FIRM:RHONE POULENC RORER
TRADE NAME:GLIADEL
GENERIC NAME:POLIFEPROSAN 20 WITH
CARMUSTINE

Summary Basis of Approval
Cover Form

Appl #: 020637 Firm: RHONE POULENC RORER
Reviewing Div: 150
Trade Name: GLIADEL (POLIFEPROSAN 20 WITH CARMUSTINE
Generic Name:
POLIFEPROSAN 20 WITH CARMUSTINE

Approval Letter:	Y	Statistician Review:	Y
SBA Form:	N	Bio/Dissolution Review:	N
Final Printed Labeling:	N	Microbiologist Review:	Y
Medical Officer Review:	Y	NAS/NRC Review:	N
Chemist Review:	Y	Pharmacologist Review:	Y
Federal Register Notice:	N	Completion Date:	20-MAY-97

AD-A220-637

Approval Letter And Related Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 2 3 1996

NDA 20-637

Guilford Pharmaceuticals Inc.
Attention: Ross S. Laderman
6611 Tributary Street
Baltimore, Maryland 21224

Dear Mr. Laderman:

Please refer to your February 6, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gliadel Wafer (polifeprosan 20 with carmustine implant).

We acknowledge receipt of your amendments dated March 13, 25, 28, April 24, May 6, 7, 8, 17, 30, June 21, 24, 27, July 11, 17, 19, 29, 30, 31, August 6, 9, 13, 26, 27, 29, September 4 and 18, 1996.

This new drug application provides for Gliadel for use as an adjunct to surgery to prolong survival in patients with recurrent glioblastoma multiforme for whom surgical resection is indicated.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-637. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated August 27, 1996 and September 4, 1996. These commitments, along with any completion dates agreed upon, are listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Oncology Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Paul Zimmerman
Consumer Safety Officer
(301) 594-5775

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

FDA Corres

FEB 16 1996

NDA 20-637

Guilford Pharmaceuticals Inc.
6611 Tributary Street
Baltimore, Maryland 21224

Attention: Ross S. Laderman
Vice President, Regulatory Affairs

Dear Mr. Laderman:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic act f the following:

Name of Drug Product: GLIADEL Wafer (polifeprosan 20 with carmustine)

Therapeutic Classification: P

Date of Application: February 6, 1996

Date of Receipt: February 7, 1996

Our Reference Number: NDA 20-637

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 7, 1996 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) and in accordance with the policy described in the Center's Staff Manual Guide 4820.6, you may request an informal conference with this division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone.

Should you wish a conference, a telephone report or if you have any questions concerning this NDA, please contact:

Paul F. Zimmerman
Project Manager
(301) 594-5775

The NDA number listed above should be referenced at the top of the first page of any communications concerning this application.

Sincerely yours,

D Wypeas 2-15-96

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-150/div. file
HFD-151/PZimmerman/2-12-96

R/D init. by: DPease/2-14-96
F/T by PZimmerman/2-15-96 2/15/96

ACKNOWLEDGEMENT LETTER

Co. Corres.

GUILFORD PHARMACEUTICALS

Ross S. Laderman
Vice President, Regulatory Affairs

February 6, 1996

VIA MESSENGER

Robert DeLap, M.D., Ph.D.
Acting Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
c/o CENTRAL DOCUMENT ROOM
Food and Drug Administration
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

RE: New Drug Application #20,637
GLIADEL® Wafer (polifeprosan 20 with carmustine)
User Fee I.D. 2833
User Fee Waiver Files WR-96-002, SBE-96-001
Orphan Drug Designation #89-24-370-6

Dear Dr. DeLap:

Guilford Pharmaceuticals Inc. is pleased to submit this New Drug Application, NDA #20,637 for GLIADEL® Wafer (polifeprosan 20 with carmustine). The Food and Drug Administration has previously granted a waiver of user fees as documented in the attached September 26, 1995 letter to Guilford Pharmaceuticals (pp. 4-7) from Amanda Pedersen, FDA's Chief Mediator and Ombudsman. FDA has assigned user fee I.D. #2833 (p. 8) to this application. GLIADEL® is also the subject of an approved orphan drug designation. See the attached December 13, 1989 letter from Dr. Marlene Haffner (p. 9).

Submitted with this NDA is a CANDA designed to accommodate the requests of the medical reviewer (Dr. Grant Williams) and the reviewing statistician (Dr. Sue Jane Wang), installed in two lap top computers on loan to FDA from Guilford. A manual accompanies each of these lap top computers and is also contained in the NDA. The text of the NDA hard copy will be submitted on disk shortly. It will contain all information to the extent possible in electronic format.

6611 Tributary Street • Baltimore, Maryland 21224 • (410) 631-6300 • (410) 631-6338 Fax

Also attached to this letter is a duplicate copy (also contained in Section 4 and elsewhere in the New Drug Application) of the product outer pouch label and carton label for GLIADEL® Wafer (pp. 10-12). We request early review and comment on these labels to permit Guilford to build an inventory of GLIADEL® wafers for timely distribution of the product after FDA approval of the NDA. This is important because the pouch label must be applied prior to packaging, sterilization and release of the product to avoid damage to the product by application of labels following packaging and sterilization. FDA's early review and comment on these labels will help to assure the availability of the product in a timely fashion following FDA approval.

The last attachment to this letter is a listing of all relevant patent information on GLIADEL® (p. 13).

GLIADEL® is a biodegradable polyanhydride polymer containing BCNU, with a proposed label indication for use as an adjunct to surgery to prolong survival in patients with a malignant glioma. At the time of surgical resection of the brain tumor, up to eight wafers are implanted and provide high local concentrations of BCNU directly to the tumor site with sustained release over a three-week period. This product provides significantly greater levels of BCNU to the tumor site than are possible with the currently approved systemic therapy.

This NDA contains reports of the five clinical studies conducted in a total of 337 patients worldwide. Of these five studies, two Phase III, double-blind, placebo-controlled, randomized trials were conducted. Four of the five studies were conducted in North America under the provisions of the IND The first of these, study 8701, was a dose-ranging protocol conducted in patients who had undergone prior surgery for grade III or IV astrocytoma. The second of the IND studies was a Phase III multi-center, randomized, placebo-controlled study (study 8802) in patients with recurrent malignant glioma. The third of the IND studies, protocol 9003, was an uncontrolled study conducted to evaluate the safety of GLIADEL® in patients with newly-diagnosed malignant glioma. The last IND study, protocol 9115, was designed to continue enrollment of patients with recurrent malignant glioma after enrollment in study 8802 had been completed.

The fifth clinical study submitted with this NDA was conducted in Finland and Norway and is the second of the two Phase III, double-blind, placebo-controlled, randomized trials conducted with GLIADEL®, this one to determine the safety and efficacy of GLIADEL in patients newly diagnosed as having malignant glioma. This European study was conducted ancillary to the IND. It is our view that the clinical studies support the use of GLIADEL in the treatment of both initially diagnosed malignant glioma and recurrent malignant glioma.

The production of GLIADEL® wafers takes place in Guilford's own recently constructed clean room containment manufacturing facility and conforms to provisions of Good Manufacturing Practice regulations. This facility was designed specifically for, and is dedicated to, GLIADEL wafer production. It was inspected recently by a team from FDA's Baltimore District Office in conjunction with the submission of our treatment protocol. GLIADEL® wafers are currently being manufactured and distributed pursuant to the provisions of the existing treatment protocol. We will provide a copy of the Chemistry, Manufacturing and Controls section of the NDA to FDA's Baltimore District Office.

We are most appreciative of the interactions we have had with FDA during the development of this New Drug Application and have strived to assure that its content is responsive to the guidance and comments we have received from FDA in the past. We also appreciate the accelerated review process which has been proposed for this NDA, and we are ready to assist FDA in any manner possible during and after the course of that review process. Please do not hesitate to contact Louise Peltier, Director of Regulatory Affairs at (410)631-6356 or me at (410)631-6306 or either of us by fax at (410)631-6338. We look forward to continuing work with the Division of Oncologic Drug Products both with this NDA and with additional clinical studies that we have proposed and will propose for this product. Should you have any immediate questions or concerns, please do not hesitate to contact us at any time.

Sincerely,

Ross S. Laderman
Vice President,
Regulatory Affairs

Attachments

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved OMB No. 0910-0001
Expiration Date: December 31, 1997
See OMB Statement on Page 1

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASSIGNED

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*

NAME OF APPLICANT	DATE OF SUBMISSION
Guilford Pharmaceuticals Inc.	2/6/96
ADDRESS *(Number, Street, City, State and ZIP Code)*	**TELEPHONE NO.** *(Include Area Code)*
6611 Tributary Street Baltimore, Maryland 21224	(410)631-6300
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* 20-637

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Polifeprosan 20 with Carmustine	GLIADEL® Wafer

CODE NAME *(If any)*	CHEMICAL NAME
GPI-100	Poly[bis(p-carboxyphenoxy) propane:sebacic acid 20:80] with 1,3-bis(2-chloroethyl)-1-nitrosourea

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Wafer	Surgical Implant	3.85% BCNU 7.7 mg BCNU/wafer

PROPOSED INDICATIONS FOR USE

GLIADEL is indicated for use as an adjunct to surgery to prolong survival in patients with a malignant glioma.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION

IND GLIADEL Wafer, Guilford Pharmaceuticals Inc., Baltimore, MD
DMF
DMF

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THIS SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
N/A	N/A

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☒ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

This application contains the following items *(Check all that apply)*

X	1 Index
X	2 Summary (21 CFR 314.50) (c))
X	3 Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4 a Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
X	b Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b)) (qualifying statement)
X	10. Statistical section (21 CFR 314.50 (d) (6))
X	11. Case report tabulations (21 CFR 314.50 (f) (1)) (reference)
X	12. Case reports forms (21 CFR 314.50 (f) (1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
X	15. OTHER *(Specify)* Waiver of User Fee, CANDA

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Ross S. Laderman Vice President, Regulatory Affairs	Ross S. Laderman	2/6/96

ADDRESS *(Street, City, State, ZIP Code)*	TELEPHONE NO. *(Include Area Code)*
6611 Tributary Street Baltimore, Maryland 21224	(410)631-6306

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

December 13, 1989

Nova Pharmaceutical Corporation
6200 Freeport Centre
Baltimore, Maryland 21224-2788

Attention: Stephen J. Rochelle
Manager, Drug Regulatory Affairs

Dear Mr. Rochelle:

Reference is made to the application of March 24, 1989 and to your amendment of June 14, 1989 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act(FFDCA) (21 U.S.C. 360bb) for the designation of Biodel™ containing BCNU (a biodegradable polymer implant containing carmustine) as an orphan drug.

Congratulations on obtaining your orphan drug designation. We have completed our review of the information submitted in accordance with the Food and Drug Administration Interim Guideline implementing section 526 of the FFDCA and have determined that Biodel™ containing BCNU qualifies for orphan designation for the localized placement in the brain for the treatment of recurrent malignant glioma. Please refer to this letter as official notification of designation.

Prior to marketing approval, sponsors of drugs that have been designated as orphan drugs are requested to submit written notification to the Office of Orphan Products Development of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another for the statutory period of exclusivity. In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of Biodel™ containing BCNU as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. Richard Bertin at (301) 443-4903.

Sincerely yours,

Marlene E. Haffner, M.D.
Director, Office of Orphan
Products Development (HF-35)

GUILFORD PHARMACEUTICALS

Ross S. Laderman
Vice President, Regulatory Affairs

August 2, 1996

VIA FEDERAL EXPRESS

Mr. Paul Zimmerman
Consumer Safety Officer
Division of Oncologic Drug Products (HFD 150)
Attn: Third Floor Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: NDA 20-637
GLIADEL® Wafer (polifeprosan 20 with carmustine implant)
General Correspondence - Debarment Certification

Dear Mr. Zimmerman:

Reference is made to Leslie Vaccari's telefax of July 29, 1996 which transmitted Dr. Rahman's biopharmaceutics review comments on the referenced NDA. These comments included a request (item #3) that we submit a Debarment Certification for NDA 20-637 as soon as possible. Accordingly, attached is our Debarment Certification statement based upon review of the June 19, 1996 debarment list prepared by FDA's Office of Enforcement, Division of Compliance Policy.

Should you have any questions relating to this Debarment Certification, please feel free to contact me at any time.

Sincerely yours,

Ross S. Laderman
Vice President,
Regulatory Affairs

Attachment

cc: Leslie Vaccari (via telefax on 8/2/96)

Submission #039

6611 Tributary Street • Baltimore, Maryland 21224 (410) 631-6306 • (410) 631-6338 Fax

GUILFORD PHARMACEUTICALS

GLIADEL® Wafer
NDA 20-637

DEBARMENT CERTIFICATION

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, Guilford Pharmaceuticals Inc. certifies that, to the best of its knowledge and belief, the services of any person listed pursuant to Section 306(c) of the Act, as debarred under Sections 306(a) or 306(b) of the Act, were not used and will not be used in any capacity in connection with this New Drug Application.

Ross S. Laderman
Vice President,
Regulatory Affairs

August 2, 1996
Date

6611 Tributary Street • Baltimore, Maryland 21224 • (410) 631-6300 • (410) 631-6338 Fax

Study CL-0190

Site 01: Simo Valtonen, M.D. 9 patients
Turku University Central Hospital (Dept of Neurosurgery)
SF-20520 Turku
Finland

Site 02: Timo Kuurne, M.D. 5 patients
Tampere University Hospital (Dept of Neurosurgery)
SF-33520 Tampere
Finland

Site 03: Olavi Heiskanen, M.D. 9 patients
Dr. Leena Kivipelto, M.D.
Helsinki University (Dept of Neurosurgery)
SF-00260 Helsinki
Finland

Site 04: Eirik Helseth, M.D. 9 patients
Geirmund Unsgard, M.D.
University Hospital of Trondheim (Dept of Neurosurgery)
N-7006
Norway

The reviewing medical officer for this application is Dr. Alison Martin (594-5783). The responsible project manager/CSO is Paul Zimmerman (594-5775).

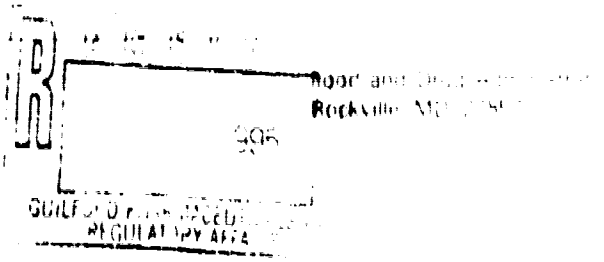
The user fee goal date is February 7, 1997.

The division's action goal date is July 25, 1996. This application will likely be presented to the Oncology Drugs Advisory Committee (ODAC) June 13 or 14, 1996.

cc: ORIG. NDA 20-637
Div. File
HFD-150/AMartin
HFD-150/PZimmerman
DPease
HFD-150/outgoing consult file

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Commissioner
5600 Fishers Lane
Room 14-105, HF
301-827-3390



September 26, 1995

Mr. Ross S. Laderman
Vice President, Regulatory Affairs
Guilford Pharmaceuticals
6611 Tributary Street
Baltimore, MD 21224

Re: Prescription Drug User Fee Act of 1992
Waiver Request and Small Business Exception Request
Our Files: WR-96-002, SBE-96-001

Dear Mr. Laderman:

This letter responds to your letter on behalf of Guilford Pharmaceuticals (Guilford), dated June 23, 1995, requesting a waiver of the application fee assessable upon submission of the marketing application for Guilford's GLIADEL Wafer [NPC 702 with Carmustine (BCNU)], IND under the Prescription Drug User Fee Act of 1992. Guilford also requested, in the event that FDA does not grant Guilford a waiver, a one year deferral of payment and a 50 per cent reduction in the application fee under the small business exception to the User Fee Act, 21 U.S.C. § 379h(b)(2). For the reasons described below, the Food and Drug Administration grants the waiver requested.

During fiscal year 1996, the User Fee Act requires a person submitting a new drug application to pay an application fee of 21 U.S.C. § 379h(a)(1). Guilford requested a waiver on the grounds that the waiver is necessary to protect the public health, 21 U.S.C. § 379h(d)(1), and that the fee is a significant barrier to innovation, 21 U.S.C. § 379h(d)(2).

Guilford's GLIADEL Wafer is an FDA-designated orphan drug product under section 526 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bb. According to Guilford, the GLIADEL Wafer is a treatment for malignant brain tumors (brain cancer), a condition affecting about 17,500 patients in the United States each year. FDA's Office of Orphan Products Development concluded in its orphan product designation review that there are no more than 50,000 patients with this disease, and due to the low survival rate, it is not likely that the number of cases in the U.S. would ever approach the 200,000 patient ceiling that would preclude orphan designation.

