas: Phase I Trial. J Neuro-oncology, 1995; 26:111-23.	Complete First patient enrolled July 5, 1990; last patient enrolled August 14, 1991 3 sites in the US	Multicenter, open-label, uncontrolled, Phase I/II, safety study in patients with newly-diagnosed malignant glioma study in patients with newly-diagnosed malignant glioma undergoing initial surgery (tumor resection)	GLIADEL [®] Wafer: Up to eight 200-mg polymer wafers each containing 7.7 mg BCNU, surgically implanted once	GLIADEL [®] : 22 patients Dropouts due to AEs: 0	Median Age: 60 Gender: M: 15 (68%) F: 7 (32%) Race: N/A	In this 22-patient study, the median survival duration was 41.7 weeks after study surgery (95% CI: 31.9 to 54.0 weeks). At 6 months, 18 patients (82%) were alive. At six months after implantation surgery, 4 patients (18%) had died; by 12 months after surgery, 14 patients (64%) had died. By 18 and 24 months after surgery, 18 (82%) and 19 (86%) patients had died, respectively.

3.6.4 Overview of Data From Adequate and Well-Controlled Trials Supporting the Effectiveness of the GLIADEL[®] Wafer for the Treatment of Malignant Glioma

3.6.4.1 PIVOTAL STUDY T-301

This was a Phase III, multicenter (38 centers in 14 countries), randomized, double-blind, placebo-controlled trial to determine the safety and efficacy of polifeprosan 20 with carmustine 3.85% (GLIADEL[®] Wafer) implants plus surgery and limited field radiation therapy, compared to placebo implants plus surgery and limited field radiation therapy, for improving survival in patients undergoing initial surgery for newly-diagnosed malignant glioma. Patients who had radiographic evidence on cranial magnetic resonance imaging (MRI) of a single contrast-enhancing unilateral supratentorial cerebral tumor for whom surgical treatment within two weeks of the baseline MRI scan was indicated were eligible for the study. Patients had to have an intra-operative pathological diagnosis of malignant glioma. Patients who had received prior cytoreductive surgery, prior radiotherapy to the brain or chemotherapy, or who had more than one focus of the tumor or a tumor crossing the midline, or concomitant life-threatening disease, were excluded from the study.

Up to eight GLIADEL[®] Wafers (each containing 7.7 mg carmustine) or placebo wafers were implanted into the tumor resection cavity after maximal tumor resection.

Patients were evaluated a maximum of 12 times during the course of the study, depending on survival time. The short-term follow-up phase included assessments during weeks 1, 2, and 4 following implantation of the wafers. All patients were to undergo a standard course of post-operative limited field radiation therapy between 2 to 4 weeks following wafer implantation. The long-term follow-up phase included evaluations at 3, 6, 12, 18, 24 and 30 months post-implantation of the wafers. The primary efficacy parameter was overall survival 12 months after enrollment of the last patient. The secondary efficacy parameters were overall survival in a subgroup of patients with GBM, survival to 12 months, progression-free survival, KPS scores, neurological evaluation, and QOL. Safety parameters included collections of adverse events and laboratory testing (hematology and serum chemistry).

Using a two-tailed log-rank test with an α level of 0.05 and a power of $1-\beta=0.90$, the estimated sample size to detect an 18% difference in 12 month survival rates between the two treatment groups (based on survival rates of 68% on the GLIADEL[®] group and 50% in the placebo group, and assuming 18 months accrual, 12 months follow-up time and a 15% patient loss rate) was 240 patients (120 per treatment group). For the efficacy analysis, all randomized patients (whether they were eligible or not) were included in the ITT population. The sub-group of patients with glioblastoma multiforme was also analyzed. All randomized patients who had at least one wafer implanted were evaluable for safety. All statistical tests were two-sided and the level of statistical significance was fixed at 5%. Categorical data were presented in contingency tables. Continuous data were summarized with at least the following: frequency (n), median, mean, standard error of the mean (SEM), minimal and maximal values. Time to event analyses were performed using the Kaplan-Meier method and compared using a log-rank test stratified by country as a

primary comparison and the Wilcoxon test as a sensitivity comparison. For the survival analysis, the treatment effect was also examined after adjusting for prognostic factors.

Median survival in the ITT population was increased by 20% in the GLIADEL[®] group (13.9 months) compared to the placebo group (11.6 months) (see Table 5). The difference in overall survival between the treatment groups was statistically significant for both the stratified log-rank test ($p=0.027$) and the stratified log-rank test adjusted for prognostic factors ($p=0.020$). Baseline KPS score, age, final histopathological diagnosis and the number of wafers implanted were shown to be statistically important predictors of survival in the ITT population ($p<0.001$, $p=0.001$, $p=0.011$ and $p=0.037$, respectively). The percentage of patients in the ITT population surviving to one year was approximately 10% higher in the GLIADEL[®] Wafer group (59.2%) compared to the placebo group (49.6%) (see Table 6). In the GBM subgroup there was a similar increase in median survival and the percentage of patients surviving to one year in the GLIADEL[®] Wafer group (13.5 months and 57.4, respectively) compared to the placebo group (11.4 months and 48.6%, respectively) (see Table 5 and Table 6). The difference between the treatment groups was not statistically significant for the main stratified log-rank test ($p=0.098$), but the treatment effect was statistically significant when the results were adjusted for prognostic factors ($p=0.050$). In the GBM subgroup, baseline KPS score ($p=0.001$), age ($p=0.040$) and the number of wafers implanted ($p=0.018$) were shown to be statistically important predictors of survival.

The results for a supportive survival analysis, censoring the two patients who had undergone further surgery with GLIADEL[®] Wafer reimplantation, were similar to the overall results. There was no statistically significant difference between the treatment groups in survival up to 12 months after initial surgery (i.e. censoring survival data after 12 months) for either the ITT population or the GBM subgroup.

The median progression-free survival (see Table 6) was almost identical for the two treatment groups for both the ITT population (5.9 months and approximately 48% of patients progression-free at one year for both groups, $p=0.901$) and the GBM subgroup (5.8 months for the GLIADEL[®] Wafer group and 5.7 months for the placebo group, and 47.6% of patients in the GLIADEL[®] group and 44.1% of patients in the placebo group progression-free at one year, $p=0.621$).

The results for other secondary efficacy parameters in the ITT population were also more favorable for patients in the GLIADEL[®] Wafer group compared to patients in the placebo group (see Table 6). The difference between the treatment groups was statistically significant and favored GLIADEL[®] Wafer for the time to KPS score deterioration ($p=0.050$) and time to deterioration of neuroperformance measures ($p<0.05$ for 10/11 neuroperformance measures assessed). The difference between the treatment groups for these secondary efficacy parameter results in the GBM subgroup were smaller (although still favoring GLIADEL[®] Wafer over placebo), and not statistically significant for any of the parameters except 5 of the 11 neuroperformance measures.

Approximately 27% of patients in this study underwent reoperation for disease progression. Since the primary endpoint for the study was survival, reoperation for tumor progression may have confounded this

endpoint. Therefore an additional supportive analysis was performed, which censored patients who had undergone second surgery after tumor progression.

The Kaplan-Meier method was used but patients were censored at the time of second surgery for tumor progression.

The median time to reoperation was longer for the GLIADEL® group (260 days) compared to the placebo group (213 days), suggesting a beneficial effect of GLIADEL® in prolonging the time to disease progression and reoperation (see Table 3).

TIME TO REOPERATION (DAYS)	GLIADEL® N=36	PLACEBO N=30
Median	260	213
Range		

Censoring patients who underwent reoperation for tumor progression, patients in the GLIADEL® group survived longer than patients in the placebo group. The median survival was 14.8 months in the GLIADEL® group compared to 11.4 months in the placebo group. The percentage of patients surviving to one year was 61.0% in the GLIADEL® group and 48.8% in the placebo group. The Kaplan-Meier estimates were compared using a stratified logrank test, and the difference between the treatment groups was statistically significant ($p=0.014$). The difference between the treatment groups was smaller for the GBM subgroup ($p=0.131$). The full results are presented in Table 4.

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PARAMETER		ITT POPULATION (N=240)		GBM SUBGROUP (N=207)	
		GLIADEL [®] N=120	PLACEBO N=120	GLIADEL [®] N=101	PLACEBO N=106
Number of deaths	n (%)	61 (50.8)	74 (61.7)	58 (57.4)	67 (63.2)
Post implantation survival	Median (months)	14.8	11.4	13.1	11.4
	95% CI	12.5, 16.1	9.9, 12.7	11.7, 15.8	9.7, 12.6
One year survival	%	61.0	48.8	57.8	47.4
	95% CI	51.4, 70.6	38.8, 58.9	47.3, 68.3	36.7, 58.1
Stratified logrank test	p	0.014		0.131	

GBM = Glioblastoma multiforme

CI = Confidence interval

Data extracted from Appendix II.F, Table 4.20 and 4.20a

The median survival time after reoperation was 6.1 months for the GLIADEL[®] group and 7.7 months for the placebo group. There was no statistically significant difference between the treatment groups in the survival times after reoperation (p=0.3).

The median time to deterioration of the KPS score and the percentage of patients deterioration-free after one year in the ITT population were both higher in the GLIADEL[®] group (11.9 months and 47.5%, respectively) than in the placebo group (10.4 months and 39.3%, respectively) (p=0.050). The median time to deterioration of the KPS score and the percentage of patients deterioration-free after one year in the GBM subgroup were both higher in the GLIADEL[®] group (11.7 months and 43.6%, respectively) than in the placebo group (10.3 months and 38.0%, respectively) (p=0.189). The difference between treatment groups in time to deterioration of neuroperformance measures was statistically significant and favored GLIADEL[®] for 10 out of 11 neuroperformance measures in the ITT population (the exception was visual status). In the GBM subgroup the time to deterioration favored GLIADEL[®] for all neuroperformance measures except visual status, but the treatment difference was only statistically significant for 5 of the 11 neuroperformance measures.

The efficacy of GLIADEL[®] Wafer treatment in special subpopulations of patients (age ≥ 65 or < 65), sex, and racial groups) was also assessed. The number of patients enrolled in T-301 trial older than 65 years of age was 4 in each of the GLIADEL[®] Wafer and placebo wafer groups. The overall survival experience of the older patient group was somewhat shorter than the younger group, but the small numbers preclude any substantive conclusion. Approximately 65% of the patients enrolled in this study were male (76 [63.3%] in the GLIADEL[®] Wafer group and 84 [70%] in the placebo group) and approximately 35% were female (44 [36.7%] in the GLIADEL[®] Wafer group and 36 [30%] in the placebo group). The overall survival experiences of the two groups were similar, with the GLIADEL[®] Wafer group showing a longer median

survival in both males and females than the placebo group. Approximately 97% of the patients enrolled in this study were Caucasian, as would be expected from a study that was predominantly conducted within the EU. Given the enrollment characteristics for this trial, no statement can be made on any differential effect of GLIADEL[®] Wafer in different racial populations.