In support of its waiver request, Guilford stated that GLIADEL is an innovative product consisting of a patented biodegradable polyanhydride polymer incorporating the chemotherapeutic drug Carmustine (BCNU). Up to eight GLIADEL wafers are implanted directly into the tumor resection cavity when a neurosurgeon removes a malignant brain tumor. Guilford stated that GLIADEL has been designed to overcome the limitations of intravenous Carmustine by delivering it directly to the tumor site in high concentrations for an extended period of time. According to Guilford, the results of a controlled clinical study with this product submitted to the FDA indicate that it extends survival and does not cause the serious or debilitating adverse effects that often occur with systemic use of Carmustine. Guilford further stated that its product represents a significant advance in the treatment of brain cancer. Other treatments for malignant brain tumors that have had limited success are cytoreduction by neurosurgery, radiation therapy, and chemotherapy.

In further support of its waiver request, Guilford stated that the assessment of a user fee for the review of the GLIADEL NDA poses a significant burden to Guilford. Guilford stated that it was incorporated in July, 1993, and began operations in September, 1993. According to Guilford, its total revenue from its inception on July 14, 1993 to March 31, 1995, was only . Also during this time, Guilford sustained operating losses totaling approximately According to Guilford, it has been operating for the most part with equity capital raised at a public stock offering in June, 1994. Guilford expects to submit its NDA for GLIADEL Wafers to FDA on or about October 31, 1995.

Ordinarily, FDA will find that a waiver is necessary to protect the public health under 21 U.S.C. § 379h(d)(1) when two criteria are fulfilled. First, a person requesting a waiver must show that it is engaged in activity that protects the public health. Second, a person requesting a waiver must show that a waiver is necessary to the continuation of the activity shown to protect the public health. In applying the second criterion, FDA balances a variety of factors, including, but not limited to, the estimated patient population and the revenue to be derived from sales of the drug product, and the total annual revenue of the entity. Ordinarily, a waiver of an application fee is not necessary because the revenue to be derived from sales of the drug product, the entity's gross annual revenue, or other factors, provide a sufficient basis for payment of the fee.

With respect to the first criterion, notwithstanding FDA's inability to predict at this time whether Guilford will be able to carry the burden of demonstrating the safety and efficacy of GLIADEL Wafers, FDA concludes that Guilford has shown that its work to research, develop, and seek market approval of GLIADEL Wafers for the treatment of malignant brain tumors, is an activity that

protects the public health. FDA [illegible] that GLIADEL Wafers is intended to provide a survival benefit to patients with brain cancer, a life threatening disease.

With respect to the second criterion, FDA concludes that Guilford has shown that the fee is necessary to the continuation of activities that protect the public health. In this case, FDA notes that Guilford's revenue is extremely limited, totaling over the period from July 14, 1993 to March 31, 1995. As explained in the Draft Interim Guidance Document for Waivers of and Reductions In User Fees, Attachment G to User Fee Correspondence 2, dated July 16, 1993, although there is no express threshold for defining a small entity, FDA generally considers an entity with less than in total annual revenue to be less likely to be able to continue to provide products that protect the public health while paying user fees.

In this case, based on this combination of factors, including Guilford's limited total annual revenue, FDA concludes that a waiver of the application fee is necessary to protect the public health. Accordingly, pursuant to 21 U.S.C. § 379h(d)(1), FDA grants Guilford a waiver of the application fee assessable upon submission of the new drug application for GLIADEL Wafers.[1] Please include a copy of this letter in the NDA submission.

Please note that as announced in User Fee Correspondence 3, dated August 5, 1993, FDA plans to disclose information about its actions granting or denying waivers, consistent with the laws and regulations governing the disclosure of confidential commercial or financial information. If found to be releasable, the agency will disclose the names of all entities requesting a waiver, the names of the products covered by the applications for which waivers were requested, the statutory provisions under which the waivers were sought, and FDA's resolution of the requests. User Fee Correspondence 3 stated that FDA would make this information public only after approval of the marketing application. However, FDA currently is reconsidering its authority to release information about resolved application fee waiver requests prior to approval of the marketing applications. Thus, information about the resolution

---

[1] Because FDA is granting Guilford's request for a waiver on the ground that the fee is necessary to protect the public health, 21 U.S.C. § 379h(d)(1), FDA need not consider whether a waiver is also justified on the ground that the fee is a significant barrier to innovation, 21 U.S.C. § 379h(d)(2). Similarly, FDA need not consider whether Guilford qualifies for a 50 per cent reduction and one year deferral of payment of the fee under the small business exception to the User Fee Act, 21 U.S.C. § 379h(b)(2).

of this waiver request may [illegible] approval of the Market Transformation.

If you have any questions, please [illegible] this office, at 301-627-[illegible].

Sincerely yours,

Amanda B. Pedersen

Amanda B. Pedersen
Chief Mediator and Ombudsman

cc 7

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # [illegible] Trade (generic) names [illegible]

Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

X 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

___ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

4-23-96
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

Final Printed Labeling

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

Medical Officers Review

MEDICAL OFFICER REVIEW OF NDA 20-637:
Gliadel® Wafer
(Polifeprosan 20 with Carmustine)

Applicant: Guilford Pharmaceuticals Inc
ODAC Meeting: June 14, 1996

1. **General Information**

- ***Name of Drug***:

  Established: Polifeprosan 20 with Carmustine
  Proprietary: Gliadel® Wafer

- ***Applicant***:

  Guilford Pharmaceuticals Inc.
  6611 Tributary Street
  Baltimore, Maryland 21224

- ***Pharmacologic Category***: Antineoplastic agent

- ***Proposed Indication***: "Gliadel® is indicated for use as an adjunct to surgery to prolong survival in patients with a malignant glioma....

  External beam radiation therapy may be used in conjunction with Gliadel® but should be delayed at least three weeks after wafer implantation. Systemic chemotherapy may also be used with Gliadel® but should be withheld at least four weeks prior to and two weeks after surgery."

- ***Dosage and Administration***: Surgical implantation of one to eight biodegradable wafer(s), each containing 7.7 mg (3.85% by weight) carmustine (maximum patient dose of 61.6 mg carmustine) into the cavity created when a malignant glioma is resected.

  The proposed labeling reads

-

2. **Background/Regulatory History**

The estimated incidence of new cancers of the brain and central nervous system is estimated to be 17,900 in 1996.[1] The incidence of brain tumors is bimodal, with one peak in childhood and the other in adults aged 45 years or older. The histology of brain tumors in these two age groups differs significantly; the majority of adult tumors are high grade gliomas, e.g., anaplastic astrocytomas (AA) or glioblastoma multiforme (GBM). Although some Phase III trials enroll both AA and GBM, a variety of clinical trials with radiation or chemotherapy have noted a difference in survival based on histology, with patients with AA living longer. The median survival of patients with GBM treated with surgery, external beam radiation therapy, and adjuvant chemotherapy is approximately one year.[2]

Despite multimodality therapy, the vast majority of patients recur at the site of their initial tumor. At the time of recurrence, there is no standard therapy. Selected patients may be eligible for a radiation boost to the tumor bed or interstitial brachytherapy, reoperation, or chemo/immunotherapy on clinical trials. Potential risks and benefits of reoperation have not been prospectively studied in a controlled trial and are arguable for all patients. Several retrospective reviews of experience in consecutive patients in limited institutions have been reported in an attempt to identify an appropriate subset of patients for reoperation.[3-6] Preoperative KPS $\geq$ 70 and extent of tumor resection predicted for improved survival in one review; preoperative neurologic status in another; and no variable predicted for improved overall survival in the third (although the authors distinguished between high-quality and overall survival). In the two reviews that included patients with glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA), the median survivals differed. After reoperation, patients with GBM had a median

survival of 29 and 36 weeks vs 61 and 88 weeks for patients with AA. In the largest controlled trial submitted with this NDA #8802, data is collected on patients with GBM and AA who meet criteria to undergo reoperation and then who are randomized to receive Gliadel® or placebo wafer.

The rationale for Gliadel® is derived from principles of regional therapy: ideally, delivering an active agent with a steep-dose response curve directly to the site of the tumor bypassing restrictions to drug delivery such as the blood-brain barrier (less of an issue for BCNU) or poor tumor vascularization, while minimizing dose-limiting systemic toxicity. The hydrophobic portion of the Gliadel® wafer is intended to promote a slow release of carmustine and a sustained concentration, a potential advantage over the rapid clearance of systemically administered BCNU (no detectable levels 15 minutes after intravenous administration). In addition, prompt delivery of adjuvant treatment at the time of surgery is hoped to exploit a potential therapeutic window before declining health or performance status precludes later treatment.

The initial IND was submitted by [redacted]. The Phase III trial #8802 opened March 1989. The IND was transferred in 1992 to the new sponsor, [redacted] after #8802 had been completed. Due to lack of drug supply, no patients were treated between May of 1993 and November of 1995. The IND was transferred to Guilford Pharmaceuticals Inc. in January of 1994. Guilford was to build its own facility to manufacture Gliadel®. Guilford's product has only been used in the Treatment IND opened November, 1995.

In meetings with the FDA, it was agreed that given the inherent difficulties with assessing tumor measurements in patients with treated malignant gliomas (i.e., tumor borders confounded by post-surgical and radiation changes as well as cerebral edema +/- concurrent steroid use), that survival would be the primary endpoint. Furthermore, that a single Phase III trial, #8802, a double blind, placebo-controlled randomized Phase III trial, when supported by the noncomparator trials for safety data, might suffice for an indication in patients with relapsed glioblastoma. The applicant has also submitted protocol #CL-0190, a Phase III placebo-controlled, randomized, multicenter trial sponsored by [redacted] and conducted under foreign IND. This trial was closed early after accrual of 32 patients due to lack of drug supply. It has not been previously reviewed or formally discussed with the FDA. If accepted as adequate, well-controlled and approvable, Gliadel's® indication as an adjunct to surgery would be expanded to initially diagnosed as well as recurrent disease.

Data from the following trials have been submitted in this NDA:

Reviewer Table 1

Protocol	Enrollment Dates	Treatment	Population	#Planned/ Entered	Primary Endpoints
CONTROLLED					
# 8802	3.1.89 –0 1.17.92	Gliadel v. Placebo	Recurrent Malignant Glioma	220 / 222	Survival; 6mo. mortality
#CL-0190	3.23.92 –0 5.14.93	Gliadel v. Placebo	Newly Diagnosed Malignant Glioma	100 / 32	DFS; Survival
UNCONTROLLED					
[redacted]					

The efficacy claims rest with the two controlled trials which entered patients with AA and GBM. The applicant states that the two controlled trials are consistent in demonstrating an improvement in survival. Study #8802, was conducted in North America in patients with *recurrent* malignant glioma. #CL-0190 was conducted in Finland and Norway in *newly-diagnosed* patients.

References

[1]Parker SL et al. Cancer Statistics, 1996. CA Cancer J Clin 1996; 46:5-2
[2]Fine HA et al. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. Cancer 1993; 71:2585-97
[3]Young et al. Reoperation for Glioblastoma. J Neurosurg 1981; 55:917
[4]Griffith et al. Reoperation for Recurrent Glioblastoma and Anaplastic Astrocytoma. Neurosurgery 1987; 21:615-621.
[5]Ammirati et al. Reoperation in the Treatment of Recurrent Intracranial Malignant Gliomas. Neurosurgery 1987; 21:607-614

3. Scope of Review

Materials reviewed by the medical officer include:

- The regulatory history of this application;
- Volumes 1.13 (Summary); volumes 1.14-1.41 (Clinical Data); volumes 1.60-61 (Case Report Forms);
- Treatment Protocol dated September 27, 1995;
- Electronic submission of the Case Report Tabulations submitted as an Access database;
- Clinical amendments responding to FDA questions, "correspondence date" May 6 and 30, 1996;
- Safety Update Report on the Treatment IND with "correspondence date" May 7, 1996.
- Four Month Safety Update Report with "correspondence date" June 24, 1996.
- Labeling submissions with "correspondence date" June 21 and July 30, 1996.

4. Chemistry/Manufacturing (refer to CMC review)

Per CMC review, there are no apparent differences between the Guilford product and the previous products used in clinical trials.

5. Preclinical Pharmacology/Toxicology

Refer to Pharmacology/Toxicology review.

6. Clinical Pharmacology/Biopharmaceutics

The absorption, distribution, metabolism, and excretion of Gliadel® in humans is unknown. Classical bioequivalence studies were hampered by assay insensitivity for uM or nM drug concentrations needed for radiolabelling studies. Obtaining tissue (i.e., brain) samples for analysis would not have been appropriate. Information on the biodegradability of the wafers in humans is based on patients who have had a reoperation or autopsy. Biodegradability of the wafers appears variable with a spectrum of remnants to wafers recovered months after implantation in some patients vs complete absence of wafers in others (see Applicant's Table 3 in Appendix 1, Table 2 in Appendix II, and Reviewer Table in Appendix I). In the few instances where BCNU content of the wafer remnants was analyzed, it has not been found to be present in the wafer remnants.

7. Related IND Submissions

IND remains open. Guilford wants to further explore a dose-response curve with Gliadel® and has submitted a protocol of a Phase I study of increasing concentrations of carmustine in the prolifeprosan wafer.

8. Phase III Trial 8802: *A Double Blind Placebo-Controlled Study of BCNU Delivered from Biodel, a Biodegradable, Surgically Implanted Polymer for the Treatment of Recurrent Malignant Glioma*

8.1 Protocol Review

- *Review of Amendments*

Amendment #1, II.17.88 -- Even if malignancy is not seen in the frozen or squash preparation, patient will be eligible if tumor is found and prior to surgery it was known that the patient's tumor was a malignant glioma.

Comment: All patients were enrolled after the amendment.

- *Objectives*

"To determine the efficacy of BCNU delivered by surgically implanted polymer wafers for improving 6 month survival, and to measure the side effects associated with this treatment."

Comment: The primary objectives in the statistical section were six-month mortality rates and overall survival.

- *Study Design/Schema*

#8802 was a multicenter, randomized, double blind, placebo-controlled phase III trial in patients with recurrent malignant glioma. Patients were enrolled after malignant glioma was pathologically confirmed during surgery. After maximal resection, up to eight wafers of either Gliadel® or placebo wafer were placed against the resection surface.

Eligibility criteria:

- 18 years of age or older
- Previous cytoreductive or biopsy surgery for a brain tumor, with a histopathologic diagnosis of AA or GBM
- KPS $\geq$ 60
- Prior definitive external beam radiation therapy (EBRT), sufficient to disqualify the patient from further radiation therapy (XRT)
- Unilateral, unifocal tumor of at least 1.0 cm diameter, as determined by tumor imaging studies, at the time of present surgery
- Confirmation of the presence of malignant glioma by frozen or squash preparation prior to wafer implantation at the time of the present surgery. If malignancy is not found, patient is eligible if tumor is found and the patient carried the prior diagnosis of a malignant glioma
- Patients must be those for whom reoperation is an appropriate therapy

Exclusion criteria:

- Previous treatment with interstitial radiation
- Patients treated with antineoplastic chemotherapeutic agents during the preceding 4 weeks (6 weeks for nitrosoureas) before enrollment
- Hypersensitivity to contrast material to an extent that imaging scans would not be obtainable

Comment: In contrast to study #CL-0190, #8802 did not define baseline laboratory parameters as an eligibility criteria.

- *Procedure, Treatment, and Schedule of Tests*

Randomization. Details of randomization were not described in the protocol, which states that "Patients will be given patient numbers to which one of the two treatments has been randomly assigned. Randomization will be stratified by center."

Treatment. Following maximal tumor resection and confirmation of malignant glioma, up to eight wafers (Gliadel® vs. Polymer placebo) were positioned to cover the entire resected surface, with overlapping permitted. The number of wafers to be placed in the tumor cavity varied depending on the exposed tumor surface area.

Schedule of Tests

Visit # Study Day	# 0 Baseline	# 1 Surgery	Discharge	# 2 14-28	# 3, etc. Q 2 mo.
History/ P.E.	X				
Karnofsky PS	X	X	X		X
Neurological Exam/ MMSE	X	X	X		X
Tumor Imaging: (CT w & w/o contrast or MRI)	X[1]	X[2]		X	X
Lab: CBC, SMA, U/A	X	X		X	
Surgery/Implantation		X			
Chemotherapy				X[3]	

[1] Baseline tumor imaging, on which the decision for surgery will be based, must be done no more than 7 days prior to surgery
[2] Tumor imaging must be done within 72 hours of surgery
[3] If chemotherapy is to be administered, tumor imaging must be done prior to initiation of chemotherapy
[4] Visits are bimonthly through month six and quarterly thereafter

The neurologic examination was designed to rate 11 parameters on a 4-point scale for a maximum abnormal score of 33: 0=normal, 3=severely abnormal, 4=could not be measured (see Appendix II). The MMSE assesses 5 parameters for a maximum score of 30 points: orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points) and language (9 points) (see Appendix II).

Chemotherapy. "Since only half the patients in the study will receive wafers containing BCNU, all patients will be eligible to receive chemotherapy." If used, chemotherapy should be initiated between Study Days 14-28 or preferably reserved until after declaration of treatment failure. If an investigator chooses to use chemotherapy, all study patients at that center were to receive the same regimen.

Reoperation. "In a previous study (#8701), necrotic brain material was found in the tumor resection cavity following BCNU wafer implantation. It is thought that this treatment may contribute to the development of tissue necrosis in some patients. In this study, additional surgery may be indicated for removal of necrotic brain material if the patient demonstrates the following signs and symptoms:

1. Increased area of enhancement on CT scan
2. Difficulty in reducing corticosteroid regimen
3. Changes in seizure frequency or character
4. Overall decline in clinical status

If the above signs and symptoms are present, serious consideration should be given to the advisability of reoperation to remove possible necrotic tissue. If this is done, pathology slides should be prepared and shipped to Nova. These materials will then be sent to the referee pathologist for examination."

- *Endpoints and Statistical Analysis*

Definition of Endpoints:

Treatment failure was defined by changes on contrast-enhanced CT or MRI scan and/or the Karnofsky performance status (KPS):

(I) An increase in tumor size on contrast-enhanced CT or MRI scan of $\geq$ 80% by *volume* as measured on all 10 mm slices, or an increase $\geq$ 50% in *planar size* (LXW) in the section showing the largest amount of tumor, compared to the smallest tumor volume measured. A change in tumor volume or size of this degree will be considered as evidence of treatment failure even if there are no deteriorating

neurologic findings.

(2) Decrease in KPS ≥ 30 points over two consecutive measurements (more than 4 weeks apart), using discharge KPS as the reference. The date of failure will be that of the first detection of a 30 point decline in Karnofsky performance status.

(3) The combination of an increase in tumor by contrast-enhanced CT or MRI of ≥ 40% but < 80% by volume or ≥ 25% but < 50% by planar size AND a tumor-related decrease in KPS of 20 points over two consecutive measurements (more than 4 weeks apart) will be considered evidence of treatment failure.

(Survival was not specifically defined.)

Statistical Analysis:

Sample size. The planned accrual of 220 patients was "based on the proportion who would survive 6 months, if one assumes the survival times are distributed exponentially and the median survival time of the controls is 36 weeks following surgery. If one assumes $\alpha = .05$, then with this number of patients one has 80% power to detect a decrease in 6-month mortality of about 18%, which is equivalent to a doubling of the median survival time."

...**The primary efficacy parameters will be survival time from study surgery, as well as sixth-month mortality rates**. In addition, duration of high-quality survival (Karnofsky score of at least 60) after study surgery, and fraction of survival at 6 months, 1 and 3 years after study surgery that is of high quality will be evaluated. Efficacy will also be based on quality of life measurements (Karnofsky, and the Mini-mental test).

Safety evaluations will be based on laboratory data, neurologic examinations, and imaging.

For each patient, survival time after study surgery will be determined. Survival curves will be estimated for each treatment group using the Kaplan-Meier method. The two treatment groups will then be compared with respect to these curves using the Log Rank and Wilcoxon tests. The effect of center will be examined using a proportional hazards model. Six-month survival rates will be computed for the two treatment groups, and compared using a Chi-square...For the Karnofsky and Mini-mental ratings the change from baseline will be determined for each of the treatment groups at each of the post-surgery time points. The significance of these changes from baseline will be evaluated at each time point using a paired t-test or a Wilcoxon signed rank test. At each timepoint the two treatment groups will be compared using eithr a t-test or Wilcoxon test...."

8.2 Results

8.2.1 Conduct of the Study

- *Randomization*

The NDA provides the details of the randomization process. Codes were generated using the SAS Proc. Plan to generate blocks of four for an anticipated16 patients at each of the 26 centers. An additional block of four followed by two blocks of 10 were generated for the biggest accruers. Different initial seed numbers were used for each of the three random number generators. The study medication was labeled sequentially. The local pharmacy was notified of a patient's surgery so that the study medication could be present at surgery. When pathology confirmed the presence of malignant glioma , the final entry criterion was met and the patient enrolled. If the patient was not enrolled, study medication was returned to the pharmacy and made available to the next candidate.

There were nine randomization deviations occurring in eight centers. Two were failure to use a designated pouch; 3 were use of study medication out of order; 4 were unblinding the study medication which in all cases occurred after implantation and in 3 cases was to provide for follow-up care. The other unblinding occurred inadvertently when filing a report with the FDA. Otherwise, medical officer review of the sequence of the

numbers and dates of surgeries were appropriate

Information on patients registered but not entered, i.e., patients for whom study drug was made available but not used, was not collected.

- *Eligibility*

All randomized patients were included in efficacy and safety analyses. The following were the protocol eligibility violoations:

Reviewer Table 2: Protocol Eligibility Violations

Eligibility Criterion	Gliadel	Placebo
KPS ≥ 60	1 pt with KPS 40 2 pts with KPS 50	1 pt with KPS 50
Nitrosourea within 6 weeks prior to surgery	3	--
No previous craniotomy or cytoreductive surgery[1]	5	13

[1] Pts had prior stereotactic or needle-biopsy proven malignant glioma prior to wafer implantation

- *Referee Neuropathologist*

Per protocol, "One H & E stained section of each block" of tumor was to be sent to the sponsor, who then forwarded the slides to The referee pathologist was blinded to treatment. The central readings are used in the analyses; diagnoses made at the individual center were not collected for #8802.

- *Referee Neuroradiologist*

Scans from only one center were evaluated by the referee neuroradiologist, Dr. Denis Melancon, Montreal Neurological Hospital.

- *Quality Assurance*

Although #8802 was sponsored by "Guilford has independently assessed the integrity and accuracy of the clinical data ure their adequacy...Audits have been conducted, including comparison of case report forms to source d nts, to assess the validity of selected key data variables...In addition, quality assurance audits have been conducted at a number of participating clinical sites...to evaluate the conduct of the studies and the content of the data at these sites.

8.2.2 Enrollment, Demographics, Baseline Characteristics

- *Study Dates*

First patient enrolled: March 1, 1989
Last patient enrolled: January 17, 1992
Last observation on last patient: November 19, 1995

- *Study Centers*

A total of 222 patients were enrolled at 27 centers in the U.S. (25) and Canada (2) between 3.1.89 and 1.17.92. Three centers enrolled ≥ 20 patients, 4 centers enrolled 11-19 patients, 9 centers enrolled 6-10, and 11 centers enrolled 1-5 patients. Gliadel® was inserted into 110 patients and polymer placebo wafer into 112.

- *Baseline Demographics and Clinical Characteristics*

Reviewer Table 3 on the following page is derived from the data listings as well as Applicant's Tables 4.3, 4.4, 4.8, 4.10, 4.11 and 4.12. There is no significant difference with regard to baseline characteristics between the arms, with the exception of the mean neurologic scores. Overall, the level of neurologic abnormalities were low (maximally abnormal score for the 11 items would be 33; see Appendix II for components of the neurologic exam). The statistically significant differences between the arms were a greater degree of abnormal vision and cranial nerve function in the placebo group (see Appendix II, Applicant Table 4.10 for details).

- *Tumor Size*

Baseline tumor dimensions were assessed in two ways: (a) imaging studies pre-operatively (length x width in cm^2 or volume in cm^3 on CT or MRI) and (b) at time of surgery (length x width x depth in cm^3). Either CT or MRI could be used to determine tumor size/volume. As shown in Applicant's Table 4.13, both measurements (area and volume) were not provided for all patients. The means and medians were similar between the arms.

Applicant's Table 4.13: Baseline Tumor Imaging Data

	GLIADEL 3.85%			PLACEBO			Chi-Square
Estimated Size	N	Mean	S.D.	N	Mean	S.D.	P-Value
Planar Size Length (cm)	73	4.9	1.6	75	4.9	1.9	0.911
Planar Size Width (cm)	73	3.9	1.1	75	4.4	2.0	0.062
Area (cm^2)[a]	73	20.2	10.0	75	22.9	13.9	0.184
Volume (cm^3)[b]	48	63.7	59.8	48	61.5	47.1	0.836

[a] Area was estimated by the product of planar size length and planar size width.
[b] Imaging tumor volume was taken directly from the CRF

Comment: Review of the data listings showed that only 7 patients (4 on Gliadel® and 3 on placebo) had neither recorded. Review of distribution of use of CT vs MRI revealed that centers tended to be consistent in their choice of one method of imaging over the other, providing for control for method of estimation within a center.

Reviewer Table 3: Baseline Demographics and Clinical Characteristics

Clinical Characteristic		Gliadel (n=110)	Placebo (n=112)	P-value[1]
AGE (years)				
mean (S.D)		48.1 (±12.3)	47.6 (±13.6)	0.746[1]
median		49	48	
range		27-79	19-80	
GENDER				
male		74 (67%)	69 (62%)	0.403[1]
female		36 (33%)	43 (38%)	
RACE				
Caucasian		100 (91)	104 (93)	0.866[1]
Black		3 (3)	3 (3)	
Hispanic		5(5)	3 (3)	
Oriental		0 (0)	1 (1)	
Other		2 (2)	1 (1)	
HISTOLOGY				0.943[2]
GBM		72 (65)	73 (65)	
AA		15 (14)	16 (14)	
Other anaplastic	mixed glioma	10 (9)	6 (5)	
	oligodendroma	4 (4)	5 (4)	
	ependymoma	0 (0)	1 (1)	
Non malignant	glioma	0 (0)	1 (1)	
	oligodendroma	2 (2)	2 (2)	
	astrocytoma	3 (3)	5 (4)	
Other	neoplasm (NOS)	2 (2)	3 (3)	
	type not specified	1 (1)	0 (0)	
	necrosis	1 (1)	0 (0)	
KARNOFSKY PS				
<60		3	1	
60		22	33	
70		24	22	
80		19	26	
90		39	29	
100		3	1	
Mean (S.D.)		77 (13.10)	75 (12.15)	0.166[2]
Median (range)		80 (40-100)	75 (50-100)	0.123[3]
PRIOR SURGERIES				
1		83 (75)	79 (71)	
2-4		27 (25)	33 (29)	0.090[1]
INTERVAL FROM 1ST SURGERY (years)				
Mean		2.11	1.96	0.742[1]
Median (range)		1.09 (0.25-14.00)	0.94 (0.23-18.24)	
PRIOR CHEMOTHERAPY		58 (53)	54 (48)	0.506
Nitrosourea		54 (49)	49 (44)	0.501
PRIOR XRT				
Amount: Mean (S.D.) [Rads]		5937 (±1107)	6188 (±1426)	0.155[1]
Median [Rads]		6000	6000	
Location: Local [N (%)]		53 (48)	54 (48)	
Whole Brain [N (%)]		28 (25)	23 (21)	
Both [N (%)]		29 (26)	34 (30)	
Unknown [N (%)]		0 (0)	1 (1)	0.649[1]
MMSE (total score)				
Mean (S.D.)		24.30 (6.87)	22.63 (8.45)	0.111[2]
NEURO EXAM (total score) Mean (S.D.)		3.95 (3.03)	5.01 (3.20)	0.012[2]

[1] Fisher's Exact Test for discrete variables; F-test from ANOVA for the continuous variables; [2] two sample t-test; [3]Wilcoxon Rank Sum

- *Characteristics of Surgery*

The maximum number of wafers (8) was implanted in 88 (80%) patients on the treatment arm and 91 (81%) on the placebo arm. Applicant's Table 4.15 presents the frequency distribution of the number of implanted wafers and the mean number of wafers implanted per patient.

Applicant Table 4.15: Number of Wafers Implanted

	GLIADEL 3.85% [N = 110]	PLACEBO [N = 112]	
Number of Wafers Implanted	Number (Percentage) of Patients		P-Value
0-2	0 (0)	0 (0)	
3	2 (2)	1 (1)	
4	2 (2)	1 (1)	
5	1 (1)	2 (2)	
6	1 (1)	7 (6)	
7	16 (15)	10 (9)	
8	88 (80)	91 (81)	
Mean ± SD	7.6±0.94	7.7±0.86	0.883

For other characteristics of surgery and comparability between the treatment arms, see Applicant's Table 4.14, on the following page. There were no statistically significant differences between the arms, with the exception of tumor volume, in contrast to volume measurements obtained from imaging studies. All but 5 patients had tumor volume recorded at time of surgery. The mean tumor volume was 68.9 vs 95.0 cm^3 in the Gliadel® arm vs placebo arm respectively, representing a 38% increase in volume in the placebo arm. Median tumor volume was 46 vs. 68 cm^3, representing a 48% increase in the placebo arm.

Applicant's Table 4.14: Characteristics of Wafer Implant Surgery

Parameter	GLIADEL 3.85% [N = 110]	PLACEBO [N = 112]	P-Value[a]
Hemisphere [N (%)]			
Right	53 (48)	55 (49)	
Left	57 (52)	56 (50)	
Both	0 (0)	1 (1)	0.946
Tumor Location by Lobe [N (%)]			
Frontal	39 (35)	26 (23)	
Temporal	21 (19)	21 (19)	
Parietal	10 (9)	20 (18)	
Occipital	7 (6)	2 (2)	
Frontal/Temporal	4 (4)	8 (7)	
Frontal/Parietal	12 (11)	8 (7)	
Temporal/Parietal	10 (9)	11 (10)	
Temporal/Occipital	1 (1)	0 (0)	
Parietal/Occipital	5 (5)	7 (6)	
Frontal/Temporal/Parietal	1 (1)	4 (4)	
Temporal/Parietal/Occipital	0 (0)	5 (4)	0.040
Duration of Anesthesia Administration (hours)			
Mean (S.D.)	5.0 (1.62)	5.0 (1.49)	
Median	4.8	4.8	0.975
Type of Surgical Resection [N (%)]			
Subtotal	81 (74)	88 (79)	
Total	24 (22)	21 (19)	
Total with lobectomy	5 (5)	3 (3)	0.614
Tumor Volume (cm^3)[b]			
Mean (S.D.)	68.9 (65.84)	95.0 (102.08)	
Median	46.0	68.0	0.028
Percentage of Tumor Resection			
Mean (S.D.)	79.9 (22.28)	78.0 (22.95)	0.536
Median	90.0	85.0	
Time from First Brain Tumor Surgery to Study Surgery (wafer implantation)			
Mean (S.D.) (months)	25.4 (30.32)	24.0 (32.93)	0.742
Median	13.2	11.4	

[a] Fisher's Exact Test for the discrete variables, F-test from ANOVA for the continuous variables.
[b] Tumor volume was estimated by the product of tumor length, width, and depth.

- *Treatment after Wafer Implantation*

Chemotherapy Fifteen of 27 centers administered chemotherapy. Of the 125 patients in the 15 centers, 50 patients (40%) received chemotherapy (percentage of treated patients within a center ranged from 11-100%). Ten agents were administered at a variety of times after wafer implantation to 29 patients on the Gliadel® arm and 21 on the placebo arm.

(1) Applicant's Table 4.106 (see Appendix II) lists the 10 agents administered, along with the mean and median total dosages. There appears to be balance between the arms, with the exception of an increase in use of tamoxifen in patients on Gliadel®.
(2) Applicant's Table 4.107 (see Appendix II) summarizes the mean and median time to delivery of chemotherapy and the mean and median durations of the administrations. There were no statistically significant differences.
(3) Applicant's Table 4.108 (see Appendix II) depicts the frequency distributions for time to onset and duration of chemotherapy.

Reoperation Data on reoperation were not systematically collected. At the request of the FDA to follow-up the #8802 protocol identifying necrosis requiring reoperation as a possible treatment-related event, Guilford extracted data on reoperations primarily from patient narratives but also from information obtained from monitoring visits, correspondence, internal memoranda and adverse event reporting. A total of 60 patients (27%) had a subsequent surgical procedure, ranging from drainage of loculated fluid to insertion of a shunt to open craniotomy (see Applicant's Table 2 in Appendix II). Thirty-four of 110 patients (31%) in the Gliadel® arm and 26 of 112 (23%) with placebo underwent a procedure. Forty-five percent of patients who underwent a procedure (27/60) were treated at two centers.