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Table 5: Overview of Study T-301 Primary and Key Secondary Efficacy Parameters - ITT Population and GBM Subgroup

PARAMETER OR FACTOR	ITT POPULATION		GBM SUBGROUP	
	GLIADEL® WAFER N=120	PLACEBO N=120	GLIADEL® WAFER N=101	PLACEBO N=106
Patient Survival (Primary Efficacy – ITT Population; Secondary Efficacy – GBM Subgroup)				
Number of deaths (%)	88 (73.3%)	93 (77.5%)	79 (78.2%)	85 (80.2%)
Post-implantation survival - median months (95% CI)	13.9 months (12.1, 15.3)	11.6 months (10.2, 12.6)	13.5 months (11.4, 14.8)	11.4 months (10.2, 12.6)
One year survival – percent of patients (95% CI)	59.2% (50.4, 68.0)	49.6% (40.6, 58.6)	57.4% (47.8, 67.1)	48.6% (39.0, 58.1)
Stratified Log-rank test:	p = 0.027		p = 0.098	
Patient Survival Potential Prognostic Factors (Stratified Log-Rank Test and Cox Proportional Hazards Model)	STRATIFIED LOG-RANK TEST P -VALUE	CPH MODEL P-VALUE	STRATIFIED LOG-RANK TEST P -VALUE	CPH MODEL P-VALUE
KPS score	<0.001	<0.001	0.001	<0.001
Age	0.001	0.003	0.040	0.063
Final histopathological diagnosis	0.011	n/a	n/a	n/a
Number of wafers implanted	0.037	n/a	0.018	n/a
Gender	0.576	n/a	0.684	n/a
Treatment Group	n/a	0.020	n/a	0.050

GBM = Glioblastoma multiforme. CI = Confidence interval. CPH = Cox Proportional Hazards model - stratified by country and number of wafers implanted.

Karnofsky Performance Status (KPS) score: ≤70% vs. >70%.

Age: ≥60 years vs. <60 years.

Final histopathological diagnosis: Glioblastoma multiforme (GBM) vs. other.

Number of wafers implanted: <6 vs. (6, 6.5) vs. (7, 7.5) vs 8.

Gender: Male vs female.

Treatment Group: GLIADEL® Wafer vs. placebo.

n/a: not applicable

Data extracted from Full Study Report T-301: Appendix II.F, Tables 4.01, 4.01a, 4.03a, 4.04a.

Table 6: Overview of Study T-301 Secondary Efficacy Parameters - ITT Population and GBM Subgroup

SECONDARY EFFICACY PARAMETER	ITT POPULATION		GBM SUBGROUP	
	GLIADEL [®] WAFER N=120	PLACEBO N=120	GLIADEL [®] WAFER N=101	PLACEBO N=106
<u>Survival Data Censored at 12 Months</u>				
Number of deaths (%)	49 (40.8%)	60 (50.0%)	43 (42.6%)	54 (50.9%)
Survival - median months (95% CI)	---	11.6 months (10.2, ---)	11.4 months (---)	11.4 months (10.2, ---)
One year survival - percent of patients (95% CI)	59.2% (50.4, 68.0)	49.6% (40.6, 58.6)	57.4% (47.8, 67.1)	48.6% (39.0, 58.1)
Stratified Log-rank test:	p = 0.108		p = 0.206	
<u>Progression-Free Survival</u>				
Number of events (%)	96 (80.0%)	95 (79.2%)	84 (83.2%)	85 (80.2%)
Progression-free survival - median months (95% CI)	5.9 months (4.4, 8.3)	5.9 months (4.7, 7.4)	5.8 months (3.9, 8.3)	5.7 months (3.6, 6.6)
Six month progression-free survival - percent of patients (95% CI)	48.8% (39.7, 58.0)	48.1% (39.0, 57.3)	47.6% (37.7, 57.6)	44.1% (34.4, 53.7)
Stratified Log-rank test:	p = 0.901		p = 0.621	
<u>Survival Data Censoring Patients with Reoperation for Tumor Progression</u>				
Number of deaths (%)	61 (50.8%)	74 (61.7%)	58 (57.4%)	67 (63.2%)
Post-implantation survival - median months (95% CI)	14.8 months (12.5, 16.1)	11.4 months (9.9, 12.7)	13.1 (11.7, 15.8)	11.4 (9.7, 12.6)
One year survival - percent of patients (95% CI)	61.0% (51.4, 70.6)	48.8% (38.8, 58.9)	57.8% (47.3, 68.3)	47.4% (36.7, 58.1)
Stratified Log-rank test:	p = 0.014		p = 0.133	

Table 6 continued on next page

Table 6: Overview of Study T-301 Secondary Efficacy Parameters --- ITT Population and GBM Subgroup

SECONDARY EFFICACY PARAMETER	ITT POPULATION		GBM SUBGROUP	
	GLIADEL® WAFER N=120	PLACEBO N=120	GLIADEL® WAFER N=101	PLACEBO N=106
<u>KPS Score Deterioration</u>				
Number of events (%)	96 (80.0%)	97 (80.8%)	86 (85.1%)	88 (83.0%)
Time to deterioration - median months (95% CI)	11.9 months (10.4, 13.7)	10.4 months (9.5, 11.9)	11.7 months (10.0, 12.7)	10.3 months (9.2, 11.6)
One year deterioration free – percent of patients (95% CI)	47.5% (38.4, 56.5)	39.3% (30.3, 48.3)	43.6% (33.8, 53.4)	38.0% (28.6, 47.4)
Stratified Log-rank test:	p = 0.050		p = 0.189	
<u>Neurological Symptoms Deterioration</u>				
Time to deterioration – median weeks				
Vital signs	54.9	49.1 *	54.3	49.1 *
Level of consciousness	52.1	45.4 *	51.6	44.7
Personality	51.7	40.0 *	50.4	40.0
Speech	49.6	36.7 *	47.3	32.4 *
Visual status	44.0	42.4	40.3	41.6
Fundus	55.1	46.3 *	54.3	46.3 *
Cranial nerves II, IV, VI	54.9	49.1 *	54.3	49.1 *
Cranial nerves, other	54.3	46.3 *	52.7	46.3 *
Motor status	45.4	31.4 *	43.3	31.0
Sensory status	51.6	44.1 *	51.0	44.1
Cerebellar status	54.1	46.7 *	53.6	46.7 *
P-Value (GLIADEL® Wafer vs. placebo):	* p ≤ 0.05		* p ≤ 0.05	

CI = Confidence interval

GBM = Glioblastoma multiforme

Data extracted from Full Study Report T-301: Appendix II.F, Tables 4.05, 4.05a, 4.07, 4.07a, 4.08 to 4.18, 4.08a to 4.18a, 4.19, 4.19a, 4.20, and 4.20a.

3.6.4.2 SUPPORTIVE STUDY F-GLI-CL-0190

This was a Phase III, multicenter (4 centers in 2 countries), randomized, double-blind, placebo-controlled trial to determine the safety and efficacy of polifeprosan 20 with carmustine 3.85% (GLIADEL® Wafer) implants plus surgery and external beam radiation therapy, compared to placebo implants plus surgery and limited field radiation therapy, in patients with newly-diagnosed malignant glioma. Patients with initially diagnosed malignant glioma, and without prior surgical, radiotherapeutic, or chemotherapeutic treatment, were eligible for the study. Patients had to have an intra-operative pathological diagnosis of malignant glioma (or high grade glioma, per amended protocol).

Up to eight GLIADEL® Wafers (each containing 7.7 mg carmustine) or placebo wafers were implanted into the tumor resection cavity after maximal tumor resection.

All patients were to undergo a standard course of post-operative limited field radiation therapy between 2 to 4 weeks following wafer implantation. Patients were evaluated for safety and efficacy during week 1, at discharge from hospital, at radiation therapy initiation, at three months following implantation of the wafers, and every three months thereafter for up to two years post-implantation (depending on survival time). The primary efficacy parameters were 12-month survival rates, median survival duration and time to treatment failure. Secondary efficacy parameters included KPS scores, Mini-Mental State Examination (MMSE) scores, and results of neurological examinations. Safety parameters included collections of adverse events and laboratory testing (hematology and serum chemistry).

The sample size for the study was calculated using the following assumptions: the expected median survival time was 12 months after first surgery and radiotherapy; GLIADEL® Wafer was to be considered effective if a 33% (4-month) longer median survival time was noted in comparison to placebo; and monitoring of the results was to be done after every tenth event (death) using a sequential restricted triangular stopping rule. This rule was established to provide a measure to terminate the study early, with 80% power and 5% one-sided type I error rate, if a 33% survival time difference was documented.

The primary efficacy analyses were to be the comparisons between the two treatment groups of survival and time to treatment failure. No patient and no patient visits were excluded from analyses. Thus, all analyses were ITT analyses using all enrolled patients. No analyses were performed that depended upon an assessment of patient evaluability as defined in the protocol. Additionally, data were analyzed separately for patients with the most severe type of malignant glioma--glioblastoma multiforme. Treatment effect was also assessed after adjustments for significant prognostic factors using a proportional hazards multiple regression method.

Time to treatment failure was analyzed using the Kaplan-Meier technique over the entire 24 month follow-up period. Survival was assessed by two methods: survival rate 12 months after wafer implantation surgery and Kaplan-Meier techniques at 12 and 24 months after wafer implantation surgery. Although not

a primary efficacy measure, survival rate at 24 months after wafer implantation surgery is also presented. In addition, the treatment effect on both 12-month and overall survival (24 months) was estimated using a proportional hazards multiple regression method. Factors of potential clinical importance were tested by univariate regression for overall survival, and those factors with P-values <0.15 were used (along with treatment) as the starting point for all multivariate regression analyses. A stepdown multiple regression method was used with successive iterations until all factors left in each model had P values ≤ 0.05 . Treatment was always constrained to remain in each model. An additional multiple regression analysis stratified by tumor type was performed; this analysis makes no assumptions about proportionality of hazards across strata. The General Estimating Equations (GEE) methods of Liang and Zeger was utilized to analyze Neurological Examination, KPS Scores, and MMSE results over time. Two types of GEE methods were used for all of these analyses: an observed cases (OC) GEE method and a last observation carried forward (LOCF) GEE method. The observed cases GEE method incorporates all data actually available at each visit. Thus, in this type of analysis, patients who died during the study contributed no further data after their death. In the last observation carried forward GEE method, the lowest possible score on each test (e.g. 10 for the KPS scale) was used to represent patients for all visits after their death.

All statistical tests were two-sided and the level of statistical significance was fixed at 5%. Categorical data were presented in contingency tables. Continuous data were summarized with at least the following: frequency (n), median, mean, standard error of the mean, minimal and maximal values. Time to event analyses were performed using the Kaplan-Meier method and compared using a log-rank test as a primary comparison and the Wilcoxon test as a sensitivity comparison.

Survival and Time to Treatment Failure (All Patients)

The effectiveness of GLIADEL® Wafer in the treatment of initially diagnosed malignant glioma was demonstrated by the statistically significant improvement in one-year survival rate compared to placebo and the statistically significantly improved survival over the 12- and 24-month period after implant surgery in the GLIADEL® Wafer treatment group when compared to placebo (see Table 7). Statistically significantly more patients who were implanted with GLIADEL® Wafers survived to one year post-surgery. Ten of 16 GLIADEL® Wafer patients (63%) compared to 3 of 16 placebo patients (19%) survived to one year (52 weeks) (P = 0.029). Overall, 11 of 16 (69%) GLIADEL® Wafer patients and 15 of 16 placebo patients (94%) died during the two year study conduct period. The overall median survival durations were 58.1 weeks and 39.9 weeks (P = 0.011) for GLIADEL® Wafer and placebo group patients, respectively (see Table 7). Additionally, results of Log-Rank and Wilcoxon tests (see Table 8) show that there were significant between-group differences in the effect on survival during both the 12-month interval after study surgery (P = 0.0087 and P = 0.0105, respectively) and the up-to-24-month interval after study surgery (P = 0.0116 and P = 0.0106, respectively).