- *Concomitant Medications*

Dexamethasone was the most commonly prescribed medication at baseline and after wafer implantation. Ninety-eight patients on Gliadel® and 105 on placebo took dexamethasone after wafer implantation. The mean and median daily doses are shown in Applicant Table 4.113. The mean daily dose between the treatment groups was statistically significant ($p = 0.018$).

Eighteen patients on Gliadel® and 17 on placebo were prescribed other steroids. There were no signiciant differences between the arms. Other frequently administered medications included ranitidine and a variety of anticonvulsants. There were no significant differences in type of medicine administered between the arms.

8.2.3 Efficacy Results

There was one interim analysis for safety, which remained blinded, after accrual of 133 patients (cutoff date of December 12, 1990). The protocol-defined primary endpoints were six-month mortality and overall survival (unadjusted).

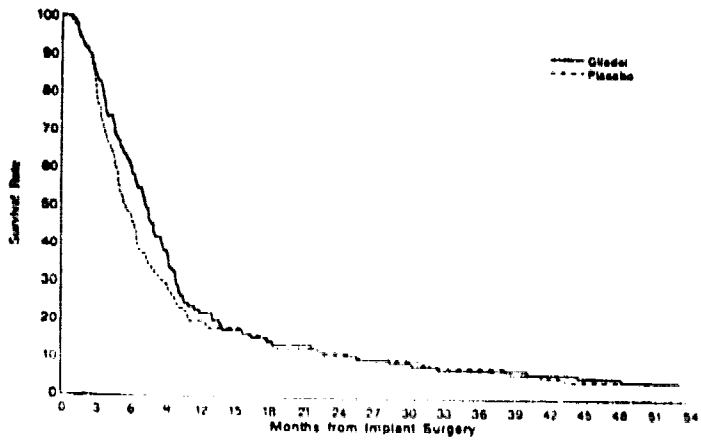
- *Six-Month Outcomes*

Mortality. Forty-four of 110 patients (40%) on Gliadel® and 59 of 112 patients (52.7%) on placebo were dead

six months after wafer implantation (p = 0.061, Fisher's Exact Test).

Survival. The overall Kaplan-Meier survival curve by treatment arm is shown in Applicant's Figure below.

Overall K-M Survival Curves for All Patients
by Treatment Group (n = 222)



Cumulative mortality through six months shows a trend toward a significantly lower mortality for the Gliadel® arm with a logrank p = 0.063 and a Gehan's generalized Wilcoxon test (GW, which weights early events) p = 0.077.

Comment: Deaths within six months of wafer implantation were not clustered in the perioperative period Agency analyses have confirmed the p values.

Six-Month Survival Adjusted for Prognostic Factors. The NDA states..."To control for the effects of strong prognostic factors on survival outcome due to chance imbalances in the treatment groups, adjusted analyses were performed using a proportional hazards regression model." A broad spectrum of prognostic factors (15) which could conceivably be important in recurrent malignant gliomas were evaluated for importance by a univariate Cox regression. Nine factors were found to be statistically important for six month survival, as defined by a P set at < 0.15. See Applicant's table 4.19, on the following page.

Applicant's Table 4.19: Estimated Risk Ratios and Confidence Intervals for Prognostic Factors, Six-Months Survival - All Patients

Prognostic Factor	Risk Ratio	95% Confidence Limits Lower	Upper	P-Value[a]
GBM Patients vs. Non-GBM Patients	2.028	1.284	3.204	**0.002**
Karnofsky Score ≥70 vs. <70	0.523	0.353	0.775	**0.001**
Local/Both vs. Whole Brain Radiation	0.784	0.505	1.216	0.277
White vs. Other	3.824	1.212	12.06	**0.022**
Tumor Resection ≥75% vs. <75%	0.726	0.478	1.103	**0.133**
Age (per decade)	1.278	1.100	1.483	**0.001**
Male vs. Female	0.933	0.627	1.390	0.734
Prior Chemotherapy vs. None	1.645	1.110	2.438	**0.013**
Years From First Surgery To Index Surgery	0.826	0.728	0.939	**0.003**
MMSE Median Scores ≥26 vs. <26	0.747	0.506	1.104	**0.144**
Prior Convulsions vs. None	0.877	0.591	1.301	0.514
Number of Wafers ≤6 vs. >6	0.392	0.144	1.067	**0.068**
Prior Steroid Use vs. None	1.452	0.777	2.713	0.243
Resection vs. Biopsy at First Surgery	1.377	0.784	2.420	0.266
Prior Brachytherapy vs. None	1.142	0.420	3.164	0.795

[a] P-Value from Chi-Square Test P-Values ≤0.15 appear in bold-face type.

By a backward elimination method of multiple regression using the Cox proportional hazards model, seven covariates were found to be statistically significant as defined by a p=0.05.

Applicant's Table 4.20: Six-Mo. Treatment Effect Adjusted for Prognostic Factors

Prognostic Factor	Risk Ratio	95% Confidence Limits Lower	Upper	P-Value[a]
All Patients				
GLIADEL 3.85% vs. PLACEBO	0.584	0.391	0.875	0.009
GBM patients vs. Non GBM patients	1.686	1.045	2.720	0.032
Karnofsky Score >70 vs. ≤70	0.651	0.428	0.991	0.045
Local/ Both vs. Whole Brain Radiation	0.570	0.359	0.905	0.017
Age (per decade)	1.188	1.005	1.405	0.043
Prior Chemotherapy vs. None	1.642	1.082	2.493	0.020
Years from first surgery to index surgery	0.874	0.764	1.000	0.050
Number of Wafers ≤6 vs. >6[b]	0.322	0.117	0.887	0.028
All Patients Stratified by Tumor Type				
GLIADEL 3.85% vs. PLACEBO	0.577	0.387	0.862	0.007
Karnofsky Score >70 vs. ≤70	0.658	0.433	0.999	0.050
Local/Both vs. Whole Brain Radiation	0.587	0.372	0.926	0.022
Age (per decade)	1.261	1.074	1.480	0.005
Prior Chemotherapy vs. None	1.539	1.022	2.318	0.039
Number of Wafers ≤6 vs. >6[b]	0.339	0.123	0.931	0.036

[a] P-value from Wald Chi-Square Test

After adjusting for the seven covariates, Gliadel® produced a statistically significant reduction in mortality compared to placebo (risk ratio = 0.58, p = 0.009), which remains when stratifying for tumor type.

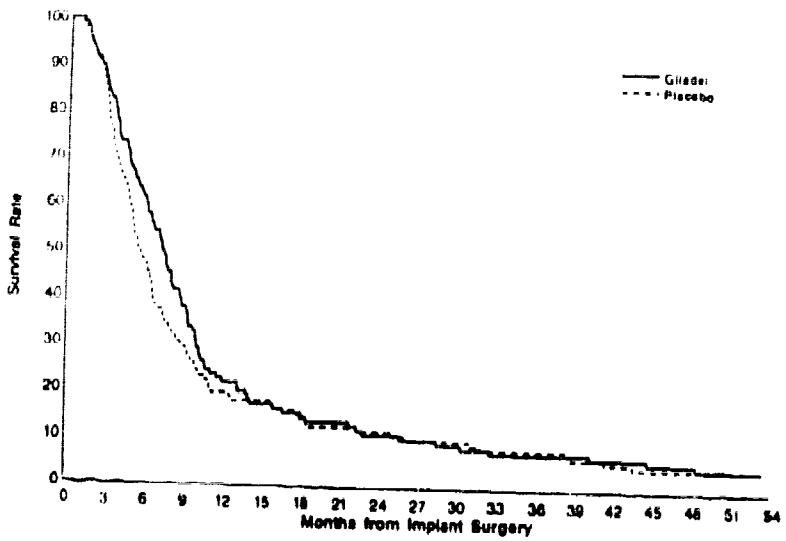
Comment: Protocol #8802 did not prospectively describe an adjusted survival analysis, nor the prognostic factors to be used. Data in the medical literature on prognostic factors that correlate with survival in patients with a recurrent malignant glioma, and especially for those selected to undergo reoperation, are quite limited (see Section 2). The robustness of the results could be questioned when the p value varies widely between the statistical analyses. See ***Statistical Review*** *for further discussion and alternative conservative analyses using a stratified logrank, which limits assumptions in the model, and fewer prognostic factors. To limit our choice of the number of prognostic factors, we chose factors explored in the retrospective reviews referenced in Section 2, i.e. factors that investigators in the field might consider important. These were tumor type, age, KPS and interval between first surgery and reoperation. The first three factors are also the generally accepted prognostic factors for initially diagnosed patients. Interval between surgeries was added to the list since it was examined in all three reviews as a potentially important factor. The applicant did include these factors in addition to others.*

- *Overall Survival*

As of the data cutoff date of November 10, 1995 (observation period of up to 71 months), ten patients were alive: 5 patients in the Gliadel® group (5%) and 5 in the placebo group (5%). The median duration of overall survival was 7.24 months (95% CI: 6.05 - 8.54 months) for Gliadel®-treated patients vs. 5.42 months (95% CI: 4.73 - 6.44 months) for placebo-treated patients.

The Kaplan-Meier survival curves by treatment group are shown in Applicant's Figure 7.

FIGURE [illegible] Overall Kaplan-Meier Survival Curves for All Patients by Treatment Group (Study 8802)



There is no statistical difference between the arms with p = 0.297 and p = 0.106 by the Log-Rank and Wilcoxon Rank Sum Tests, respectively.

Overall Survival Adjusted for Prognostic Factors. **Univariate regression analyses applied to the previously listed**

important

Applicant's Table 4.29 **Estimated Risk Ratios and Confidence Intervals for Prognostic Factors, Overall Survival - All Patients**

Prognostic Factor	Risk Ratio	95% Confidence Limits		P-Value[a]
		Lower	Upper	
GBM Patients vs. Non-GBM Patients	2.017	1.500	2.713	**0.000**
Karnofsky Score >70 vs. ≤70	0.552	0.419	0.726	**0.000**
Local/Both vs. Whole Brain Radiation	0.736	0.533	1.018	**0.064**
White vs Other	1.616	0.983	2.656	**0.058**
Tumor Resection ≥75% vs. <75%	0.560	0.409	0.766	**<0.001**
Age (per decade)	1.232	1.105	1.372	**<0.001**
Male vs. Female	0.798	0.601	1.058	**0.117**
Prior Chemotherapy vs. None	1.512	1.151	1.986	**0.003**
Years from First Surgery to Index Surgery	0.908	0.854	0.967	**0.002**
MMSE Median Scores ≥26 vs. <26	0.708	0.537	0.934	**0.014**
Prior Convulsions vs. None	1.035	0.782	1.370	0.809
Number of Wafers ≤6 vs. >6	0.610	0.360	1.033	**0.066**
Prior Steroid Use vs. None	1.310	0.884	1.940	0.178
Resection vs. Biopsy at First Surgery	1.297	0.901	1.867	0.162
Prior Brachytherapy vs. None	1.082	0.533	2.197	0.828

[a] P-Value from Chi-Square Test P-Values ≤0.15 appear in bold-face type.

By a backward elimination method of multiple regression in the Cox proportional hazards model, six covariates were selected in the overall survival analysis. (In comparison to the factors selected for six-month survival, prior chemotherapy and years from initial surgery are dropped; tumor resection ≥ 75% vs. ≤ 75% is added.) As shown in Applicant's Table 4.30 below, the treatment difference between the arms, when adjusted for prognostic factors, is statistically significant with a p = 0.45 for all patients, and p = 0.017 for patients stratified for tumor type.

TABLE 4.30 Overall Treatment Effect Adjusted for Prognostic Factors - All Patients

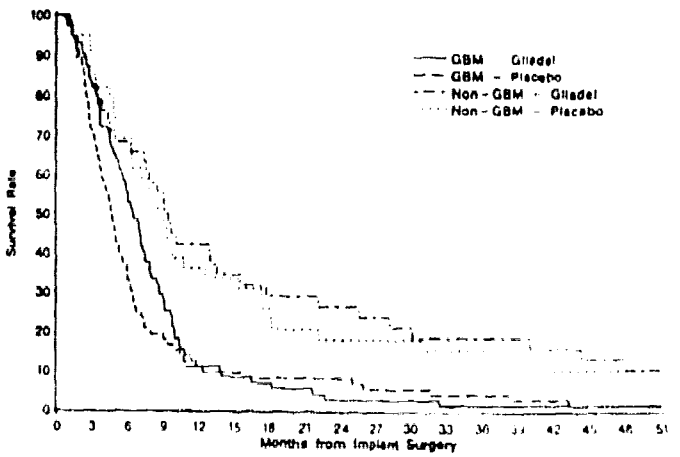
Prognostic Factor	Risk Ratio	95% Confidence Limits		P-Value[a]
		Lower	Upper	
All Patients				
GLIADEL 3.85% vs PLACEBO	0.752	0.568	0.994	0.045
GBM patients vs Non GBM patients	2.081	1.524	2.842	<0.001
Karnofsky Score >70 vs ≤70	0.693	0.513	0.938	0.018
Local/ Both vs Whole Brain Radiation	0.590	0.420	0.829	0.002
Tumor Resection ≥75% vs <75%	0.536	0.387	0.742	<0.001
Age (per decade)	1.257	1.119	1.410	<0.001
Number of Wafers ≤6 vs >6	0.510	0.291	0.892	0.018
All Patients Stratified by Tumor Type				
GLIADEL 3.85% vs PLACEBO	0.704	0.528	0.938	0.017
Karnofsky Score >70 vs ≤70	0.666	0.490	0.906	0.010
Local/ Both vs Whole Brain Radiation	0.614	0.436	0.864	0.005
Tumor Resection ≥75% vs <75%	0.525	0.378	0.729	<0.001
Age (per decade)	1.256	1.118	1.410	<0.001
Number of Wafers ≤6 vs >6	0.534	0.305	0.935	0.028
Resection vs Biopsy at First Surgery	1.492	1.010	2.203	0.044

[a] P-Value from Wald Chi Square Test

- *Subgroup Analyses GBM vs Non-GBM Patients*

A subgroup analysis was performed for the two primary endpoints comparing patients with GBM vs patients with another histology, "non-GBM" (see Reviewer Table 3, page 10, for breakdown of histology per arm). GBM patients treated with Gliadel® had a statistically significant reduction in six month mortality by the logrank and Gehan's Wilcoxon test. At the end of the overall (71-month) observation period, 10 patients were alive: 5 (1 GBM, 4 non-GBM) treated with Gliadel® and 5 (1 GBM, 4 non-GBM) with placebo. In patients with GBM, median survival was 6.51 months (95% CI: 5.32 - 7.49 mo.) in the Gliadel® arm and 4.63 months (95% CI: 3.78 - 5.52 mo.) in the placebo group. This was statistically significant by the Gehan Wilcoxon Test which weights early events (p = 0.021), but not by the logrank test (p = 0.180).

Overall K-M Survival Curves by Treatment Group &Tumor Type; GBM n = 145; Non-GBM n = 77



GBM Patients

6 Month Survival			Overall (up to 71 months) Gliadel: 6.51 mo. Placebo: 4.63 mo.		
Unadjusted		Adjusted	Unadjusted		Adjusted
logrank	GW*	Cox	logrank	GW*	Cox
p=.013	p=.015	p=.0073	p=.181	p=.021	p=.051

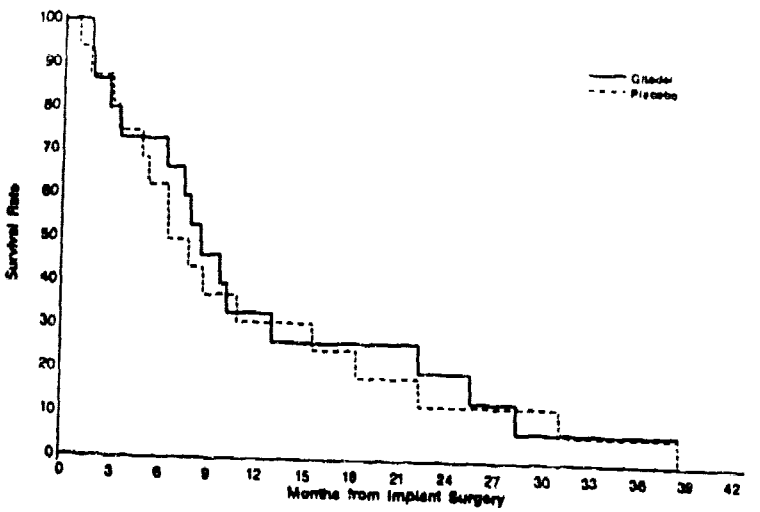
*Gehan's generalized Wilcoxon test.

Non-GBM Patients

6 Month Survival			Overall (up to 71 months) Gliadel: 9.30 months Placebo: 5.67 mo.		
Unadjusted		Adjusted	Unadjusted		Adjusted
logrank	GW*	Cox	logrank	GW*	Cox
p=.849	p=.775	p=.649	p=.754	p=.864	p=.613

*Gehan's generalized Wilcoxon test

The most common histology in the non-GBM subgroup was anaplastic astrocytoma (n = 31, 15 on Gliadel® and 16 on placebo). The overall Kaplan-Meier survival curve for this group of patients is shown in Applicant's Figure 2A. There was no statistically significant difference in six month or overall survival.



- *Secondary Efficacy Analyses*

Quality of life analyses based on repeated measures of KPS and the mini-mental status exam did not show statistical differences between the arms, per applicant's analyses . For further discussion, see the Statistical Review. Although definitions for treatment failure were provided in the protocol, it was not identified in the statistical section as a specific endpoint and data or analyses on time to treatment failure are not provided by the applicant.

- *Drug-Demographic Interactions*

Age. The applicant analyzed patients ≥ 65 (n = 20) with those < 65 (n = 202) years of age and found no significant difference in six month or overall survival within these two subgroups. There was no treatment-by-age interaction by the Cox model. See Appendix II (Applicant's Tables 4.24, 4.34 and Figure 9) for details.

Comment: The analyses of age based on these two discrete subgroups must be considered exploratory given the small number of patients ≥ 65.

Gender. There were 143 men and 79 women entered onto #8802. There was no statistically significant difference in either six month or overall survival between the gender subgroups; however, there was a trend toward significance in males treated with Gliadel® during the first six months. There was no treatment-by-gender interaction dected by Cox regression. See Appendix II (Applicant's Tables 4.25, 4.35 and Figure 10) for details.

Race. There were 204 patients listed as white and 18 patients as non-white (10 on Gliadel®, 8 on placebo; see Reviewer Table 3 for further details of race). The six month and overall survival benefit in whites treated with Gliadel® trended toward significance. There was a significant difference in overall survival for nonwhites treated with Gliadel®. There was a statistically significant treatment-by-race interaction for overall survival using Cox regression. See Appendix II (Applicant's Tables 4.26, 4.36 and Figure II) for details.

Comment: Few patients of color were entered onto this trial and it is not clear that "non-white" is a valid racial category. These analyses should only be considered exploratory.

- *Systemic Chemotherapy*

Overall survival of patients who did or did not receive systemic chemotherapy, by treatment arm, is presented below in Reviewer Table 4. Gliadel® shows a survival advantage, with or without chemotherapy, that is not statistically significant.

Reviewer Table 4 : Median Survival by Treatment Group and +/- Systemic Chemotherapy

	Chemotherapy		No Chemotherapy	
	Gliadel® n=29	Placebo n=21	Gliadel® n = 81	Placebo n=91
Median Survival (mo.)	9.13	8.38	6.31	4.90
Analyses	Logrank p = 0.856 Wilcoxon p = 0.495		Lograng p = 0.385 Wilcoxon p = 0.257	

Comment: Patients who received systemic chemotherapy survived longer, whether or not they received Gliadel®. Because patients were not randomized and the regimens not standardized, this information must be interpreted cautiously. It is possible that patients with the best prognosis were selected to receive further chemotherapy. This point, however, could not be proven by the Agency's comparison of age, baseline KPS, number of wafers implanted, time from first surgery or tumor type.

8.2.4 Safety Results

Specific adverse events (A.E.s) were not solicited on the CRF. An A.E. was to be listed on the CRF along with its gravity (insignificant, minor, serious, life-threatening); severity (mild, moderate, severe); whether it was treatment related (not related, unknown, possible, probably or definite), onset and end date; and any action taken.

Treatment-emergent adverse events were defined as those not seen at baseline or worsened if present at baseline. Multiple events of the same nature in the same patient but having different severities were coded once by the worst severity.

- *Deaths*

By the data cutoff date, 105 patients (95%) in the Gliadel® arm and 107 patients (96%) in the placebo arm had died. The majority in both arms died of tumor progression: 90 (82%) who received Gliadel® and 94 (84%) who had received placebo. See Applicant Table 4.46, below.

Applicant's Table 4.46.: All Causes of Deaths Summarized by Treatment

Cause of Death	GLIADEL 3.85% [N = 110]	PLACEBO [N = 112]
	Number (Percentage) of Patients who Died	
Tumor recurrence/tumor progression[a]	90 (82)	94 (84)
Unknown[b]	6 (5)	3 (3)
Respiratory complications[c]	2 (2)	3 (3)
Pulmonary embolus[d]	2 (2)	2 (2)
Postoperative complications[e]	1 (1)	2 (2)
Other cancer	1 (1)	2 (2)
Cardiopulmonary arrest	1 (1)	0 (0)
Increased intracranial pressure (with fever/sepsis)	1 (1)	0 (0)
Dementia	1 (1)	0 (0)
Suicide	0 (0)	1 (1)
TOTAL	**105 (95)**	**107 (96)**

[a] Tumor recurrence/pneumonia reported for one patient (GLIADEL treatment group - Patient No.) and progressive disease reported for one patient (GLIADEL treatment group - Patient No.)
[b] 'Unknown' entered by investigator or no cause of death was recorded
[c] Includes pneumonia or acute respiratory distress secondary to staphylococcus infection.
[d] Includes 1 patient (Patient No.) who died from "pulmonary embolus or myocardial infarction."
[e] Includes postoperative deterioration with pulmonary problems or pneumothorax, sepsis and pneumonia or multiple medical conditions.

Comment: A difference in causes of early vs. late death was not seen.

CRFs were provided on the 4 patient deaths that occurred within the first 30 days. Three of the 4 had received placebo and 1 Gliadel®. Two of the 4 patient deaths appear in Applicant's Table 4.46 as suicide and postoperative complications. The other two presumably appear under tumor recurrence or progression. One of these two, patient , had a normal level of consciousness the day of surgery, received placebo wafer, and after surgery was unarousable until his death. Patient treated with Gliadel®, was readmitted to the

hospital on study day 20 for a DVT which was treated with heparin. Neurologic status decreased precipitously the following day, with CT showing severe increased intracranial pressure and a cystic enhancing mass. Comparison to discharge scan is not provided. No autopsy was granted in either case. At least one, if not both of these deaths could be classified under postoperative complications, which would raise the incidence slightly to 2.2%.

- *Treatment Withdrawal due to Toxicity*

*Comment: Since treatment is not ongoing, the category of treatment withdrawal is open to interpretation. The reviewer considered that reoperations for a complication during which the surgeon also removed the wafers might qualify. Of the 8 cases with an indication for surgery that could be interpreted as for a complication, 6 occurred in the first month, i.e., perioperatively (see Reviewer Table 5). If we accept the animal data that carmustine has diffused from the wafer by 3 weeks, then 2/110 patients treated with Gliadel® had treatment withdrawal (indicated by * in Reviewer Table 5).*

Reviewer Table 5

Treament	Study Day	Reason for Reoperation	Procedure	Survival (wks)*
Gliadel®	11*	wound infection, seizure, increased left hemiparesis	bone flap and wafer remnants removed	31.9
Gliadel®	22	fever spikes and decline in mental status	wound exploration with debridement; removal of wafer-like remnants	25.9
Placebo	24	prevalent discharge from scalp wound	bone flap removal; polymer wafer fragment removed	9.4
Gliadel®	65	drainage and swelling in area of incision, edema with ventricular compression	bone flap removed, 3-4 wafer remnants removed	26.3
Gliadel®	4*	"polymer wafers were a source of concern"	removal of polymer wafers	?
Placebo	15	intracranial hemorrhage	exploration, removal of bone flap, removal of clot, removal of 8 wafer remnants	21.6
Gliadel®	68	deterioration due to meningitis	debridement of tumor cavity; abscess drained and wafer-like remnants removed	12.3
Placebo	18	lethargy, midline shift on CT	removal of necrotic tissue; wafer remnants removed	?

*Survival is dated from Gliadel® vs. placebo surgery, not from date of reoperation

- *Frequent (≥ 5%) Treatment-Emergent Adverse Events (A.E.s.)*

The incidence of common A.E.s defined as occurring in ≥ 5% of patients and irrespective of causality are shown in Applicant's Table 4.48, on the following page. Taken as a whole, rather than as specific events, the most common A.E.s related to the nervous system. Hematologic abnormalities, as seen with systemic BCNU, were uncommon.

Applicant's Table 4.48: **Treatment-Emergent Adverse Events Occurring in ≥5% of Patients by Treatment Group and by Body System and COSTART Term**

	GLIADEL 3.85% [N = 110]	PLACEBO [N = 112]	Fisher's Exact Test
Body System / COSTART Term*	Number (Percentage) of Patients		P-Value
Body as a Whole			
Fever	13 (12)	9 (8)	0.377
Infection	8 (7)	9 (8)	1.000
Pain	8 (7)	1 (1)	0.018
Cardiovascular			
Deep thrombophlebitis	10 (9)	12 (11)	0.823
Pulmonary embolus	6 (6)	8 (7)	0.784
Digestive			
Nausea	6 (6)	6 (5)	1.000
Nausea and vomiting	9 (8)	7 (6)	0.613
Oral moniliasis	6 (6)	6 (5)	1.000
Hemic and Lymphatic			
Anemia	8 (7)	12 (11)	0.483
Metabolic and Nutritional			
Healing abnormal	15 (14)	6 (5)	0.040
Hyponatremia	5 (5)	7 (6)	0.768
Nervous			
Aphasia	10 (9)	12 (11)	0.823
Ataxia	2 (2)	6 (5)	0.280
Confusion	11 (10)	9 (8)	0.646
Convulsion	21 (19)	21 (19)	1.000
Headache	16 (15)	14 (13)	0.698
Hemiplegia	21 (19)	22 (20)	1.000
Intracranial hypertension	4 (4)	7 (6)	0.539
Somnolence	15 (14)	12 (11)	0.543
Stupor	7 (6)	7 (6)	1.000
Respiratory			
Pneumonia	7 (6)	7 (6)	1.000
Skin and Appendages			
Rash	6 (6)	4 (4)	0.537
Urogenital			
Urinary tract infection	23 (21)	19 (17)	0.496

*The investigator verbatim term was used in place of a COSTART preferred term when the verbatim term was so nonspecific that assignment to an appropriate COSTART preferred term could not be made unambiguously, or when the most appropriate COSTART preferred term was either misleading or so general as to be uninformative.

Comment: The p-value is statistically significant only for pain and healing abnormality, although since the control arm involved placement of a foreign body into the resection cavity, it is possible that the incidence of certain A.E.s secondary to Gliadel® may be underestimated, e.g., convulsion and/or healing abnormalities could have been increased by a placebo wafer.

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

Sixty-four severe treatment-emergent events were reported in 43 of 110 (39%) of patients treated with Gliadel® vs. 68 severe treatment-emergent events in 37 of 112 (33%) patients who received placebo (see Applicant Table 4.50, with superimposed reviewer subtotals, in Appendix II). The body system with the most severe A.E.s

was the nervous system; 43 of 64 severe A.E.s in patients treated with Gliadel® and 47 of 68 severe A.E.s in patients who received placebo.

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

Forty-six A.E.s in 21 of 110 patients (11%) on Gliadel® were considered definitely, probably, or possibly related to study drug. Forty-two A.E.s in 20 of 112 (10%) patients on placebo were considered definitely, probably, or possibly related to wafer implantation. The body system with the most frequently reported A.E.s that might be related to treatment was in the nervous system: 29 of the 46 on the Gliadel® arm and 23 of 42 on the placebo arm. There were no A.E.s in the Gliadel® group that were assessed by the investigator as definitely related to treatment; there were 3 events in the placebo group that the investigator considered definitely related to treatment. This occurred in a single patient and appears to the sponsor and this reviewer to be related to post-wafer administration of intra-arterial cisplatin. See Applicant Table 4.52, with reviewer subtotals (Appendix II).

Comment: Given the circumstance of regional delivery of chemotherapy to a recently operated site in an area of pre-existing deficits, it might be expected that toxicities would be scored as possibly or probably-related to treatment, rather than definitely, i.e., the lack of this latter category of toxicities may say as much about the clinical setting as the study drug.

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

The sponsor discusses convulsions, abnormal healing, infections, meningitis, and hydrocephalus in further detail because of the possibility of a causal relationship and the clinical importance of the A.E.s.

Convulsion. Reviewer Table 6 summarizes the incidence of convulsion (or grand mal seizure) in patients with treatment-emergent convulsions, which allows differences to be seen between the treatment arms that are not apparent when looking at all patients with a convulsion (i.e., including patients with preexisting convulsions that did not change in severity on study). Patients treated with Gliadel® had an earlier onset of their convulsions relative to placebo treatment. For patients with at least one treatment-emergent convulsion, the median time to onset of the earliest, most severe episode was 3.5 days vs. 61 days in the placebo group. In patients who received Gliadel® and had a treatment-emergent seizure, 54% (12/22) had the onset of their earliest, most severe treatment-emergent episode within the first 5 days of surgery vs. 9% (2/22) who received placebo.

Reviewer Table 6: Treatment-Emergent Convulsions

	Gliadel®	Placebo	P-value*
Convulsions			
(All, After Wafer Implantation)	41 (37%)	32 (29%)	
Treatment-Emergent Only	22 (20%)	22 (19.6%)	1.000
Time to Onset of Treatment (days)			
Mean	26.09 (36.05)	62.36 (48.66)	0.008
Median	3.5	61.0	0.006
Severity, Treatment Emergent			
Mean	1.91 (0.75)	2.09 (0.68)	0.406
Median	2.0	2.0	0.406
Median Survival (wks)			
Treatment-Emergent Convulsions	36.3	26.8	0.352
All patients	31.5	23.6	0.106

* F-test from ANOVA for testing equality of two means; Wilcoxon Rank Sum for testing equality of two medians

Because of missing data for end dates, it is difficult to fully compare duration of convulsions between the treatment arms. If end dates are deleted, there is no statistically significant difference between the arms for

average total duration. If the missing end date is imputed (to start of next episode of convulsion, death date or study cutoff date, whichever is shortest), the average total post-baseline duration of convulsive episodes was longer in the Gliadel® group, although not statistically significant: mean 148.23 (318.91) vs. 29.23 (50.64) p = 0.091; median 7.0 vs 3.5, p = 0.178.

Healing Abnormality. As previously seen in Applicant's Table 4.48 (page 22), 15 patients (14%) on Gliadel® and 6 patients (5%) on placebo had a healing abnormality reported (p = 0.04). The sponsor has grouped the events into four major categories (see Applicant's Table 4.55 in Appendix II for a by-patient listing including investigator-rated severity and relationship to drug):

(1) Fluid, CSF, or subdural fluid collection;
(2) CSF leak;
(3) Wound dehiscence, breakdown, or poor healingl; and
(4) Subgaleal or wound effusions (including yellow discharge at the incision)

Comment: Using the list of patients who underwent reoperation, an additional 3 patients are identified who had an abnormality warranting a procedure. These patients were not coded under either healing abnormality or infection in the database (1-118, 3-105, 16-113). Two patients received Gliadel® and one placebo, slightly changing the numbers of patients with healing abnormalities to 17 (15%) on Gliadel® and 7 (6%) on placebo..

The applicant notes that not all healing abnormalities occurred in the perioperative period, defined as within one month of surgery and therefore may not be treatment related. An alternative grouping of data recognizes two groups, early (range of study day 1 - 42) and late (range 79-175). By these cutpoints, 12 patients had early complications and 5, late on Gliadel® while all 7 of the healing abnormalities on the placebo arm occurred early, i.e. by study day 33. The applicant argues that late healing abnormalities are unlikely to be treatment-related because BCNU diffuses out of the wafer early and should not be available to interfere with cell division. The hypothesis that mechanisms differ for early and late wound healing complications is plausible. Of the 5 late cases (all of which occurred on the Gliadel® arm), 4 were fluid collections (vs. 3 of 19 early cases, combining the arms) and only 1, wound breakdown. (One of the 4 cases of late fluid collection followed a repeat craniotomy). It is unproven, however, that the wafers are noncontributory to early or late wound healing abnormalities since they are variably biodegradable and space-occupying.