When the data were adjusted for important prognostic factors (age and MMSE), whether stratified by tumor type or not, a significant GLIADEL® Wafer treatment effect was observed (see Table 7 and Table 9). For the 12-month period after study surgery the adjusted risk ratios for GLIADEL® Wafer vs.

placebo treatment were 0.154 for all patients by nonstratified analysis ($P = 0.0044$) and 0.179 for all patients stratified by tumor type ($P = 0.0059$). For the 24-month (overall) period after study surgery the adjusted risk ratios for GLIADEL[®] Wafer vs. placebo treatment were 0.177 for all patients by nonstratified analysis ($P = 0.0005$) and 0.214 for all patients stratified by tumor type ($P = 0.0029$).

Twelve patients (75%) in the GLIADEL[®] Wafer treatment group and 14 patients (88%) in the placebo treatment group were considered treatment failures. The median time to treatment failure was 1.12 months (7.79 months vs. 6.67 months; log rank $P = 0.4668$ and Wilcoxon p -value = 0.9635).

Survival and Time to Treatment Failure (GBM Patients)

Six of 11 GBM patients (55%) in the GLIADEL[®] Wafer treatment group and 3 of 16 GBM patients (19%) in the placebo treatment group survived to one year ($P = 0.097$). In the GLIADEL[®] Wafer group the median post implantation survival duration for GBM patients was 53.3 weeks compared with 39.9 weeks in the placebo treatment group ($P = 0.093$) for overall survival (see Table 7).

Overall, 9 of 11 (82%) patients with GBM in the GLIADEL[®] Wafer group died compared with 15 of 16 (94%) patients with GBM in the placebo group. After adjustment for prognostic factors, GLIADEL[®] Wafer produced a statistically significant reduction in mortality relative to placebo in GBM patients for both the 12- and 24-month periods after wafer implantation surgery. The adjusted risk ratios were 0.196 (95% CI: 0.060 to 0.642) for 12 months and 0.213 (95% CI: 0.076 to 0.601) for 24 months, with P values of 0.0072 and 0.0035, respectively.

Secondary Efficacy Measures

Among patients in both treatment groups, the mean KPS Scores declined from Baseline [GLIADEL[®] Wafer 79 (± 14) and placebo 82 (± 15)] to the Final Visit [GLIADEL[®] Wafer 52 (± 30) and placebo 43 (± 24)]. The mean change from Baseline to the Final Visit [-27 (± 29) in the GLIADEL[®] Wafer group, and -40 (± 27) in the placebo group] was not statistically significant in between-treatment-group comparisons.

Using the OC method of the GEE analyses for both the continuous outcome (mean values over time) and the categorical outcome (treatment frequencies by visit for patients with worsening from Baseline), the results of overall tests for both treatment effect and treatment-by-visit interaction effects were not statistically significant. The results of the overall tests for visit effect were statistically significant for the continuous outcome ($P=0.010$ for mean values over time) and there was a trend toward statistical significance for the categorical outcome ($P = 0.056$ for categorical analysis of worsening over time). There was no statistically significant overall treatment-by-visit interaction for either analysis. Longitudinal assessments of both continuous and categorical variables evaluated by a last observation carried forward (LOCF) method of GEE analyses showed a statistically significant result in testing for overall visit effect ($P \leq 0.001$), but not for treatment effect or overall treatment-visit interaction.

Among patients in both treatment groups, the mean MMSE Scores declined from Baseline to Final Visit for all parameters. The mean total score worsened by 6.1 (± 9.7) points in GLIADEL[®] Wafer patients and

by 4.9 (± 5.7) points in placebo patients ($P = 0.683$). This change from Baseline to the Final Visit was not statistically significantly different in the two treatment groups.

Of the 11 parameters evaluated in neurological examinations, improvements in mean scores were noted in only four parameters and only for the GLIADEL[®] Wafer treatment group patients. In the GLIADEL[®] Wafer treatment group, the greatest improvement in the mean change from Baseline to the Final Visit was seen in the following parameters: visual change, fundus (papilledema), cranial nerves III, IV, VI, and cerebellar signs.

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Table 7: Study CL-0190 Primary Efficacy Parameters — ITT Population and GBM Subgroup

PARAMETER OR FACTOR	ITT POPULATION		GBM SUBGROUP	
	GLIADEL® Wafer N=16	PLACEBO N=16	GLIADEL® Wafer N=11	PLACEBO N=16
<u>Post Implantation Patient Survival</u>				
Post-implantation survival - median weeks (95% CI)	58.1 weeks (42.00, --)	39.9 weeks (37.57, 45.00)	53.3 weeks (40.14, 77.71)	39.9 weeks (37.57, 45.00)
Wilcoxon-Rank Sum test:	p = 0.011		p = 0.093	
<u>One Year Survival (12 months)</u>				
Number (%) of patients	88 (73.3%)	93 (77.5%)	78 (77.2%)	85 (80.2%)
Fisher's Exact test:	p = 0.029		p = 0.097	
<u>Post Implantation Patient Survival Prognostic Factors</u> <u>(Univariate Cox Regression for ITT population):</u>	RISK RATIO (95% CI)	WALD CHI-SQUARE TEST P-VALUE	N/A	N/A
KPS score (≤70% vs. >70%)	0.723 (0.327, 1.597)	0.4226		
Age (per decade)	1.826 (1.131, 2.950)	0.0138		
Final histopathological diagnosis (GBM vs. non-GBM)	4.715 (1.092, 20.35)	0.0377		
Number of wafers implanted (≤6 vs. >6)	1.037 (0.449, 2.395)	0.9328		
Gender (male vs. female)	1.370 (0.629, 2.987)	0.4280		
Resection (≥75% vs. <75%)	0.941 (0.419, 2.113)	0.8824		
MMSE Scores ≥ median	0.377 (0.170, 0.833)	0.0159		
Prior seizures vs. none	0.774 (0.309, 1.938)	0.5845		

GBM = Glioblastoma multiforme. CI = Median Confidence Interval. N/A = Not applicable

Data extracted from Full Study Report CL-0190: ATTACHMENT 1 - Tables 13B, 14A, and 15B; Appendix 9 - Data Listings 2, 5, 7, 8, 16, and 20.

Table 8: Study CL-0190 Overall Life Table Summary (Primary Efficacy) — ITT Population and GBM Subgroup

PARAMETER AND TIMEPOINTS	ITT POPULATION				GBM SUBGROUP			
	GLIADEL® WAFER N=16		PLACEBO N=16		GLIADEL® WAFER N=11		PLACEBO N=16	
<u>Overall Life Table</u>	Cumulative Death Rate (Cumulative No. of Deaths)	S.E. of Death Rate ^a	Cumulative Death Rate (Cumulative No. of Deaths)	S.E. of Death Rate ^a	Cumulative Death Rate (Cumulative No. of Deaths)	S.E. of Death Rate ^a	Cumulative Death Rate (Cumulative No. of Deaths)	S.E. of Death Rate ^a
3 Months	6 (1)	6.051	6 (1)	6.051	9 (1)	8.668	6 (1)	6.051
6 Months	6 (1)	6.051	19 (3)	9.758	9 (1)	8.668	19 (3)	9.758
9 Months	6 (1)	6.051	38 (6)	12.103	9 (1)	8.668	38 (6)	12.103
12 Months	38 (6)	12.103	81 (13)	9.758	46 (5)	15.01	81 (13)	9.758
15 Months	56 (9)	12.402	81 (13)	9.758	73 (8)	13.43	81 (13)	9.758
18 Months	63 (10)	12.103	94 (15)	6.051	82 (9)	11.63	94 (15)	6.051
21 Months	69 (11)	11.588	--	--	--	--	--	--
Log-Rank Test:	Overall = 0.0116		12-Month = 0.0087		Overall = 0.1261		12-Month = 0.0702	
Wilcoxon Test:	Overall = 0.0106		12-Month = 0.0105		Overall = 0.0931		12-Month = 0.0587	

^a S.E. obtained using Greenwood's formula.

Cross-Reference Full Study Report CL-0190: ATTACHMENT I - Tables 13A and 15A; Appendix 9 - Data Listing 20

Table 9: Study CL-0190 Primary Efficacy Parameters Adjusted for Significant Prognostic Factors — ITT Population and GBM Subgroup

PARAMETER AND PROGNOSTIC FACTOR	ITT POPULATION	GBM SUBGROUP
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<u>Overall Treatment Effect</u>	RISK RATIO (95% CI)	WALD CHI-SQUARE TEST P-VALUE (significant at p<0.05)	RISK RATIO (95% CI)	WALD CHI-SQUARE TEST P-VALUE
All Patients				
GLIADEL® Wafer vs. placebo	0.177 (0.067, 0.468)	0.0005	0.213 (0.076, 0.601)	0.0035
Age (per decade)	2.248 (1.208, 4.182)	0.0106	2.030 (1.070, 3.850)	0.0303
MMSE Scores (≥ median vs. <median)	0.250 (0.100, 0.626)	0.0031	0.222 (0.081, 0.606)	0.0033
All Patients Stratified by Tumor Type				
GLIADEL® Wafer vs. placebo	0.214 (0.078, 0.590)	0.0029	N/A	N/A
Age (per decade)	2.219 (1.193, 4.131)	0.0119	N/A	N/A
MMSE Scores (≥ median vs. <median)	0.241 (0.094, 0.619)	0.0031	N/A	N/A
12-Month Treatment Effect				
All Patients				
GLIADEL® Wafer vs. placebo	0.154 (0.051, 0.467)	0.0010	0.196 (0.060, 0.642)	0.0072
Age (per decade)	2.302 (1.089, 4.864)	0.0290	N/A	N/A
MMSE Scores (≥ median vs. <median)	0.207 (0.070, 0.613)	0.0044	0.179 (0.055, 0.587)	0.0045
All Patients Stratified by Tumor Type				
GLIADEL® Wafer vs. placebo	0.179 (0.056, 0.574)	0.0038	N/A	N/A
Age (per decade)	2.266 (1.075, 4.777)	0.0315	N/A	N/A
MMSE Scores (≥ median vs. <median)	0.218 (0.074, 0.645)	0.0059	N/A	N/A

GBM = Glioblastoma multiforme. CI = Median Confidence Interval. N/A = Not applicable

Data extracted from Full Study Report CI-0190: ATTACHMENT 1 - Tables 14B, 14C, 14E, and 14F; Appendix 9 - Data Listings 2, 4, 6, 7, 8, 16, and 20.

3.6.5 Overview of Safety Data From All Known Studies of the GLIADEL® Wafer

3.6.5.1 SAFETY DATA FROM CLINICAL TRIALS T-301, CL-0190, AND 9003

3.6.5.1.1 Adverse Events

The following table displays the most frequent adverse events for the controlled studies (T-301 and CL-0190) and the uncontrolled study (9003).