Infection. Applicant Table 4.69 (see Appendix II) lists the 65 treatment-emergent infections in patients on Gliadel® and the 64 in patients who received placebo by body system and COSTART Term. The only significant difference in incidence by body system was in the occurrence of meningitis (4 patients on Gliadel® vs. none on placebo; p = 0.059). Two cases of meningitis were bacterial; one patient underwent reoperation on study day 4 for removal of the wafer. The other case of bacterial meningitis was the only late case of meningitis. Review of the details of this case reveals that the meningitis occurred on study day 155, after the patient underwent reoperation for recurrent tumor on study day 154. A third case was chemical and treated with steroids, resolving by day 43. The fourth case was unspecified, but required hospitalization and treatment with antibiotics; the meningitis resolving by study day 34.

Comment: Reviewer Table 7 presents the incidence of infections related to the surgical site as derived from the Access database and using the investigator descriptions, rather than COSTART preferred term. This table confirms the applicants claim that meningitis was the only type of infection with an increase in incidence and further defines which of the infections listed in Applicant's Table 4.69 were related to the surgical site.

REVIEWER TABLE 7: Cranial Infections

	GLIADEL®	PLACEBO
Wound, including bone flap and epidural	9	10
Cellulitis, scalp	0	2
Meningitis	4	0
Abscess	1 (stitch)	1 (brain)

Hydrocephalus/cerebral edema/intracranial hypertension.

Incidence of treatment-emergent hydrocephalus, cerebral edema and intracranial hypertension is displayed below in Reviewer Table 8.

Reviewer Table 8: Hydrocephalus, Cerebral Edema, Intracranial Hypertension

	Gliadel®	Placebo	P-value
Hydrocephalus	5 (5%)	2 (2%)	0.278
Cerebral Edema	4 (4%)	1 (1%)	
Intracranial HTN	4 (4%)	7 (6%)	0.539

8.3 ***Reviewer's Conclusion:*** *Trial #8802 appears to be an adequate and well-controlled study. The treatment effect on survival in all patients with high grade malignant glioma does not reach statistical significance. The largest treatment differences are seen at six months, which does not carry over to overall survival. The biologic meaning of an improvement in six-month survival is unclear since it appears not to be a surrogate for overall survival. It's robustness can be questioned from two standpoints: (1) the discrepant results depending on the type of the analysis ; (2) lack of support from other quality of life parameters, e.g., performance status (see Statistical Review for KPS analyses). However, the robustness improves for the subgroup of patients with glioblastoma multiforme. Here, the survival advantage for patients treated with Gliadel® is seen not only at six-months, but is reflected in overall survival in an unadjusted analysis (Gehan's generalized Wilcoxon test).*

The toxicity profile of Gliadel® is consistent with a regional delivery system at the time of operation. The primary toxicities were related to neurologic function and wound healing/infectious complications. The incidence of perioperative convulsions, wound healing abnormalities, and meningitis was greater in patients treated with Gliadel®. The toxicities could be considered acceptable given the clinical setting; however, the incidence may be underestimated since the control arm was a foreign body.

9. Phase III Trial CL-0190: *Interstitial Chemotherapy for Malignant Glioma: A Phase III Placebo Controlled Study to Examine the Safety and Efficacy of Gliadel®*

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

9.1 Protocol Review

- *Review of Amendments*

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

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

Comment: All patients were enrolled after both amendments.

- *Objectives*

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

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

- *Study Design/Schema*

CL-0190 was a multicenter, randomized, double blind placebo-controlled phase III trial, designed to compare the safety and efficacy of interstitial BCNU chemotherapy in treatment-naive patients with malignant glioma. Patients were enrolled after malignant glioma was pathologically confirmed during surgery. After maximal tumor resection, up to eight wafers, Gliadel® or placebo, were placed against the resection surface.

Eligibility Criteria:

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

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

Exclusion Criteria:

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

- *Procedure, Treatment, and Schedule of Tests*

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

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

Schedule of Tests.

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

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

- *Endpoints and Statistical Analysis*

Definitions of Endpoints:

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

(Survival was not specifically defined.)

Statistical Analysis:

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

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

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

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

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

9.2 Results

9.2.1 Conduct of the Study

- *Early Termination.*

Patient accrual was terminated early by the sponsor, Orion-Farmos, after enrollment of 32 patients due to inadequate drug supply. The applicant, Guilford, references internal memoranda from identifying two reasons. First, after noting three cases of infection, was concerned about the lack of documentation that wafers from lot SR042-49-7 had not been retested at intervals for sterility (subsequent testing by confirmed sterility and the incidences of wound infection/meningitis were attributed to a single center mistakenly placing the unsterile packet in the sterile surgical field). The second reason is that lot SR042-49-10 did not pass a 6-month retest because of a "slightly low BCNU content". There was no other drug supply; the last patient treated on CL-0190 was the last patient treated with Gliadel® on any trial until Guilford assumed manufacture, opening a Treatment IND in the U.S. in November 1995. An interim analysis of CL-0190 was performed in the Spring of 1994 after data was collected on 16 patients (analysis not provided with the NDA). On March 9, 1994, notified the Finnish regulatory authorities that the study was completed December 22, 1993.

- *Randomization.*

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

- *Eligibility.*

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

Reviewer Table 9

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

- *Referee Neuropathologist.*

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

- *Quality Assurance.*

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

9.2.2 Enrollment, Demographics, Baseline Characteristics

- *Study Dates:*

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

- *Study Centers:*

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

Reviewer Table 10

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

- *Baseline Demographics and Clinical Characteristics*

Reviewer Table 11 is a composite of Applicant's Tables 4.2, 4.5, 4.6, 4.8, 4.11, and 4.12. The only statistically significant difference between the treatment arms was tumor type. All patients randomized to placebo carried

the diagnosis of GBM; however, 11/16 (69%) treated with Gliadel® had GBM.

Reviewer Table 11: Baseline Demographics and Clinical Characteristics

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

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

- *Tumor Size*

The mean tumor area was 22.4 (± 8.6) cm^2 in the Gliadel® arm vs. 19.2 (±6.[illegible]) cm^2 in the placebo group. Median tumor areas were 20 cm^2 in both arms. Tumor volume estimates were not provided for this study because data was not available for one patient.

- *Characteristics of Surgery*

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

Applicant's Table 4.15: Gliadel Dosage

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

* Fisher's Exact test

Excerpts from Applicant's Table 4.12 comparing other characteristics of surgery are shown below. There were no statistically significant differences between the arms.

Applicant's Table 4.12: Characteristics of Wafer Implantation Surgery

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

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

- *Treatment After Wafer Implantation Surgery*

Radiation Therapy. All but one patient, who died on study day 35 of a rapidly growing tumor, received post-operative radiation therapy. Applicant's Table 4.14 presents the mean and median doses of radiation delivered.

Applicant's Table 4.14:Radiotherapy Treatment Regimen Summary

	GLIADEL 3.85% (N = 16)	PLACEBO (N = 18)	P-value*
	Number (Percentage) of Patients		
Cumulative Radiotherapy (cGy)			
N	15	16	
Mean (SD)	5849.5 (333.0)	5362.9 (878.1)	0.2454
Median	5575	5403	
Range			

* Fisher's Exact Test

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

- *Concomittant Medicatiions*

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

9.2.3 Efficacy Results

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

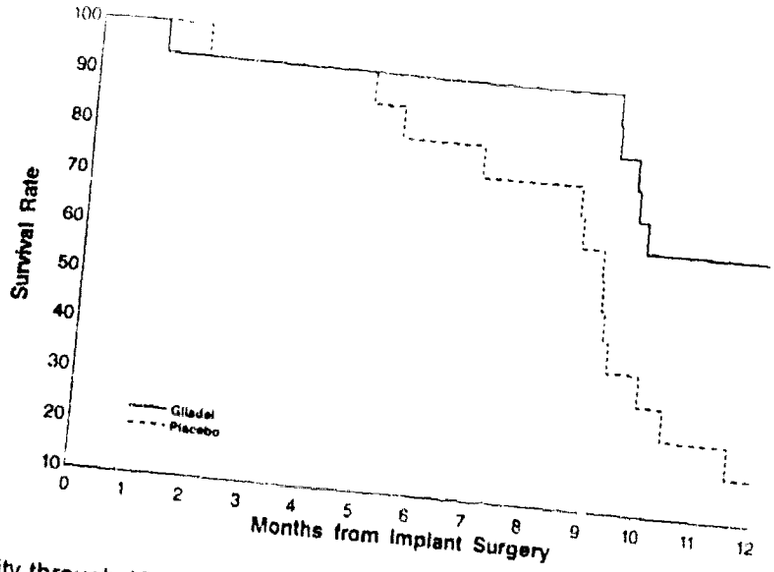
Comment The p-values provided by Guilford for the final reported survival analysis are unadjusted for this first look. However, since the p values are not borderline, this should not have a significant impact on the results.

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

- *Twelve-Month Outcomes*

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

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



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

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

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

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

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

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

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

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

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

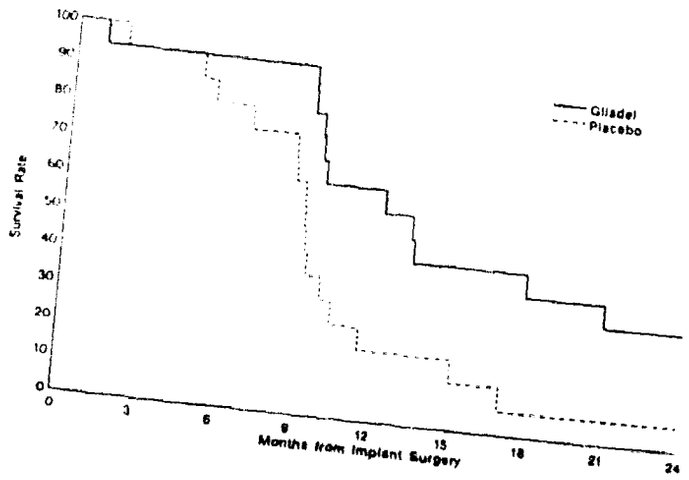
*Wald Chi-Square test

- *Overall Survival*

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

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

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



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

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

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

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

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

* Wald Chi-square test

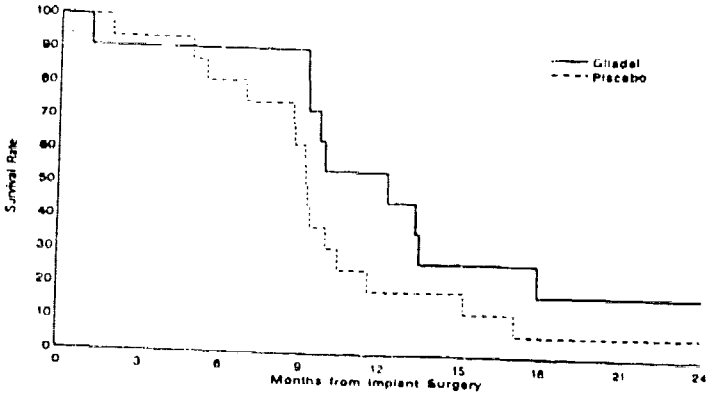
- *Subgroup Analysis: GBM Patients*

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

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

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

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



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

*Gehan's generalized Wilcoxon test

- *Time to Treatment Failure (All Patients)*

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

- *Secondary Efficacy Analyses*

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

- *Drug-Demographic Interactions*

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

four point scale of mild, moderate, severe, life-threatening; (3) judge its relationship to treatment as not assessable, none, remote, possible, or probable (i.e., no "definite" category); (4) provide start and end dates; and (5) describe outcome. Specific A.E.s were not solicited.

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

- *Deaths*

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

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

*Death due to pulmonary embolus

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

- *Treatment Withdrawal Due to Toxicity*

There were no reports of wafer removal in this study.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9.3 *Reviewer Conclusion:* Although many of the criteria for an adequate and well-controlled study are met, e.g., statement of objectives, trial design, randomization, and methods of assessment of the endpoint, the early closure of the trial and limited patient numbers are serious flaws. Since there was no further study drug for almost 2 years, the early closure could in some sense be considered unbiased. Nevertheless, the statistical endpoints of the protocol were not met and conclusions from a 32 patient Phase III trial are critically limited. Of

the 32 patients, 5 had the more favorable histology of anaplastic astrocytoma and all 5 were randomized to the Gliadel® arm. If these patients are excluded from analysis, the statistical significance of the treatment effect is lost (vs. trial #8802 in which statistical significance was gained when excluding patients with anaplastic astrocytoma).

10. Uncontrolled Trials

10.1 #8701: Safety and Efficacy of BCNU Delivered From a Biodegradable, Surgically Implanted Polymer for the Treatment of Grade III or IV Astrocytoma: A Phase I/II Clinical Study.

#8701, the first clinical trial with Gliadel®, was a multicenter open-label, dose-escalation study in 21 patients with recurrent malignant glioma. J Neurosurg 1991; 74:441-446.

10.1.1 Protocol Review

Objective: "To determine the safety and efficacy of BCNU delivered by a surgically implanted polymer" in patients with malignant astrocytoma or gliobastoma multiforme.

Eligibility/Exclusion Criteria: Criteria matched #8602 with the additional specifications: (1) tumor at least 1.5 cm diameter; (2) prior EBRT ≥ 5000 rads; (3) life expectancy > 49 days; (4) limits to hepatic, renal, and hematologic dysfunction.

Procedure: A maximum of 3 patients per center could be entered at a dose level. When all patients had been observed for seven weeks, safety results with regard to mortality, neurologic elamination, KPS and tumor imaging would be reviewed prior to deciding to escalate to the next dose level (*no specific grades of toxicity were identified as unacceptable).*

Baseline and Followup Examinations: Patients were seen weekly the first month, at 7 weeks, 3 months, then q 2 months. Neurologic examination and KPS were obtained at each visit. Tumor imaging was obtained post-operative within 72 hours, at weeks 2, 7 and q 2 months as appropriate.

Amendments: **Amendment #1** dated January 14, 1988 redefined dose levels after the first level to be more consistent with a modified Fibonacci schema:

1. Gliadel 1.925%, 3.85 mg BCNU/wafer; max=30.8 mg BCNU
2. Gliadel 3.85%, 7.7 mg BCNU/wafer; max=61.6 mg BCNU
3. Gliadel 6.35%, 12.7 mg BCNU/wafer; max=101.6 mg BCNU
4. Gliadel 9.625%, 19.23 mg BCNU/wafer; max=153.9 mg BCNU
5. Gliadel 13.47%, 21.87 mg BCNU/wafer; max=215.46 mg BCNU

It was also stipulated that patients would be followed until death. **Amendment #2**, 3/30/88, added exclusions for previous interstitial therapy and treatment with Gliadel®.

10.2.2 Results

Twenty one patients were entered at 5 sites in the U.S from 9.24.87 until 7.7.88. After 8 patients were treated in Group 3, the results were reviewed. "Although the MTD had not been reached, the increases in local BCNU concentration achieved by the Gliadel® wafer, relative to the brain concentration produced by conventional intravenous BCNU therapy, were expected to be very large (~3000 fold). Further increases in local BCNU concentrations from doses planned in Groups 4 and 5 were expected to have no added therapeutic benefit and were canceled."

The number of patients per dose level and clinical characteristics are displayed in Reviewer Table 13, derived from Applicant's Tables 4.2, 4.3, 4.8, 4.11 and 4.14.

Reviewer Table 13

	Group 1 Gliadel 1.92% 3.85 mg BCNU/wafer n=5	Group 2 Gliadel 3.85% 7.7 mg BCNU/wafer n=5	Group 3 Gliadel 6.35% 12.7 mg BCNU/wafer n=11
GBM[1]	0-40%	40-60%	91%
median age (years)	34	50	49
Baseline KPS ≤70	20%	20%	36%
median time from first brain tumor surgery to study surgery	12.5 months	13.3 months	8.1 months
mean number of wafers implanted	7.7	7.9	7.5

[1] Variability reflects different pathological diagnoses depending on source

- *Deaths*. Tumor progression was considered the cause of death in 20 of 21 patients, one patient died from a pulmonary embolus. Cerebrovascular accident was a secondary cause of death in a patient who died due to tumor progression. Survival differences were felt secondary to tumor type and patient characteristics. See Reviewer Table 14.

- *Reoperation*. Gliadel® wafer remnants were noted on Day 49 CT or MRI in 11 patients. Two patients experienced intracranial mass effect uncontrolled with steroids that led to reoperation both at 91 days after study surgery. Operative findings included tumor, necrosis and wafer remnants which were intact in one patient and removed. For details of the patients who underwent a surgical procedure after study surgery, see Applicant's Table 1 in Appendix III. Wafer remnants with an appearance similar to that at the time of implantation were recovered from the tumor resection cavity in three additional patients at autopsy at 40 days, 52 days, and 137 days after wafer implantation (see Applicant's Table 3 in Appendix I).