Table 10: Most Frequent Treatment-Emergent Adverse Events By Body System, COSTART Term And Treatment Group

BODY SYSTEM	STUDY T-301 AEs OCCURRING IN ≥5% OF PATIENTS		STUDY CL-0190 AEs OCCURRING IN ≥2 OF PATIENTS		STUDY 9003 AEs OCCURRING IN ≥2 OF PATIENTS
	GLIADEL® N=120 N (%)	PLACEBO N=120 N (%)	GLIADEL® N=16 N (%)	PLACEBO N=16 N (%)	GLIADEL® N=22 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)	—	—	2 (9)
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)	—	—	—
Overdose	—	—	—	—	2 (9) ^a
Pain	16 (13.3)	18 (15.0)	—	—	—
Cardiovascular system					
Deep thrombophlebitis	12 (10.0)	11 (9.2)	—	—	2 (9)
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)	—	—	—

Table 10: Most Frequent Treatment-Emergent Adverse Events By Body System, COSTART Term And Treatment Group

BODY SYSTEM	STUDY T-301 AEs OCCURRING IN ≥5% OF PATIENTS		STUDY CL-0190 AEs OCCURRING IN ≥2 OF PATIENTS		STUDY 9003 AEs OCCURRING IN ≥2 OF PATIENTS
	GLIADEL® N=120 N (%)	PLACEBO N=120 N (%)	GLIADEL® N=16 N (%)	PLACEBO N=16 N (%)	GLIADEL® N=22 N (%)
	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)	2 (13)	1 (6)	—
Ataxia	7 (5.8)	5 (4.2)	—	—	—
Brain edema	27 (22.5)	23 (19.2)	—	—	2 (9)
Coma	5 (4.2)	6 (5.0)	—	—	—
Confusion	28 (23.3)	25 (20.8)	—	—	2 (9)
Convulsion	40 (33.3)	45 (37.5)	3 (19)	2 (13)	11 (50)
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)	6 (38)	4 (25)	—
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)	—	—	—
Necrosis	—	—	—	—	3 (14)
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)	—	—	4 (18)
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)	2 (13)	—	2 (13)
Urogenital system					
Urinary incontinence	9 (7.5)	9 (7.5)	—	—	—

Table 10: Most Frequent Treatment-Emergent Adverse Events By Body System, COSTART Term And Treatment Group

BODY SYSTEM	STUDY T-301 AEs OCCURRING IN ≥5% OF PATIENTS		STUDY CL-0190 AEs OCCURRING IN ≥2 OF PATIENTS		STUDY 9003 AEs OCCURRING IN ≥2 OF PATIENTS
	GLIADEL® N=120 N (%)	PLACEBO N=120 N (%)	GLIADEL® N=16 N (%)	PLACEBO N=16 N (%)	GLIADEL® N=22 N (%)
Urinary tract infection	10 (8.3)	13 (10.8)	—	—	3 (14)

^aDilantin toxicity

Data extracted from the Integrated Summary of Safety.

3.6.5.1.1.1 Pivotal Study T-301

Treatment-emergent adverse events (TEAEs) were summarized using the COSTART preferred terms. Treatment-emergent AEs were 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. For a patient who experienced multiple occurrences of the same TEAE (i.e., an event that was coded to a single COSTART preferred term), only the most severe episode was counted as a TEAE.

Incidence of All Adverse Events

The total number of AEs was very similar for both treatment groups, with 1244 AEs reported in the GLIADEL® group and 1224 TEAEs reported in the placebo group. In the GLIADEL® group, 119 patients (99.2%) experienced at least one TEAE during the study, and one patient (0.8%) had no reported AEs. In the placebo group, all 120 patients (100%) experienced at least one TEAE.

The TEAEs were consistent with those expected in patients with malignant glioma undergoing maximal tumor resection.

Nearly all patients in the study experienced TEAEs in the “body as a whole” system [111 patients (92.5%) in the GLIADEL® group and 113 patients (94.2%) in the placebo group] and the nervous system [111 patients (92.5%) in the GLIADEL® group and 109 patients (90.8%) in the placebo group]. For each body system, the number of patients reporting TEAEs was similar for both treatment groups, although approximately twice as many patients in the placebo group compared to the GLIADEL® group had TEAEs in the hemic and lymphatic, musculoskeletal, and respiratory body systems.

Overall there were few observable differences between the treatment groups in the frequency of TEAEs. The frequency of the most common TEAEs (those occurring in 10% or more of patients in either treatment group) were compared across treatment groups using the Fisher’s exact test. There was no statistically significant difference between the treatment groups for any of the TEAEs tested ($p > 0.05$).

Adverse Events by Severity

The severity of each TEAE was rated as mild, moderate, severe, or life-threatening by the investigator. Approximately one third of the events reported in each treatment group were considered by the investigator to be severe or life-threatening. Overall, 379 events in the GLIADEL® group and 371 events in the placebo group were classed as severe or life-threatening. Severe and life-threatening events were experienced by 104 patients (86.7%) in the GLIADEL® group and 106 patients (88.3%) in the placebo group.

The most frequently reported severe or life-threatening event was aggravation reaction. Eighty-four patients (70.0%) in the GLIADEL® group and 83 patients (69.2%) in the placebo group had severe or life-threatening aggravation reactions. All other TEAEs in the "body as a whole" system were severe/life-threatening for less than six patients in each group, with the exception of headache, which was severe/life-threatening for eight patients (6.7%) in the GLIADEL® group and 15 patients (12.5%) in the placebo group.

In the cardiovascular body system, pulmonary embolus was severe/life-threatening for 10/10 patients in the GLIADEL® group and 9/10 patients in the placebo group who experienced this TEAE.

There were few patients with severe/life-threatening TEAEs involving the digestive system, endocrine system, hemic and lymphatic system, metabolic and nutritional disorders, musculoskeletal system, respiratory system, skin and appendages, special senses, or urogenital system (all reported by 10 or fewer patients in each treatment group).

Nervous System Severe/Life-Threatening Adverse Events

Seventy patients (58.3%) in the GLIADEL® group and 68 patients (56.7%) in the placebo group had severe/life-threatening TEAEs involving the nervous system. The most frequently occurring severe/life-threatening nervous system TEAEs were (with number and percentage of patients in the GLIADEL® and placebo groups, respectively): hemiplegia [27 patients (22.5%) and 26 patients (21.7%)], convulsion [14 patients (11.7%) and 24 patients (20.0%)], brain edema [14 patients (11.7%) in each group], aphasia [13 patients (10.8%) and 10 patients (8.3%)], confusion [11 patients (9.2%) and 8 patients (6.7%)], intracranial hypertension [10 patients (8.3%) and two patients (1.7%)], and speech disorder [nine patients (7.5%) and one patient (0.8%)].

The number of patients with severe/life-threatening convulsions was noticeably higher in the placebo group, and the number of patients with severe/life-threatening intracranial hypertension and speech disorder was noticeably higher in the GLIADEL® group. These differences were not subjected to formal statistical testing.

Adverse Events by Relationship to Study Drug

Adverse events occurring during the study were classified by the investigator as having one of the following relationships to study treatment: none, remote, possible or probable. The number of patients with

AEs classed as possibly or probably related to study treatment is presented by body system, COSTART preferred term, and treatment group in Appendix II.F, Table 5.02, of the Final Study Report.

Less than 10% of all AEs were considered to be possibly or probably related to study treatment, with a total of 103 treatment related AEs (i.e. possibly and probably related AEs), reported in the GLIADEL® group and 104 treatment related AEs reported in the placebo group. Thirty-two patients (26.7%) in the GLIADEL® group and 39 patients (32.5%) in the placebo group had at least one treatment-related AE. The majority of patients in the study [88 patients (73.3%) in the GLIADEL® group and 81 patients (67.5%) in the placebo group], had no AEs that were considered by the investigator to be possibly or probably related to study treatment.

The most frequently occurring treatment-emergent, treatment-related AEs (excluding nervous system AEs), were headache [six patients (5.0%) in the GLIADEL® group and five patients (4.2%) in the placebo group], vomiting [three patients (2.5%) in each group], fever [one patient (0.8%) in the GLIADEL® group and five patients (4.2%) in the placebo group], healing abnormal [five patients (4.2%) in the GLIADEL® group and one patient (0.8%) in the placebo group], infection, and aggravation reaction [both reported by two patients (1.7%) in the GLIADEL® group and three patients (2.5%) in the placebo group].

There were no noticeable differences between the treatment groups in the frequency of treatment-related, TEAEs. The frequency of the most common treatment-related, TEAEs (those occurring in 10% or more of patients in either treatment group), were compared across treatment groups using the Fisher's exact test. The only treatment-related TEAE occurring in 10% or more of patients in either treatment group was convulsions. There was no statistically significant difference between the treatment groups for convulsions ($p=0.534$).

Nervous System Treatment-Related Adverse Events

The most frequently occurring treatment-related nervous system AEs were convulsion [11 patients (9.2%) in the GLIADEL® group and 15 patients (12.5%) in the placebo group], hemiplegia [seven patients (5.8%) in the GLIADEL® group and nine patients (7.5%) in the placebo group], and brain edema [seven patients (5.8%) in the GLIADEL® group and eight patients (6.7%) in the placebo group].

There were no noticeable differences between the treatment groups in the frequency of treatment-related TEAEs involving the nervous system. The frequency of all treatment-related neurological AEs was compared across treatment groups using the Fisher's exact test. There were no statistically significant differences between the treatment groups for any of the AEs tested ($p>0.05$).

Treatment-Related, Severe/Life-threatening Treatment-Emergent Adverse Events

A total of 26 TEAEs in the GLIADEL® group and 37 TEAEs in the placebo group were classified as both treatment-related and severe/life-threatening. These events were reported for 14 patients (11.7%) in the GLIADEL® group and 19 patients (15.8%) in the placebo group. The number of patients with TEAEs classed as severe or life-threatening, and possibly or probably related to study treatment is presented by

body system, COSTART preferred term, and treatment group in Appendix II.F, Table 5.04, of the final study report.

3.6.5.1.1.2 Supportive Study CL-0190

Incidence of All Adverse Events

A total of 51 adverse events were reported in the postoperative period, 32 in the GLIADEL[®] treatment group and 19 in the placebo treatment group. Forty-seven events were TEAEs, 31 in the GLIADEL[®] group and 16 in the placebo group. Treatment-emergent AEs were experienced by 12 of 16 patients (75%) in the GLIADEL[®] treatment group and 9 of 16 patients (56%) in the placebo treatment group. The TEAs experienced were consistent with those expected in postoperative patients with malignant glioma.

Adverse Events Occurring in ≥5% of Patients

In both treatment groups, hemiplegia was the most frequently reported adverse event [GLIADEL[®] 6 (38%); placebo 4 (25%)], followed by convulsions [GLIADEL[®] 3 (19%); placebo 2 (13%)]. There were no statistically significant between-treatment-group differences in reporting frequencies for any TEAEs.

Adverse Events by Severity

Adverse event severity was rated as mild; moderate, severe, or life-threatening by the investigator. Within a patient, the most severe rating of each post-Baseline adverse event was used for the analysis of TEAEs. In the GLIADEL[®] treatment group, 6% (2 events) of the TEAEs recorded were considered to be life-threatening in severity, 55% (17 events) were considered severe, and 32% (10 events) were considered moderate. In the placebo treatment group, 44% (7 events) of the TEAEs recorded were severe in severity and 38% (6 events) were considered to be moderate. There were no TEAEs in the placebo treatment group considered life-threatening.