- *Adverse Events*. The treatment-emergent adverse events reported in 2 or more patients were: headache, abnormal healing, convulsions, fever, hyperglycemia, intracranial hypertension, drug level decreased, drug level increased, infection, neck pain, pain, hypertension, nausea, hypokalemia, brain edema, dizziness, and UTI. 20/113 events (18%) were considered to be possibly related to study drug. See Reviewer Table 14.

Reviewer .ble 14

	Group 1 Gliadel 1.925% 3.85 mg BCNU/wafer n=5	Group 2 Gliadel 3.85% 7.7 mg BCNU/wafer n=5	Group 3 Gliadel 6.35% 12.7 mg BCNU/wafer n=11
Median survival	65 weeks	47 weeks	23 weeks
6-month mortality 12-month mortality 18-month mortality	1 (20%) 2 (40%) 3 (60%)	0 3 (60%) 4 (80%)	6 (55%) 8 (73%) 11 (100%)
Neurological Assessment[1] Baseline (mean) Visit 6 (mean)	 3.5 (± 2.8) 3.2 (± 3.8)	 3.5 (± 1.5) 2.4 (± 2.3)	 5.1 (± 4.1) 6.2 (± 5.7)
KPS Baseline (mean) Visit 6 (mean)	82 (±13) "at least equivalent to baseline"	86 (±9) "at least equivalent to baseline"	82 (±13) "mean decline of almost 10 points"[2]
Serious and Unexpected adverse events	0	1 (20%)[3]	1 (9%)[3]
# Possibly related A[illegible] treatment-emerge[illegible]	10% (4/41)	23% (3/13)	22% (13/59)

[1] Scale: 0-33; 33 was maximally abnormal.
[2] The magnitude of this decline can largely be attributed to the deterioration of one patient whose score decreased from 70 (baseline) to 10 (visit 6).
[3] Reoperation for intracranial mass effect, see below

10.1.3 Conclusion

The sponsor concluded that no dose-limiting toxicity was observed upon implantation of up to 8 wafers containing 1.925%, 3.85%, or 6.35% BCNU. Wafers with BCNU 3.85% were chosen as the dose for study #8802.

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

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

10.2.1 Protocol Review

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

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

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

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

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

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

10.2.2 Results

Twenty two patients were enrolled at three institutions (JHOC 10, Columbia Presbyterian Medical Center 6, Charlotte Memorial Hospital 6) from July 5, 1990 to August 14, 1991. Seven patients were female (32%) and 15 male (68%) with a median age of 60 (range 40-86). Referee and institutional pathologists agreed that 20 patients had a glioblastoma multiforme and one had anaplastic astrocytoma (the diagnosis of one patient is missing). The median KPS was 85 (range 40-100).Eighteen patients had 8 wafers implanted; four had 7. Three patients (14%) had total resections, 5 patients (23%) had total resection by lobectomy, and 14 patients (64%) had subtotal resections. Twenty-one of the 22 patients received XRT (median dose 5816 cGy, range 4500-8280); followup on the remaining patient is unclear.

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

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

Reviewer Table 15

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

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

- *Reoperation.* Nine of 19 patients underwent reoperation. All patients had completed a course of ESRT. For details, see Applicant's Table 3 in Appendix 3.

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

10.2.3 Conclusion

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

10.3 #9115: The Safety and Tolerability of the Use of Gliadel® for the Treatment of Recurrent, Malignant Glioma

This study was opened to allow continued evaluation of Gliadel® after completion of accrual to #8802.

10.3.1 Protocol Review

Objective: "The purpose of this protocol is to provide a framework for the collection and analysis of safety data related to patients who have already received brain tumor surgery for a malignant glioma, maximum radiation therapy, have experienced tumor regrowth, and who are candidates for surgical removal of recurrent tumor and implantation of Gliadel®..."

Eligibility/Exclusion Criteria: Criteria match #8802.

Baseline and Followup Examinations: Baseline assessment matched #8802. Followup examinations were less frequent than in #8802: 4-6 weeks post surgery, and then every 6 months measured from the time of surgery. Assessments were limited to include a neurologic examination and KPS.

Procedure: Up to eight wafers of Gliadel® were to be placed in the resection cavity. Sample slides were to be sent to the sponsor who would forward them to the referee pathologist.

Concomitant Medications: Data would not be collected.

Statistical Section: "Safety evaluations would be based on neurological examinations, KPS, laboratory data and adverse medical events."

10.3.2 Results

Forty patients were enrolled in 11 centers (10 in the U.S. and 1 in Canada) from January 30, 1992 and March 16, 1993. There were 24 male patients (60%) and 16 female (40%) with a median age of 48 (range to 68). Thirty-one patients carried the diagnosis of GBM, 6 of astrocytoma, and 3 of glioma, gliosarcoma and delayed radiation necrosis. Thirty-two patients had 8 wafers implanted; the remainder had from 5-7 wafers.

- *Deaths.* Thirty of the 31 patients who died during the course of the study had cause of death of tumor recurrence or progression. Cerebral edema or increased intracranial pressure were listed as secondary causes of death in 3 patients. For one patient, the cause of death was not entered.

- *Adverse Events.* 122 treatment emergent A.E.s were reported in 36 of 40 patients (90%). The most frequent A.E.s were related to the nervous system, fever, or abnormal healing. See Reviewer Table 16 compiled from the data listings, on the following page

10.3.3 Conclusion.

No new toxicities were seen in this trial

Reviewer Table 16

Body System	# Patients with A.E.	# Patients with Severe A.E.	Treatment-Related Probable Possible		Unrelated
Nervous					
CVA	1	0	0	1	0
Seizures	6	1	0	0	6
Increased intracranial pressure	4	0	0	2	2
Cerebral edema	4	2	0	0	4
Hydrocephalus	3	3	0	0	3
Air collection in tumor bed cavity	1	0	0	0	1
CSF/shunt infection	3	2	0	1	2
Hemiparesis/hemiplegia	8	2	0	2	6
Aphasia/dysphasia	6	0	0	1	5
Ataxia	1	0	0	0	1
Dizziness	1	1	0	1	0
Change in consciousness/confusion	8	5	0	2	6
Neurological decline	1	1	0	1	0
CN palsy	1	0	0	0	1
Headache	4	2	0	1	3
Visual changes	4	2	0	1	3
Infection					
Pneumonia	2	2	0	0	2
UTI	2	0	0	0	2
Cardiovascular					
DVT/PE/"clot"	7	6	0	0	7
CHF	1	1	0	0	1
Orthostasis	1	0	0	0	1
Nutritional/Metabolic					
Wound Healing Abnormality	7	3	0	2	5
Hyperglycemia	1	0	0	0	1
Hyponatremia	1	0	0	0	1
Digestive					
GI hemorrhage	1	1	0	0	1
Nausea/ Vomiting	4	0	0	2	2
Other					
Anticonvulsant toxicity	3	0	0	0	3
Subgaleal abcess	3	0	0	0	3
Wound infection	2	1	0	1	1
Fever	6	0	0	0	6
Drug reaction	1	1	0	0	0
Decrease ability to perform ADLs	1	1	0	0	0
Superficial Cellulitis	1	0	0	0	0

10.4 Treatment IND: Open-Label, Multi-Center, Clinical Trial of Gliadel® for Patients with Recurrent Malignant Glioma

The Treatment IND opened in II/95 and continues to accrue patients. See Appendix V (Four Month Safety Update) for any additional toxicities. This IND is the only protocol to use the Guilford-manufactured product.

10.4.1 Protocol Review

The objective of the study was to collect 6 months of safety data . Eligibility criteria matched #8802 with the exception that prior Gliadel® therapy was allowed after an eight week interval from the first implantation. After discharge from the hospital, patients were evaluated at 3 and 6 months for notation of adverse events and assessment of survival, again at one year for survival assessment only, and notification of death. (Neurologic assessment, tumor imaging and laboratory evaluations are not a formal component of the Treatment IND) Accrual was not limited and there was no hypothesis testing. Adverse event incidence rates would be estimated with 95% confidence intervals; all data with descrete variables would be summarized by frequency tables.

10.4.2 Results

Fifty patients were enrolled at 22 sites by the cutoff date of April 18, 1996 (study is still open to accrual). Of the

47 patients with gender available in the data listings, 28 were male and 19 female with a median age of 47.5 (range 23 - 70) in the 46 patients with information on age in the data listings. KPS data was collected "yes/no" answer to the eligibility criterion of ≥ 60; all patients met this criterion. The median number of wafers implanted was 8 (range 1-8).

- *Deaths.* Seven deaths have been reported to Guilford; information is available on 5. No death was considered to be related to Gliadel®. The following were listed as cause of death: aspiration pneumonia, pulmonary embolus, cardiopulmonary arrest, and progressive tumor in two patients.

- *Adverse Events.* See Appendix III for Applicant's Tables 6 7, and 8 for tabulation of all A.E.s, frequent A.E.s, and severe A.E.s that occurred on this study and compared to the other submitted studies. The product manufactured by Guilford appears to have a similar safety profile.

10.4.3 Conclusion. Of the 22 sites entering patients, only 3 had previously participated in #8802. Despite a broadening base of physicians and use of the "to be marketed product," the safety profile appears to be consistent.

11.0 Non-U.S. Postmarketing Experience (Gliadel® is not marketed in any country)

12.0 Summary

Kaplan-Meier curves and analyses of the survival data from the two controlled trials are summarized on the following page.

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

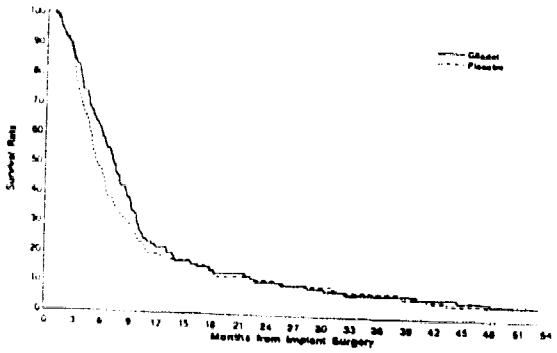
Study CL-0190, which had not been discussed with the FDA prior to NDA submission, meets many of the criteria for an adequate and well-controlled study; however, the early closure of the trial and limited patient numbers are serious flaws. Even accepting the early closure as unbiased, i.e., no further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

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

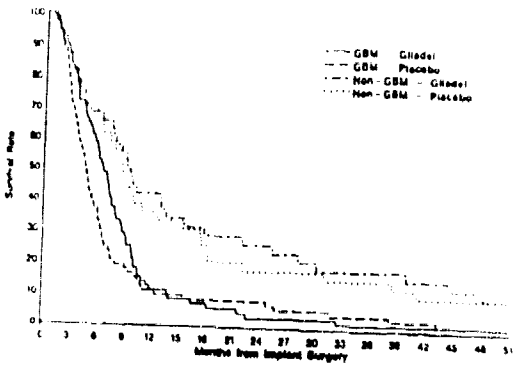
The toxicity profile of Gliadel® in relapsed patients is consistent with a regional delivery system at the time of operation. The primary toxicities in relapsed patients were related to neurologic function and wound healing/infection. The toxicities could be considered acceptable given the clinical setting; however, it should be noted that the incidence may be underestimated since the control arm was a foreign body. The biodegradability of the wafers appears to be variable, the clinical significance of which is not yet known.

STUDY 8802

Overall K-M Survival Curves for All Patients by Treatment Group (n = 222)



Overall K-M Survival Curve, by Treatment Group & Tumor Type
GBM n = 145; Non-GBM n = 77



All Patients

6 Month Survival			Overall (up to 21 months)		
Unadjusted		Adjusted	Unadjusted		Adjusted
logrank	GW*	Cox	logrank	GW*	Cox
p=.063	p=.077	p=.009	p=.297	p=.106	p=.0301

*Gehan's generalized Wilcoxon test.

GBM Patients

6 Month Survival			Overall (up to 21 months)		
Unadjusted		Adjusted	Unadjusted		Adjusted
logrank	GW*	Cox	logrank	GW*	Cox
p=.013	p=.015	p=.0073	p=.181	p=.021	p=.051

*Gehan's generalized Wilcoxon test.

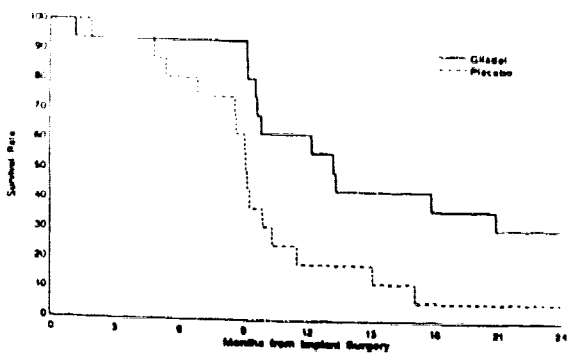
Non-GBM Patients

6 Month Survival			Overall (up to 21 months)		
Unadjusted		Adjusted	Unadjusted		Adjusted
logrank	GW*	Cox	logrank	GW*	Cox
p=.849	p=.775	p=.649	p=.754	p=.864	p=.613

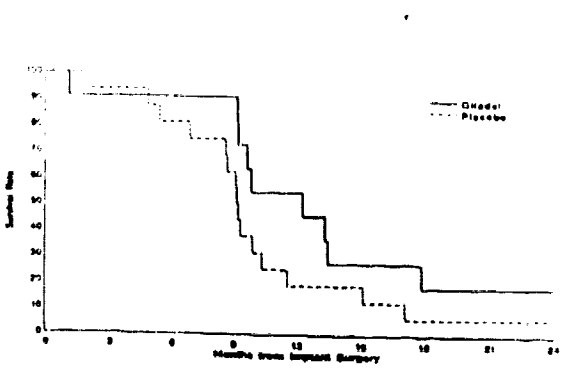
*Gehan's generalized Wilcoxon test

STUDY CL-0190

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



Overall K-M Curves for GBM Patients by Treatment Group (n = 27)



6 Month Survival			Overall (up to 21 months)		
Unadjusted		Adjusted	Unadjusted		Adjusted
logrank	GW**	Cox	logrank	GW*	Cox
p=.0087	p=.0105	p=.0010	p=.012	p=.011	p=.0005

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

6 Month Survival			Overall (up to 21 months)		
Unadjusted		Adjusted	Unadjusted		Adjusted
logrank	GW*	Cox	logrank	GW*	Cox
p=.059	p=.070	p=.0072	p=.126	p=.093	p=.0035

*Gehan's generalized Wilcoxon test

13. Oncology Drugs Advisory Committee Summary

Dr. Paul Bunn chaired the ODAC meeting held June 14, 1996 The following is a summary of the votes and pertinent comments to the questions posed by the FDA.

Questions re. Study #8802:

1. **Is Study #8802 an adequate and well-controlled study?** 8/8 Yes.

2. **Do the survival data provide convincing evidence of efficacy of Gliadel® wafers?** Much discussion ensued (see transcript for details). Dr. Buckner highlighted the imbalances between the arms. It was countered that the standard for trials in recurrent disease at the time this trial was conducted was not to prospectively stratify. Dr. Gelber added that survival analyses adjusting for these covariates augments the treatment effect rather than eliminating it. Dr. Bunn was influenced by the consistency of all BCNU data, i.e., that BCNU-impregnanted wafers exerted an effect not unlike systemic BCNU, lending credence to a treatment effect. The final vote was 4/8 Yes; 4/8 No.

3. **Is the toxicity profile of Gliadel® acceptable for patients with recurrent malignant gliomas?** Dr. Buckner emphasized that only short-term toxicity data is available and that leukoencephalopathy has been seen with intra-arterial BCNU. 7/8 Yes; 1/8 abstention.

4. **Is Gliadel® approvable in conjunction with surgical resection for treatment of recurrent malignant gliomas?** The committee commented that the labeling should be clear that Gliadel® is an adjunct for patients in whom surgical resection is indicated, i.e., a surgical procedure is not recommended for the sole purpose of implanting Gliadel®. 6/8 Yes; 2/8 No.

5. **If so, should approval be limited to glioblastoma multiforme or be for all types of malignant gliomas?** 7/8 Yes; 1/8 abstention.