Two TEAEs judged to be life-threatening were reported in the GLIADEL[®] treatment group. Patient No. 302 experienced a life-threatening pulmonary embolus and Patient No. 404 was noted to have stupor rated by the investigator as life-threatening. The life-threatening stupor was considered by the investigator to be unrelated to study drug and the life-threatening pulmonary embolus was considered by the investigator to be remotely related to study medication.

In the GLIADEL[®] treatment group, 17 TEAEs were severe and in the placebo treatment group, 7 TEAEs were judged to be severe. In the GLIADEL[®] treatment group, more than one severe episode was documented in two categories; five severe episodes of hemiplegia and two severe episodes of aphasia were documented. In the placebo treatment group, the only adverse event category for which there was more than one severe episode was hemiplegia; four severe episodes of hemiplegia were documented.

Adverse Events by Relationship to Study Drug

Adverse events occurring during the study were defined by the investigator, as having one of the following relationships to study drug: probable, possible, remote, none, or not assessable. There were no probably-

related adverse events reported in either treatment group in this study. In the GLIADEL® treatment group, three events (10%) were considered possibly related, five events (16%) were considered remotely related, 22 events (71%) were considered to have no relationship to study drug, and one event (3%) was considered not assessable. In the placebo treatment group, one event (6%) was considered possibly related, five events (31%) were considered remotely related, and 10 events (63%) were considered to have no relationship to study medication.

3.6.5.1.1.3 Uncontrolled Study 9003

Incidence of All Adverse Events

A total of 66 adverse events were reported in the postoperative period. Of those, 59 were considered to be TEAEs, i.e., the events had not occurred prestudy at the same or less severe intensity, and multiples of on-study events with a single COSTART term within a patient that had varying severity scores were counted as a single event of the worst-recorded severity. TEAEs were reported by 21 of 22 patients (95%) treated in the study. The TEAEs reported were consistent with those expected in patients with malignant glioma following craniotomy.

Seventy-three percent of patients (N = 16) experienced one or more Nervous System TEAEs and 32% (N = 7) experienced events in Body as a Whole.

Adverse Events Occurring in ≥5% of Patients

The four most frequently reported TEAEs were: convulsions (50%), pneumonia (18%), necrosis (14%), and urinary tract infection (14%).

Adverse Events by Severity

Adverse events were rated as mild, moderate, or severe by the investigator. Within a patient, the most severe rating of each event was carried forward to the analysis of TEAEs. Fifty-four percent (32 events) of the TEAEs recorded were moderate in severity; only 17 events (29%) were considered to be severe. The only adverse event category for which there was more than one severe episode was convulsion; two severe episodes of convulsion were documented.

Adverse Events by Relationship to Study Drug

Adverse events occurring during the study were defined by the investigator as having one of the following relationships to study drug: unrelated, possible, probable, or definite. There were no definitely-related adverse events reported in this study. Nine TEAEs (15% of the 59 total) were considered possibly related; one adverse event (2% of the total TEAEs) was considered probably related and 49 adverse events (83% of all treatment-emergent events) were considered by the investigator to be unrelated to study drug.

3.6.5.1.2 Serious Adverse Events Including Death

3.6.5.1.2.1 Pivotal Study T-301

Deaths

Overall, 88 patients (73.3%) in the GLIADEL® group and 93 patients (77.5%) in the placebo group died before the study cut-off date. Five patients (4.2%) in the GLIADEL® group and two patients (1.7%) in the placebo group died within 30 days of randomization.

Only one patient (0.8%) in each treatment group was known to have had an autopsy. It was not known whether four patients (3.3%) in the GLIADEL® group and 10 patients (8.3%) in the placebo group had autopsies, and the remaining patients [83 patients (69.2%) in the GLIADEL® group and 82 patients (68.3%) in the placebo group] did not have an autopsy.

The majority of patients in each group who died during the study died of malignant disease [75 patients (62.5%) in the GLIADEL® group and 84 patients (70.0%) in the placebo group]. Two patients (1.7%) in the GLIADEL® group died due to a complication of the initial surgical procedure; both these patients died within 30 days of randomization. One patient in the GLIADEL® group died due to a surgical complication following further surgery for tumor recurrence; this patient also died within 30 days of randomization. No patients in the placebo group died due to surgical complications. Ten patients (8.3%) in the GLIADEL® group and nine patients (7.5%) died due to other reasons,

The most common reason for death classed as “other” was pulmonary embolism (two patients in the placebo group and four patients in the GLIADEL® group).

Reasons for death classed as “other” in the placebo group included sepsis (Patient 01008), bronchopneumonia (Patient 01106), pneumonia (Patient 01140), “cardiac” reasons (Patient 01143), pulmonary embolism (Patients 01165 and 01210), committed suicide (Patient 1187), progressive neurologic deficits due to tumor progression (Patient 02028) and seizure related to the tumor (Patient 02045).

In the GLIADEL® group, “other” reasons for death included pulmonary embolism [Patient 01022 (pulmonary embolism as a consequence of immobilization due to massive tumor progression), Patient 01139 (massive pulmonary embolism), Patient 01159 and Patient 01212 (pulmonary embolism)], an acute abdominal or coronary event (Patient 01007), bleeding of gastric ulcer (Patient 01028), lung embolism (Patient 01051), pneumonia (Patient 01093), pneumothorax (Patient 01256) and tumor progression (Patient 02027).

Serious Adverse Events

The majority of patients experienced at least one SAE during the study. A total of 374 SAEs were reported in the GLIADEL® group and 370 SAEs were reported in the placebo group. Overall, 112 patients (93.3%)

in the GLIADEL[®] group and 110 patients (91.7%) experienced an SAE during the study. Eight patients (6.7%) in the GLIADEL[®] group and 10 patients (8.3%) in the placebo group had no SAEs.

Most SAEs fell into the "body as a whole" and nervous system body systems. Ninety-four patients (78.3%) in the GLIADEL[®] group and 92 patients (76.7%) in the placebo group had SAEs in the "body as a whole" category and 76 patients (63.3%) in the GLIADEL[®] group and 77 patients (64.2%) had SAEs involving the nervous system.

Treatment-Related Serious Adverse Events

Less than 20% of the total number of SAEs reported in either group were considered to be treatment-related (i.e. possibly or probably related to treatment). Sixty-six of the 374 SAEs reported in the GLIADEL[®] group and 55 of the 370 SAEs reported in the placebo group were considered to be treatment-related by the investigator. These treatment-related SAEs were reported for 26 patients (21.7%) in each treatment group.

The SAE that was most frequently considered to be related to study treatment was convulsion [11 patients (9.2%) in the GLIADEL[®] group and 15 patients (12.5%) in the placebo group]. Convulsions were reported as an SAE more than once for some patients, with the 11 patients in the GLIADEL[®] group having 21 convulsion SAEs and the 15 patients in the placebo group also having 21 convulsion SAEs.

Reports of cyst formation and mass development following GLIADEL[®] Implantation

Two individual patient safety reports were filed with FDA and subsequently resulted in notification to investigators of possible new adverse events associated with GLIADEL[®] implantation.

Patient RPR132596/T-301-01110, who underwent craniotomy for resection of malignant glioma and insertion of GLIADEL[®] Wafers, developed a left temporal cyst at the site of the GLIADEL[®] implant 3 months post-implantation that was thought by the investigator to be possibly related to GLIADEL[®].

Patient RPR132596/T-301-01273, who underwent craniotomy for resection of malignant glioma and insertion of GLIADEL[®] Wafers, developed a mass lesion of tumor cavity at the site of the GLIADEL[®] implant 7 months post-implantation that was thought by the investigator to be possibly related to GLIADEL[®].

3.6.5.1.2.2 Supportive Controlled Study CL-0190

Deaths

A total of 11 patients (69%) in the GLIADEL[®] treatment group and 15 patients (94%) in the placebo treatment group are known to have died during the study. For these patients, narrative summaries are provided in APPENDIX 6. For those patients who died, the cause of death given by the investigator was brain tumor for 10 of 11 patients in the GLIADEL[®] treatment group and 13 of 15 patients in the placebo treatment group. One patient in the placebo treatment group died of a pulmonary embolism. Additionally, for one patient in each of the GLIADEL[®] and placebo treatment groups the cause of death was listed as

not assessable by the investigator. Treatment with GLIADEL® or placebo Wafers was not listed as a cause of death for any patient.

Treatment-Emergent Adverse Events That Were Serious

Nine patients (five GLIADEL® and four placebo) had a total of 15 adverse events that met the definition of serious given in the protocol (FDA criteria), and were reported to the national authorities in Finland and Norway and to the FDA. Information in italics was submitted to regulatory authorities but is not substantiated in the case report forms. The reports of serious adverse events filed with the U.S. and Norwegian Regulatory Authorities is presented in APPENDIX 10 of the final study report.

3.6.5.1.2.3 Uncontrolled Study 9003

Deaths

Nineteen of the 22 patients (86%) are known to have died, and the duration of survival after GLIADEL® Wafer implantation is known for all 19 of these patients. For 18 of the 19 patients (95%) who died, tumor progression or a synonym was given as the cause of death. Patient No. 001010 died due to intra-abdominal malignant lymphoma. Treatment with GLIADEL® Wafers was not listed as a cause of death in any patient.

Serious Adverse Events

There were two patients with serious and unexpected adverse events. One patient (Patient No. 080001) with a pre-existing seizure disorder was briefly readmitted to the hospital after wafer implantation surgery because of headaches, lethargy and a subsequent grand mal seizure. A second patient (Patient No. 001004) became unresponsive approximately 48 hours after wafer implantation surgery and underwent surgical removal of a hematoma from the area of tumor resection. Reports of these events were submitted as IND Safety Reports to the Food and Drug Administration (FDA).

3.6.5.1.3 Discontinuations Due to Adverse Events

3.6.5.1.3.1 Pivotal Study T-301

Only one patient discontinued from the study due to an AE. Patient 01056, a 65-year-old female patient with glioblastoma multiforme, had 5.5 GLIADEL® Wafers implanted during initial surgery on 02 October 1998. On the day of surgery (Day 1) the patient suffered local brain edema, which the investigator considered was probably related to study treatment and moderate in nature. She underwent reoperation with total wafer removal on 06 October 1998 (Day 5) due to suspected toxic edema by BCNU. The patient's condition improved after wafer removal and the event resolved on Day 6. The patient discontinued the study on 23 October 1998 (Day 22) due to AEs (mild headache, moderate aphasia and severe confusion). These AEs were previously existing signs and symptoms which had started 93 days before the study.

3.6.5.1.3.2 Supportive Controlled Study CL-0190

No patients were discontinued from the study. All patients were followed until their death or to the time of data cut-off (May 14, 1995).

3.6.5.1.3.3 Uncontrolled Study 9003

No patients were discontinued from the study. All patients were followed until their death or, for survival, to the time of data cut-off (November 10, 1995).

3.6.5.1.4 LABORATORY PARAMETERS

3.6.5.1.4.1 Pivotal Study T-301

Overall Changes in Serum Chemistry

There were no notable differences between the treatment groups in the number of patients with abnormal results for any of the biochemistry parameters at any timepoint during the study.

Overall, there were no clinically significant patterns of change in any biochemistry parameter that could be associated with study treatment. Very few significant changes were observed in any of the biochemistry parameters during the study. There were a few parameters [e.g.: AST (SGOT), ALT (SGPT) and total bilirubin] for which small changes were observed, but mean values did not exceed the upper limit of normal (ULN) and changes were comparable between the treatment groups.

Overall Changes in Hematology

There were no differences between the treatment groups in the number of patients with abnormal results for any of the hematology parameters at any time point during the study. The number of patients with missing values was high at all visits for most parameters, therefore the results should be interpreted with caution.

Overall, there were no clinically significant patterns of change in any hematology parameter that could be associated with study treatment. The pattern of changes in mean hematology laboratory values was similar for both treatment groups and the changes seen were generally to be expected in a population of patients undergoing major surgery for resection of a malignant glioma (for example a drop in hemoglobin, hematocrit and RBC count was seen after surgery).

Overall Changes in Urinalysis

There were no notable changes in urine protein, glucose or bilirubin results for either treatment group during the course of the study. In addition there were no differences between the treatment groups.

Between 50.8% and 58.3% of patients overall had negative urine protein results at each visit. Between 14.2% and 19.6% of patients overall at each visit had trace protein in their urine and between 4.2% and 8.3% of patients overall at each visit had a positive urine protein result. The number of patients whose

results were not recorded rose from 16.7% in the GLIADEL® Wafer group and 15.8% in the placebo group at Baseline to 29.2% in the GLIADEL® group and 30.0% in the placebo group at Visit 6.

At each visit between 61.7% and 72.9% of patients overall had negative urine glucose results. Between 2.5% and 5.4% of patients overall had trace glucose in their urine and between 2.1% and 12.1% of patients overall had a positive urine glucose result at Visits 1, 3, 4, 5 and 6. The number of positive urine glucose results increased from 7.5% in both groups at Baseline to 12.5% in the GLIADEL® group and 11.7% in the placebo group at Visit 3, then decreased to less than 5% for both groups for the remainder of the study. The number of patients whose results were not recorded rose from 15.8% in both treatment groups at Baseline to 30.0% in the GLIADEL® group and 31.7% in the placebo group at Visit 6.

The majority of patients had a negative result for urine bilirubin at each visit (between 61.7% and 73.3% patients overall). Overall 3.3% or less of patients at any visit had trace bilirubin in their urine, and 5.4% or less of patients at each visit had a positive urine bilirubin result. The number of patients whose results were not recorded rose from 21.7% in the GLIADEL® group and 25.8% in the placebo group at Baseline to 34.2% in both groups at Visit 6.

Clinically Significant Test Result Abnormalities

There were no clinically significant abnormal test results.

3.6.5.1.4.2 Supportive Controlled Study CL-0190

Laboratory data from all sites were converted to conventional U.S. units and were statistically normalized to Site 001's (Turku University Central Hospital) normal laboratory ranges, and it is these normalized data that were pooled and used to display mean and median values, ranges and changes from Baseline.

Overall Changes in Serum Chemistry

Shifts from normal Baseline levels to elevated out-of-range levels were noted at several time points for SGPT (ALT), and alkaline phosphatase; however, these shifts occurred in both the GLIADEL and placebo populations in very low frequencies.

Clinically notable abnormalities in serum chemistry were principally those of SGPT (ALT). Four of 16 patients (25%) in each treatment group had clinically notably high values of SGPT (ALT) on at least one occasion post-Baseline. The between-treatment-group difference was not statistically significant.

In the placebo treatment group, there were no shifts in SGOT (AST) levels from normal at Baseline to out-of-range levels post-Baseline and only one or two shifts at occasional visits in the GLIADEL® Wafer group.

In the GLIADEL® Wafer treatment group, there were no shifts from normal Baseline bilirubin level to a level elevated outside the NR and only one decrease to below the normal range. For the placebo group, one shift from normal to high was noted at each of Visits 5 and 9 and one shift from normal to low was documented at Visit 4.

Serum Creatinine

There were no statistically significant differences in the median changes from Baseline for serum creatinine in either female patients or male patients in between-treatment-group comparisons.

The shifts in serum creatinine levels from normal at Baseline to out-of-range levels post-Baseline were infrequent in both the GLIADEL[®] Wafer and placebo treatment groups.

SGPT

In female patients, Baseline mean SGPT (ALT) values were elevated in the GLIADEL[®] Wafer treatment group [90 (\pm 135) U/L] but were within the normal range in the placebo treatment group [40 (\pm 33) U/L] [Normal Range (NR): 0 - 44 U/L]. Median values were normal in both the GLIADEL[®] Wafer treatment group (32 U/L) and the placebo treatment group (28 U/L). Among female patients in the GLIADEL[®] Wafer treatment group, the Visit 2 and Visit 3 SGPT (ALT) values, though decreased on average from Baseline, were still elevated outside the upper limit of the normal range. The mean SGPT (ALT) value in female patients in the GLIADEL[®] Wafer population remained elevated through Visit 7, was normal at Visits 8 through 11, and was elevated again at Visit 12. The mean SGPT (ALT) level among female patients in the GLIADEL[®] Wafer treatment group at the Final Visit was elevated at 78 (\pm 103) U/L. Among female patients in the placebo treatment group, mean SGPT (ALT) levels were elevated outside the upper limit of the normal range for Visits 2 through 7. At the Final Visit, the mean SGPT (ALT) level for placebo group female patients was 84 (\pm 93) U/L. There were no statistically significant between-treatment-group differences in the median changes noted from Baseline to any on-study visit.

In male patients, Baseline mean SGPT (ALT) values were normal in the GLIADEL[®] Wafer treatment group [47 (\pm 28) U/L] but were elevated in the placebo treatment group [63 (\pm 38) U/L (NR: 0 - 59 U/L)].

With the following exceptions, the mean SGPT (ALT) values among male patients were normal at subsequent on-study visits: Visit 8 - GLIADEL[®] Wafer mean: 75 (28) U/L; Visit 3 - placebo mean: 83 (\pm 72) U/L. At the Final Visit, the mean SGPT (ALT) levels for GLIADEL[®] Wafer and placebo group male patients were 38 (\pm 28) U/L and 46 (\pm 42) U/L, respectively. There were no statistically significant between-treatment-group differences in the median changes noted from Baseline to any on-study visit.

SGOT (AST)

In female patients, mean Baseline SGOT (AST) values in both treatment groups were within the normal range [GLIADEL[®] Wafer - 29 (\pm 27) U/L; placebo - 20 (\pm 12) U/L] [NR: 0 - 39 U/L]. Mean SGOT (AST) levels remained normal throughout the course of the study, with only one exception of a mean level of 43 (\pm 50) U/L at Visit 5 in the GLIADEL[®] Wafer treatment group. At Final Visit, the mean SGOT (AST) levels for GLIADEL[®] Wafer and placebo group female patients were 27 (\pm 16) U/L and 18 (\pm 10) U/L, respectively. There were no statistically significant between-treatment-group differences in the median changes noted from Baseline to any on-study visit.

In male patients, the Baseline mean SGOT (AST) values in both treatment groups were within the normal range [GLIADEL[®] Wafer - 17 (5) U/L; placebo - 24 (16) U/L] and remained normal throughout the course of the study [NR: 0 - 44 U/L]. The median change from Baseline in SGOT (AST) values was statistically significantly different in the GLIADEL[®] Wafer and placebo treatment groups at Visit 3 (P = 0.04). Visit 3 data show an increase in SGOT (AST) level for male GLIADEL[®] Wafer patients but no change for male placebo patients.

Alkaline Phosphatase

In female patients, mean Baseline alkaline phosphatase values in both treatment groups were normal [GLIADEL[®] Wafer - 122 (\pm 27) U/L; placebo - 122 (\pm 27) U/L] [NR: 60 - 270 U/L]. Without exception, mean alkaline phosphatase levels remained normal throughout the course of the study. At Final Visit, the mean alkaline phosphatase levels for GLIADEL[®] Wafer and placebo group female patients were 204 (\pm 113) U/L and 162 (\pm 42) U/L, respectively. There were no statistically significant between-treatment-group differences in the median changes noted from Baseline to any on-study visit.

In male patients, the Baseline mean alkaline phosphatase values in both treatment groups were within the normal range [GLIADEL[®] Wafer - 188 (\pm 69) U/L; placebo - 133 (\pm 42) U/L] and remained normal throughout the course of the study [NR: 60 - 270 U/L]. The median change from Baseline in alkaline phosphatase values was statistically significantly different in the GLIADEL[®] Wafer and placebo treatment groups at Visit 3 (P = 0.04). Visit 3 data show an increase in alkaline phosphatase level for male GLIADEL[®] Wafer patients but a decrease for male placebo patients.

Bilirubin

In female patients, mean Baseline total bilirubin values were normal in both treatment groups [GLIADEL[®] Wafer - 0.5 (\pm 0.4) mg/dL; placebo - 0.4 (\pm 0.2) mg/dL] [NR: 0 - 1.1 mg/dL] and remained normal throughout the course of the study. At the Final Visit, the mean total bilirubin levels for GLIADEL[®] Wafer and placebo group female patients were 0.4 (\pm 0.2) mg/dL and 0.3 (\pm 0.2) mg/dL, respectively. The median changes in total bilirubin values were significantly different in the GLIADEL[®] Wafer and placebo treatment groups at Visit 2 (Day of Surgery). Visit 2 data show a decrease in total bilirubin level among female GLIADEL[®] Wafer patients but an increase among female placebo patients.

In male patients, mean Baseline total bilirubin values were normal in both treatment groups [GLIADEL[®] Wafer - 0.7 (\pm 0.5) mg/dL; placebo - 0.6 (\pm 0.2) mg/dL] [NR: 0 - 1.1 mg/dL] and remained normal throughout the course of the study with one exception: at Visit 9 the single patient in the placebo group had a total bilirubin level of 1.3 mg/dL representing a 0.4 mg/dL increase from Baseline. At the Final Visit, the mean total bilirubin levels for GLIADEL[®] Wafer and placebo group male patients were 0.4 (\pm 0.2) mg/dL and 0.4 (\pm 0.3) mg/dL, respectively. The median changes in total bilirubin values were statistically similar at all visits.

Overall Changes in Hematology

The numbers of shifts in hematological parameters from normal Baseline values to out-of-range on-study values were comparable in the GLIADEL[®] Wafer and placebo groups. Shifts from normal levels of WBC to elevated levels were common in both populations. Shifts from normal to out-of-range levels in hemoglobin and platelet count were less frequent. There were only small numbers of high to low or low to high shifts in levels for any of the hematological parameters.

Overall Changes in Urinalysis

Baseline urinalysis results were, in general, normal. Five parameters were analyzed to assess overall changes over time in urinalysis results, including measurements of protein, glucose, casts/crystals, leukocytes, and erythrocytes. Only a small number of changes were noted among patients in either treatment group.

Clinically Significant Test Result Abnormalities

Nine of 16 (56%) patients in the GLIADEL[®] Wafer treatment group and 12 of 16 (75%) patients in the placebo treatment group had a clinically notable post-Baseline laboratory abnormality. The highest percentage of clinically notable laboratory findings were abnormalities in hematological values followed by high SGPT (ALT) values for both treatment groups. There were no statistically significant between-treatment-group differences in any clinically notable hematological parameters.

3.6.5.1.4.3 Uncontrolled Study 9003

Overall Changes in Serum Chemistry

There were no notable differences between the treatment groups in the number of patients with abnormal results for any of the biochemistry parameters at any timepoint during the study.

Overall, there were no clinically significant patterns of change in any biochemistry parameter that could be associated with study treatment. Very few significant changes were observed in any of the biochemistry parameters during the study. There were a few parameters [e.g.: AST (SGOT), ALT (SGPT) and total bilirubin] for which small changes were observed, but mean values did not exceed the ULN and changes were comparable between the treatment groups.

SGPT

Both mean and median SGPT values were elevated at Baseline [41 (\pm 34) U/L and 31 U/L, respectively (NR: 0 - 30 U/L)]. These values increased on the Day of Surgery [52 (\pm 57) U/L and 35 U/L, respectively]. Over time, as the number of patients having tests at each visit declined, the mean values remained elevated, with the lowest mean value at Visit 6 [40 (\pm 33) U/L] and the greatest mean value at Visit 7 [59 (\pm 29) U/L]. The median value decreased into the normal range at Visits 4 and 6, and was slightly above the normal range at Visit 5 (32 U/L), and more than two times the upper limit of normal (64 U/L, N = 6) at Visit 7.

SGOT

Mean and median SGOT values were in the middle of the normal range at Baseline [20 (\pm 11) U/L and 18 U/L, respectively (NR: 0 - 35 U/L)], and remained within the normal range throughout the study.

Alkaline Phosphatase

Mean and median alkaline phosphatase values were within normal limits (WNL) at Baseline [84 (\pm 24) U/L and 85 U/L, respectively (NR: 30 - 120 U/L)], declined on the Day of Surgery [77 (\pm 41) U/L and 69 U/L, respectively], but increased above the Baseline values at all subsequent post-Baseline time points.

The only average values that were at or exceeded the upper limit of the normal range were the mean values at Visit 3 [120 (.52) U/L], Visit 7 [134.(89) U/L], and Final Visit [121 (.61) U/L].

Bilirubin

Baseline mean and median total bilirubin values were within the normal range at Baseline [0.4 (\pm 0.3) mg/dL (NR: 0.2 - 1.2 mg/dL)] and were unchanged or decreased at subsequent visits.

Total Protein

Mean and median total protein values were within the normal range at Baseline [6.8 (\pm 0.7) g/dL and 6.7 g/dL, respectively (NR: 6.0 - 8.2 g/dL)], and declined to abnormally low values on the Day of Surgery (both to values of 5.8 g/dL). On subsequent visits, average values increased into the normal range but remained lower than at Baseline.

Albumin

Mean and median albumin values were within the normal range at Baseline [4.4 (\pm 0.4) g/dL and 4.3 g/dL, respectively (NR: 3.5 - 5.3 g/dL)], and decreased on average by about 15% on the Day of Surgery [mean and median change scores of -0.7 (\pm 0.5) g/dL and -0.6 g/dL, respectively]. Mean and median albumin values for Visit 3 were similar to the Day of Surgery values. Mean and median values at subsequent visits were all 4.2 g/dL or greater, except for the Visit 7 mean value. At Visit 7, mean and median albumin levels were 4.0 (\pm 0.4) g/dL and 4.1 g/dL, respectively.

Glucose

Both mean and median glucose values were abnormally elevated at Baseline, with values of 145 (\pm 68) mg/dL and 120 mg/dL, respectively [NR: 70 - 115 mg/dL]. Both mean and median values increased sharply on the Day of Surgery [190 (\pm 46) mg/dL and 170 mg/dL, respectively]. The mean glucose value remained abnormally high at Visits 3 and 4, declined into the normal range for Visits 5 and 6, and became minimally abnormal at Visit 7 [116 (\pm 50) mg/dL]. Median glucose values were WNL at all visits after the Day of Surgery.

Shift Analyses

Blood Urea Nitrogen

For blood urea nitrogen (BUN), the shift analysis shows that for those values which were normal at Baseline, there were seven that shifted to low, the majority of the values remained WNL and three values shifted to out of range at post-Baseline visits. Of the patients with elevated post-Baseline values, a maximum of two patients (Visit 3) at each time point had within normal limit values at Baseline. No patients with Baseline values WNL had values out of range at visits 5, 6 or 7.

The shift analysis shows that no patient who had serum creatinine WNL at Baseline had abnormally elevated creatinine values on the Day of Surgery or at subsequent post-Baseline visits.

SGPT

The SGPT shift analysis shows that at Visit 1 (Day of Surgery) there were two patients with high values whose values were normal at Baseline. There were two to five patients at each visit after the Day of Surgery with Baseline values WNL but high values at these time points.

SGOT

The shift analysis shows nine SGOT values changed from normal at Baseline to high values post-Baseline.

Alkaline Phosphatase

For alkaline phosphatase, the shift analysis shows that for values that were normal at Baseline, there were 19 values that shifted to high at post-Baseline visits, while 61 values remained in the normal range post-Baseline. At each visit after the Day of Surgery, there were from two to six high values in patients with WNL Baseline values.

Total Bilirubin

Only one patient at one visit had a post-Baseline total bilirubin value greater than the upper limit of normal, which had been WNL at Baseline.

Sodium

The shift analysis shows that a maximum of three patients at Visits 1 through 6 had serum sodium values within the normal range at Baseline that became abnormally low at that time point. The majority of WNL values at Baseline remained WNL post-Baseline. Only 8 values shifted from normal at Baseline to abnormally low post-Baseline.

Potassium

The shift analysis shows that for those serum potassium values that were WNL at Baseline, there was one shift to a low value, 77 values remained within normal range, and 5 values shifted high at post-Baseline time points.

Chloride

The shift analysis shows that four patients with chloride values within the normal range at Baseline had abnormally high values on the Day of Surgery. After this time point, only one patient with a Baseline value within normal range had an elevated post-Baseline value at one time point. In all, there were three shifts to low, 62 values remained within normal range, and 5 values shifted to high at post-Baseline visits. On the Day of Surgery, all 19 patients with data available had elevated glucose values. Of these 19 patients, eight had glucose values within normal range at Baseline and 11 had elevated Baseline values. At each subsequent visit, from two to five patients had elevated glucose values.

Overall Changes in Hematology

In female patients, Baseline mean and median hematocrit values were WNL [38.3% ($\pm 4.5\%$)] and 38.6%, respectively (NR: 36.0% - 46.0%). On the Day of Surgery, both mean and median values became abnormally low [31.5% ($\pm 6.1\%$) and 31.6%, respectively]. Mean and median values remained below the lower limit of normal at Visits 3 and 4, returned to WNL at Visit 5, and remained WNL through Visit 7 (mean and median values were both 42.7%; there was only a single female patient at Visit 7).

In male patients, Baseline mean and median hematocrit values were WNL [44.5% ($\pm 4.4\%$) and 43.8%, respectively (NR: 41.0% - 53.0%)]. On the Day of Surgery, both mean and median values decreased to just below the lower limit of normal [39.8% ($\pm 3.3\%$) and 40.0%, respectively]. Mean and median values remained slightly low at Visit 3. Mean and median values were just at or below the lower limit of the normal range at Visit 5 [40.6% ($\pm 4.3\%$) and 38.7%, respectively] and Visit 7 [40.9% ($\pm 3.5\%$) and 40.9%, respectively], but well within the normal range at Visits 4 and 6.

The changes in average values over time for hemoglobin and erythrocyte (RBC) count generally followed closely those for average changes in hematocrit over time. Post-Baseline mean and median RBC number for males were more persistently below the lower limit of normal than was hematocrit, attaining within normal range values only at Visit 6 for mean ($4.6 (\pm 0.4) \times 10^6/\text{mm}^3$) and only at Visit 4 for median ($4.5 \times 10^6/\text{mm}^3$) [NR for males: $4.5 - 5.9 \times 10^6/\text{mm}^3$].

WBC Count

WBC counts were above the upper limit of the normal range at Baseline in 10 patients and within the normal range in 12 patients, with mean and median Baseline values of $11,900 (\pm 6,400)/\text{mm}^3$ and $10,200/\text{mm}^3$, respectively [NR: 4,500 - 11,000/ mm^3]. The mean and median values increased on the Day of Surgery to $17,100 (\pm 5,500)/\text{mm}^3$ and $16,400/\text{mm}^3$, respectively, and 19 of 22 patients had WBC counts above the upper limit of the normal range. On all subsequent visits, the mean and median values were WNL.

Neutrophils

Baseline mean and median percentage neutrophils were both at the upper limit of normal, with values of 80% (\pm 18%) and 76%, respectively [NR: 31% - 76%]. On the Day of Surgery, mean and median values became abnormally high, with values of 95% (\pm 23%) and 88%, respectively. Mean and median values at all subsequent visits were WNL, ranging from 63% - 75%. The mean and median percentages of bands were WNL at Baseline [6% (\pm 8%) and 3%, respectively (NR: 0% - 6%)]. The mean values became abnormally high on Visits 3 and 7 [9% (\pm 18%) and 7% (\pm 11%), respectively], while median values were WNL at all visits.

Lymphocytes

The Baseline mean and median percentages of lymphocytes were low, with values of 17% (\pm 9%) and 17%, respectively [NR: 24% - 44%]. On the Day of Surgery these values declined to 9% (\pm 8%) and 10%, respectively. From Visit 3 to Visit 7, both mean and median values were below normal at three visits (Visits 3, 5 and 7) and WNL at Visit 4 and Visit 6.

Mean and median percentages were WNL at Baseline and remained so at all post-Baseline visits for monocytes, eosinophils, basophils, and platelets.

Shift Analysis for Hematological Parameters

The changes over time in average RBC-related parameters were reflected in the shift tables.

Hematocrit

The percentages of patients with Baseline hematocrit values WNL, but low values at post-Baseline time points, was 65%, 69%, 46%, 43%, 25%, and 43% at Visits 1 (Day of Surgery) through 7, respectively. All patients with low Baseline values had low values through Visit 5; three of the total of four values for this patient group at Visit 6 and Visit 7 were WNL.

Hemoglobin

The shift table shows that in the first three post-Baseline visits at least half of the patients' hemoglobin values shifted from normal to low. In Visits 5 through 7, normal to low shifts occurred in 29% to 43% of the patients with only one patient's values shifting to higher than normal at Visits 5 and 6 (Patient No. 001002). A total of 35 values were lower than Baseline, 32 remained normal, and 3 were higher than Baseline.

Leukocytes

The shift table shows that at visits after the Day of Surgery there were eight normal Baseline leukocyte values that shifted to below the lower limit of normal range at post-Baseline visits. A total of 29 values were within the normal range at Baseline and remained within the normal range at post-Baseline Visits and 17 normal Baseline values shifted to high. Normal values ranged from 67% - 80% of the total values at

each visit after the Day of Surgery. There were both normal to low and normal to high shifts in leukocyte values at all visits except Visit 6 and 7, when there were no normal to high shifts.

Platelets

The shift table shows that for platelet counts, the majority of values were WNL at Baseline and remained WNL post-Baseline. There were three values that were normal at Baseline and shifted to abnormal, one low and two high during the post-Baseline period.

Overall Changes in Urinalysis

Specific Gravity

Mean and median urine specific gravity and urinary pH values were WNL at Baseline [1.017 (\pm 0.007) and 1.015, respectively (NR: 1.003 - 1.030)], and remained so throughout the study.

Urinary Protein

At Baseline, 18 patients had no urinary protein and one patient had trace protein. At post-Baseline visits, no patients had more than trace urinary protein. Six of 66 post-Baseline values were positive for trace protein; one on the Day of Surgery, three at Visit 3, and one each at Visits 4 and 5.

At Baseline, 16 patients had no evidence of glycosuria, one patient had trace glucose, one had 2+ and one had 4+. Eight of 65 post-Baseline values were greater than 0: two patients had 2+ and one had 3+ on the Day of Surgery; two patients had 1+ and one had 3+ at Visit 3, and 1 patient had 1+ and 1 patient had 2+ at Visit 4.

Shift Analysis for Urinalysis

The shift table shows that only one patient at one time point (Visit 4) had a specific gravity value outside of the normal range and all values at all time points for pH values were normal.

Clinically Significant Test Result Abnormalities

Laboratory values were considered to be clinically notable abnormalities if they met established FDA (Division of Neuropharmacology) criteria.

The numbers of patients with low hematocrit levels (47% of males and 43% of females) and the numbers of patients with leukocytosis (45%) were not unexpected in this postoperative patient population. Other clinically notable abnormalities were infrequent.

The highest percentage of clinically notable laboratory findings were abnormalities of hematological and SGPT values. About one-half of the patients (7 of 15 males and 3 of 7 females) had clinically notably low hematocrit levels during the study.

Ten patients had clinically notable high WBC counts. Of these, five patients had WBC counts of at least 20,000/mm³ during the study.

There were no patients with clinically notably low WBC counts during the study. However, three patients had clinically notably low (0%) neutrophils on WBC differential counts. Thus, the interpretation of these low neutrophil percentages is unclear.

Clinically notable abnormalities other than hematological were principally those of SGPT. Seven patients had clinically notably high values of SGPT on at least one occasion.

There were no clinically notably abnormal values for SGOT, alkaline phosphatase, or total bilirubin during the study.

Two patients had clinically notably high post-Baseline BUN values. Serum creatinine levels for these two patients were WNL at all visits.

One patient had a serum uric acid value that was elevated significantly at Baseline; all of this patient's post-Baseline values were WNL.

For two patients at Day of Surgery, increases from Baseline of at least two units in urinary glucose were noted. For Patient No. 001007, all subsequent urinary glucose values were 0. For Patient No. 080002, urinary glucose was 1+ at Visit 3 and "1/4" at Visit 4.

Patient No. 001002 had two to three casts in his urinary sediment at Visits 5 and 6, and one to two hyaline casts at Visit 7. At Visit 6 he also had "10-12 gr" (the meaning of gr is unknown) in his sediment, as well as 2 - 4 WBC and 15 - 20 epithelial cells. His BUN values at these two visits were 23 mg/dL and 22 mg/dL, respectively; his serum creatinine at these visits was 1.0 mg/dL and 1.1 mg/dL, respectively. Thus, the clinical significance of these urinary microscopic abnormalities is unclear.

Four patients had urinalysis test results considered to be clinically notable abnormalities. In all patients, the abnormalities were transient.

3.6.5.2 GLIADEL® WAFER PERIODIC SAFETY SUMMARIES

Adverse event reports summarized here were gathered from both company-sponsored clinical trials and spontaneous reports. The majority of events included in these safety reports were derived from clinical studies. The blind was not broken when events occurred during double-blind controlled studies and did not represent a significant departure from adverse event profiles developed from previous reports. Consequently, many reported events could not be specifically attributed to GLIADEL® Wafer administration.

In reports from controlled clinical trials, the adverse event profile was consistent with adverse events observed in patients undergoing craniotomy for resection of malignant glioma, namely, convulsions, intracranial infections, and healing abnormalities. A similar pattern was reported in limited post-marketing surveillance with GLIADEL® Wafer administration. The safety reports reflect a high incidence of adverse experiences related to the central and peripheral nervous system. The most commonly observed CNS-

related adverse event was seizure in the early postoperative period. Intracranial hypertension and CSF leaks were also commonly reported.

With the exception of the following reports, all adverse events occurring during the report intervals were consistent with the sequelae of craniotomy for resection of primary or recurrent malignant glioma.

3.6.5.3 OTHER SAFETY INFORMATION

3.6.5.3.1 Study 100-9703: Phase II Trial of Surgery with GLIADEL[®] Wafer and Radiation in Patients with Operable CNS Metastasis from Systemic Cancer

The primary objective for this study is to determine the incidence and nature of toxicity associated with GLIADEL[®] Wafer implantation in patients with brain metastases from systemic cancer, and associated with subsequent CNS radiotherapy. Secondary objectives are efficacy (survival and time to tumor progression), patterns of recurrence (local and distant control), quality of life and AGT (a BCNU metabolizing enzyme) activity in tumor tissue. Twenty-five patients were enrolled in this multi-center, open-label clinical trial. Study subjects received radiotherapy after recovery from surgery, but no more than four weeks after resection and implantation of GLIADEL[®] Wafer. The minimum study follow-up period will be for twelve months after the last evaluable patient has been treated with GLIADEL[®] Wafer. The first patient was enrolled on June 4, 1998 and enrollment has been completed. Final follow-up data collection is currently underway. As of November, 2000, 7 of 25 patients in this open-label study have had adverse events possibly or probably related to treatment, including seizures (n=2), nausea/vomiting (n=2), fever (n=1), constipation (n=1), alopecia (n=1), respiratory distress (n=1), and eye pain (n=1). There were no infections related to surgery or wafer placement. Median survival of the 16 patients with more than one year of follow-up was 434 days, with 8 patients still alive (as of November, 2000). Follow-up for the remaining patients is ongoing.

3.6.6 Summary of Benefits and Risks Associated with the Administration of the GLIADEL[®] Wafer

The approved use of carmustine in the treatment of malignant brain tumors is limited by the occurrence of delayed myelosuppression and pulmonary fibrosis when it is administered intravenously in doses sufficient to maintain tumoricidal concentrations within the central nervous system. Preclinical data obtained in a model of established intracranial 9L gliosarcoma show that intracerebrally-implanted polymers containing carmustine produce high sustained concentrations of carmustine within the central nervous system while causing only local inflammatory changes at the site of implantation and no evidence of systemic toxicity.

GLIADEL[®] Wafer is an implantable, biodegradable wafer (carmustine 3.85% in a matrix of polifeprosan 20) designed to deliver carmustine directly into the surgical cavity created when a brain tumor is resected. Implantation of the GLIADEL[®] Wafer after resection of recurrent glioblastoma produces a survival advantage compared to placebo treatment when survival is adjusted for certain prognostic factors.

Accordingly, GLIADEL® Wafer is presently indicated for the treatment of patients with recurrent glioblastoma multiforme.

Two randomized, double-blind, placebo-controlled clinical trials, studies T-301 and CL-0190, were conducted to test the GLIADEL® Wafer as first-line treatment after maximal resection of primary malignant glioma. These studies demonstrated that GLIADEL® Wafer produced a survival advantage compared to placebo.

Study RPR132596/T-301, the 240-patient pivotal controlled study showed that GLIADEL® Wafer implants increase overall survival by approximately 20% compared to placebo (13.9 mo vs. 11.6 mo, $p=0.027$). GLIADEL® Wafer significantly delayed time to decline in overall function as measured by Karnofsky Performance Status score ($p=0.05$), as well as time to neurological decline as measured by significant improvement in 10 of 11 specific neuro-performance assessments ($p<0.05$). The survival advantage associated with GLIADEL® Wafer treatment remained after adjustment for prognostic factors ($p=0.02$), and was evident as well in the subset of patients with glioblastoma multiforme, the most common and severe form of malignant glioma (207 of the 240 patients enrolled; 13.5 mo vs. 11.4 mo, $p=0.10$; $p=0.05$ when adjusted for prognostic factors).

Since reoperation for tumor progression could confound the survival endpoint, censoring patients who underwent reoperation showed a benefit favoring GLIADEL® Wafer treatment compared to placebo, with one year survival being 61.0% versus 48.8%, respectively. Comparison of the Kaplan-Meier survival curves showed GLIADEL® Wafer treatment to significantly prolong survival ($p=0.014$).

The supportive controlled Study CL-0190, consisting of 32 patients treated with either GLIADEL® Wafer or placebo wafer, showed a statistically significant survival benefit favoring GLIADEL® Wafer treatment compared to placebo (13.4 mo vs. 9.2 mo, $p=0.011$).

The adverse event profile was similar in the GLIADEL® Wafer-treated and placebo-treated groups, and was consistent with adverse events observed in patients undergoing craniotomy for resection of malignant glioma, namely, convulsions, intracranial infections, and healing abnormalities. Intracranial hypertension (9.2% vs. 1.7%) and CSF leak (5% vs. 0.8%) were more common in the GLIADEL® Wafer-treated patients compared to placebo-treated patients. However, most (9/11) patients in the GLIADEL® Wafer treated group with intracranial hypertension experienced this AE late in the disease course at the time of tumor recurrence. Thus, this AE is not directly related to GLIADEL treatment. Similarly, for the GLIADEL treated patients with CSF leak only two of these occurred in proximity to surgery and, therefore, are likely possibly related to GLIADEL therapy. GLIADEL® Wafer may be associated with seizures in the early postoperative period in patients with recurrent glioblastoma but not in patients with initially diagnosed and previously untreated tumors. Overall survival of patients experiencing a seizure was similar to those not having a seizure. There was no evidence of systemic toxicity as determined by monitoring clinical laboratory results, and no investigator considered GLIADEL® Wafer to be the sole, or a contributory, cause of death for any patient.

For the supportive controlled study CL-0190, 12 of 16 patients (75%) in the GLIADEL® treatment group and 9 of 16 patients (56%) in the placebo treatment group experienced at least one treatment-emergent adverse event during the study period. The most frequently documented treatment-emergent adverse events in the GLIADEL® treatment group were hemiplegia (38%) followed by convulsion (19%), aphasia (13%), and visual field defect (13%). In the placebo treatment group, the most frequently reported treatment-emergent adverse events were hemiplegia (25%) and convulsion (13%). Six percent (two events) of the treatment-emergent adverse events in the GLIADEL® treatment group were considered by the investigator to be life-threatening in severity, 55% (17 events) were considered to be severe and 32% (10 events) were considered to be moderate in severity. In the placebo treatment group, 44% (7 events) of the treatment-emergent adverse events were considered to be severe and 38% (6 events) were considered to be moderate. In both the GLIADEL® treatment group and the placebo treatment group, most events were considered by the investigator to have no relationship to study drug [22 of 31 events (71%) in the GLIADEL® treatment group and 10 of 16 events (63%) in the placebo treatment group]. No event was considered to be definitely or probably related to GLIADEL® or placebo wafers by the investigator. In the GLIADEL® treatment group, 3 of 31 treatment-emergent adverse events (10%) were considered to be possibly related. One of 16 treatment-emergent adverse events (6%) in the placebo treatment group was considered by the investigator to be possibly related to study medication.

The uncontrolled, open-label safety study (Study 9003) conducted in 22 patients with glioma or high-grade glioma who received GLIADEL® Wafer as first-line treatment showed a median survival of 9.6 months at the time of final assessment. The incidence of adverse events in these patients was similar to that observed in studies T-301 and CL-0190.

The favorable risk-benefit assessment for GLIADEL® Wafer is therefore supported by a consistently observed improvement in survival with preservation of overall neurological function, and without an increase in the risk of an adverse outcome.

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