Questions re. Study #CL-0190:

I. **Is CL-0190 an adequate and well-controlled study?** The question was amended to be answered in two parts: (a) to provide supportive data for #8802, and (b) to provide efficacy data for Gliadel® in newly diagnosed patients. (a) 6/8 Yes; 2/8 No. (b) 8/8 No. Other comments accompanying this unanamous vote were that the results were not robust enough to qualify for early stopping of a trial; that non-GBM patients were randomized only to the Gliadel® arm; and that the survival curves for patients with GBM lost their significance when the non-GBM patients were removed and a subgroup analysis was performed.

14.0 Recommended Regulatory Action

Approval for Gliadel® as an adjunct to surgery, for patients with recurrent glioblastoma multiforme for whom surgical resection is already indicated.

Alison Martin, M.D. 8-12-96
Primary Reviewer

John Johnson, M.D. 8-16-96
Team Leader

Robert Delap, M.D.
Division Director, DODP

cc: Original NDA
Div file
HFD-150 / Amartin / JRJohnson / PZimmerman / RDelap

TABLE 3: SUMMARY OF BRAIN AUTOPSY DATA

Patient Number	Treatment Group BCNU Concentration	Death Days Post Implant Surgery	Brain Autopsy Results Wafer-Related
	1.925%	646	No wafers noted
	6.35%	40	Eight wafers present and intact measuring 13 mm
	6.35%	137	Five 1.5 x 0.2 cm disks
	6.35%	52	Numerous chemotherapy wafers
	placebo	51	Sector of wafer adherent to tumor bed
	placebo	556	No wafers mentioned
	3.85%	54	Seven wafers are stacked within this region
	3.85%	232	Markedly compressed, thin flat structures consistent with wafers
	3.85%	77	No wafers mentioned
	3.85%	422	No wafers mentioned
	placebo	168	No wafers mentioned
	3.85%	105	No wafers mentioned
	placebo	78	No wafers mentioned
	placebo	236	No wafers mentioned
	3.85%	316	No wafers mentioned

REVIEWER TABLE

WAFER BIODEGRADABILITY IN HUMANS

I. Reoperation

STUDY	# Pts with NS Procedure	# Pts with Comment on Wafer	# Pts with Wafers or Wafer Remnants	NS Study Day
#8701	13	4	3	91-162
#9003	9	4	4	3-204
#9115	12	3	3	2-70
#9501	8	6	6	9-137
#8802	60	13	12	4-127
#CL-0190	3	0	N/A	N/A

II. Brain Autopsy

STUDY	# Pts with Autopsy	Wafers Mentioned	Present or Absent	Autopsy Study Day in Pts with P
#8701	4	4	3 P; 1 A	40-137
#8802	11	3	3 P	54-232

NOVA Pharmaceutical Corporation

NPC 8802

Pt.#: 8802-_____-_____

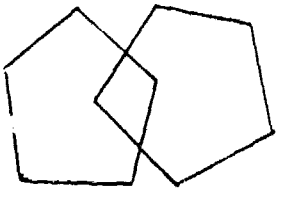
Pt. ID:_____

DATE:___-____-___ (dd MON yy)

Visit # 0 1 [illegible]
2 3 [illegible]
5 6

MINI MENTAL STATE EXAM

Max Score	Score		
			ORIENTATION
5	( )	What is the (year) (season) (date) (day) (month)?	
5	( )	Where are we: (state) (county) (town) (hospital) (floor)?	
			REGISTRATION
3	( )	Name 3 objects: 1 second to say each. Then ask patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until patient learns all 3. Count trials and record.	
			ATTENTION AND CALCULATION
5	( )	Serial 7's. 1 point for each correct. Stop after 5 answers. Alternatively spell "world" backwards.	
			RECALL
3	( )	Ask for 3 objects repeated above. Give 1 point for for each correct.	
			LANGUAGE
9	( )	Name a pencil and a watch. (2 points)	
		Repeat the following "no ifs, ands or buts". (1 point)	
		Follow a 3-stage command. "Take a piece of paper in your right hand, fold it in half and put it on the floor." (3 points)	
		Read and obey the following: "Close your eyes". (1 point)	
		Write a sentence. (1 point)	
		Copy design. (1 point)	



[ ] **TOTAL SCORE**

Assess level of consciousness along a continuum.

_____

Alert Drowsy Stupor Coma

MM

INVESTIGATOR'S SIGNATURE:_____

TABLE 4.10 presents the mean Baseline neurological examination scores for each treatment group by individual item and the number and percentage of patients with an abnormality in any of the 11 items evaluated.

TABLE 4.10: Baseline Neurological Examination (Study 8802)

	GLIADEL 3.85%				PLACEBO				
Neurological Examination	N	Mean[a]	S.D.	[N = 110] N (%)	N	Mean[a]	S.D.	[N= 112] N (%)	P-Value[b]
Vital Signs Instability	110	0.04	0.19	4 (4)	112	0.01	0.09	1 (1)	0.170
Level of Consciousness	110	0.14	0.39	13 (12)	112	0.13	0.36	13 (12)	0.822
Personality Change	109	0.47	0.65	42 (38)	111	0.55	0.75	45 (40)	0.387
Speech Disorder	110	0.77	0.99	50 (46)	111	0.86	1.02	55 (49)	0.497
Visual Change	107	0.49	0.88	28 (25)	111	0.80	1.03	49 (44)	0.016
Fundus (Papilledema)	98	0.22	0.53	17 (16)	103	0.28	0.66	19 (17)	0.502
Cranial Nerves III, IV, VI	110	0.11	0.39	10 (9)	112	0.07	0.26	8 (7)	0.398
Cranial Nerves, Other	110	0.25	0.55	22 (20)	112	0.47	0.72	38 (34)	0.012
Motor Involvement	110	0.87	0.97	60 (55)	112	1.12	0.97	76 (68)	0.063
Sensory Changes	108	0.31	0.64	25 (23)	111	0.46	0.72	37 (33)	0.118
Cerebellar Signs	107	0.19	0.48	16 (15)	107	0.20	0.50	17 (15)	0.889
TOTAL SCORE	**110**	**3.95**	**3.03**		**112**	**5.01**	**3.20**		**0.012**

[a] If the number of missing values from the 11 items was <6, the total score was estimated by multiplying the mean of the remaining items by 11

[b] P-Value from a two sample t-test for comparing means between two treatment groups

N (%) = Number (Percentage) of Patients with any abnormality for each item

Cross-Reference ATTACHMENT 1 - TABLES 8A and 8B, APPENDIX 1 - Data Listing 11

TABLE 4.106: Post-Baseline Chemotherapy Total Dose Summary (Study 8802)

Chemotherapy	GLIADEL 3.85% [N = 110]					PLACEBO [N = 112]					P-Value	
	N[a]	N[b]	Mean	S.D.	Median	N[a]	N[b]	Mean	S.D.	Median	Mean[c]	Median[d]
"Cancell" (Alternative Cancer Therapy)	1	--	--	--	--	0	--	--	--	--	--	--
Carboplatin	1	1	2192.00	--	2192.00	0	--	--	--	--	--	--
Carmustine	5	4	756.75	377.48	685.00	4	4	570.00	199.00	550.00	0.415	0.309
Cisplatin	5	5	238.00	199.74	142.00	3	3	332.00	86.56	390.00	0.479	0.233
Etoposide	2	2	426.00	246.07	426.00	1	1	800.00	--	800.00	0.432	0.540
Lomustine	7	7	429.29	186.47	420.00	6	6	625.00	591.46	360.00	0.422	0.830
Procarbazine	7	5	7048.00	4390.39	5600.00	5	5	5460.00	3846.82	4200.00	0.560	0.528
Tamoxifen	5	2	2360.00	735.39	2360.00	1	1	320.00	--	320.00	0.265	0.530
Thiotepa	3	3	46.67	46.19	20.00	1	1	60.00	--	60.00	0.826	1.000
Vincristine	9	9	10.26	8.40	8.00	10	10	10.87	6.66	10.00	0.861	0.742
Any Chemotherapeutic Agent	29					21					0.200[e]	

[a] Number of patients in each treatment group who received this particular chemotherapy

[b] Number of patients included in the calculation of mean values. Patients omitted are those for which either no dosing information is available or no end dates are available for the omitted treatment episodes. No patient had both an omitted episode of chemotherapy and an included episode of chemotherapy for the same drug

[c] P-Value from a GLM model

[d] P-Value from a Wilcoxon Rank Sum Test

[e] P-Value from a two-sided Fisher's Exact Test

Dash (--) indicates that there was no data available

Cross-Reference: ATTACHMENT 1 - TABLE 33A, APPENDIX 10 - Data Listing 27

TABLE 4.107: Time to Onset of Chemotherapy and Duration of Treatment (Study 8802)

Chemotherapy	GLIADEL 3.85% [N = 110]				PLACEBO [N = 112]				P-Value	
	N[a]	Mean	S.D.	Median	N[a]	Mean	S.D.	Median	Mean[b]	Median[c]
"Cancell" (Alternative Cancer Therapy)										
Days to First Episode	1	58.00	--	58.00	0	--	--	--	--	--
Days to All Episodes	1	58.00	--	58.00	0	--	--	--	--	--
Duration of All Episodes[c]	1	261.00	--	261.00	0	--	--	--	--	--
Carboplastin										
Days to First Episode	1	128.00	--	128.00	0	--	--	--	--	--
Days to All Episodes	1	144.50	--	144.50	0	--	--	--	--	--
Duration of All Episodes[d]	1	4.00	--	4.00	0	--	--	--	--	--
Duration of All Episodes[c]	1	4.00	--	4.00	0	--	--	--	--	--
Carmustine										
Days to First Episode	5	94.60	57.47	91.00	4	130.50	13.38	131.50	0.266	0.323
Days to All Episodes	5	132.77	42.66	149.00	4	140.75	17.33	139.50	0.735	0.903
Duration of All Episodes[d]	5	1.60	1.34	1.00	4	1.75	0.96	1.50	0.857	0.662
Duration of All Episodes[c]	5	1.60	1.34	1.00	4	1.75	0.96	1.50	0.857	0.662
Cisplatin										
Days to First Episode	5	88.40	56.53	88.00	3	57.00	42.04	59.00	0.404	0.554
Days to All Episodes	5	97.53	48.69	118.67	3	94.92	18.55	89.75	0.933	0.766
Duration of All Episodes[d]	5	1.40	0.89	1.00	3	1.00	0.00	1.00	0.482	0.606
Duration of All Episodes[c]	5	1.40	0.89	1.00	3	1.00	0.00	1.00	0.482	0.606

(Continued on next page.)

TABLE 4.107: Time to Onset of Chemotherapy and Duration of Treatment (Study 8802)

Chemotherapy	GLIADEL 3.85% [N = 110]				PLACEBO [N = 112]				P-Value	
	N[a]	Mean	S.D.	Median	N[a]	Mean	S.D.	Median	Mean[b]	Median[c]
(Continued from previous page.)										
Etoposide										
Days to First Episode	2	103.50	48.79	103.50	1	98.00	--	98.00	0.942	1.000
Days to All Episodes	2	103.50	48.79	103.50	1	115.50	--	115.50	0.874	1.000
Duration of All Episodes[d]	2	2.50	0.71	2.50	1	2.00	--	2.00	0.667	1.000
Duration of All Episodes[e]	2	2.50	0.71	2.50	1	2.00	--	2.00	0.667	1.000
Lomustine										
Days to First Episode	7	74.14	50.00	47.00	6	55.50	34.59	42.50	0.459	0.617
Days to All Episodes	7	113.65	46.43	122.50	6	80.00	41.43	93.00	0.199	0.134
Duration of All Episodes[d]	7	1.00	0.00	1.00	6	48.17	115.53	1.00	0.300	0.355
Duration of All Episodes[e]	7	1.00	0.00	1.00	6	48.17	115.53	1.00	0.300	0.355
Procarbazine										
Days to First Episode	7	111.00	42.50	108.00	5	94.20	42.90	91.00	0.517	0.417
Days to All Episodes	7	129.87	25.34	130.00	5	119.00	34.29	122.00	0.540	0.626
Duration of All Episodes[d]	5	14.08	1.60	14.67	5	17.00	6.16	14.00	0.336	1.000
Duration of All Episodes[e]	7	305.77	707.02	15.00	5	17.60	6.16	14.00	0.389	0.410
Tamoxifen										
Days to First Episode	5	158.20	63.34	176.00	1	64.00	--	64.00	0.246	0.242
Days to All Episodes	5	158.20	63.34	176.00	1	64.00	--	64.00	0.246	0.242
Duration of All Episodes[d]	2	41.00	7.07	41.00	1	4.00	--	4.00	0.146	0.540
Duration of All Episodes[e]	5	70.00	40.88	46.00	1	4.00	--	4.00	0.215	0.242

(Continued on next page.)

TABLE 4.107: Time to Onset of Chemotherapy and Duration of Treatment (Study 8802)

Chemotherapy	GLIADEL 3.85% (N = 110)				PLACEBO (N = 112)				P-Value	
	N[a]	Mean	S.D.	Median	N[a]	Mean	S.D.	Median	Mean[b]	Median[c]
(Continued from previous page.)										
Thiotepa										
Days to First Episode	3	112.00	36.72	128.00	1	98.00	--	98.00	0.773	1.000
Days to All Episodes	3	120.17	44.05	138.00	1	115.50	--	115.50	0.935	1.000
Duration of All Episodes[d]	3	1.00	0.00	1.00	1	1.00	--	1.00	--	1.000
Duration of All Episodes[e]	3	1.00	0.00	1.00	1	1.00	--	1.00	--	1.000
Vincristine										
Days to First Episode	9	65.44	53.41	35.00	10	44.20	35.89	29.00	0.319	0.307
Days to All Episodes	9	91.03	53.69	75.67	10	66.70	43.82	60.12	0.292	0.253
Duration of All Episodes[d]	9	4.28	7.70	1.00	10	8.66	13.33	1.00	0.400	0.400
Duration of All Episodes[e]	9	4.28	7.70	1.00		8.66	13.33	1.00	0.400	0.400

[a] Number of patients in each treatment group taking each chemotherapy.
[b] P-Value from a GLM model.
[c] P-Value from a Wilcoxon Rank Sum Test.
[d] Duration in days. Method 1: If end date is missing, then the episode is deleted from analysis.
[e] Duration in days. Method 2: If end date is missing, then use the earliest of the following dates: 11/10/95 or date of death.
Dash (--) indicates that there was no data available

Cross Reference: ATTACHMENT I - TABLE 33B; APPENDIX 10 - Data Listing 27

TABLE 4.108 Frequency Distribution of Time to Onset of Chemotherapy and Duration of Treatment (Study 8802)

Chemotherapy	Duration (Days)	Surgery Date to Start of First Episode		Surgery Date to Start of All Episodes		Duration of All Episodes[a]		Duration of All Episodes[b]	
		GLIADEL [N = 110]	PLACEBO [N = 112]	GLIADEL [N = 110]	PLACEBO [N = 112]	GLIADEL [N = 110]	PLACEBO [N = 112]	GLIADEL [N = 110]	PLACEBO [N = 112]
"CANCELL" (Alternative Cancer Therapy)	51-60	1	0	1	0	0	0	0	0
	>90	0	0	0	0	0	0	1	0
Carboplatin	2-5	0	0	0	0	2	0	2	0
	>90	1	0	2	0	0	0	0	0
Carmustine	1	0	0	0	0	10	3	10	3
	2-5	0	0	0	0	3	3	3	3
	6-10	1	0	1	0	0	0	0	0
	61-70	0	0	1	0	0	0	0	0
	81-90	1	0	1	0	0	0	0	0
	>90	3	4	10	6	0	0	0	0
Cisplatin	1	0	0	0	0	5	8	5	8
	2-5	0	0	0	0	3	0	3	0
	11-20	0	1	0	1	0	0	0	0
	31-40	2	0	2	0	0	0	6	0
	51-60	0	1	0	1	0	0	0	0
	61-70	0	0	1	1	0	0	0	0
	81-90	1	0	1	0	0	0	0	0
	>90	2	1	4	5	0	0	0	0
Etoposide	2-5	0	0	0	0	2	2	2	2
	61-70	1	0	1	0	0	0	0	0
	>90	1	1	1	2	0	0	0	0

(Continued on next page.)

TABLE 4.108: Frequency Distribution of Time to Onset of Chemotherapy and Duration of Treatment (Study 8802)

Chemotherapy	Duration (Days)	Surgery Date to Start of First Episode		Surgery Date to Start of All Episodes		Duration of All Episodes[a]		Duration of All Episodes[b]	
		GLIADEL [N = 110]	PLACEBO [N = 112]	GLIADEL [N = 110]	PLACEBO [N = 112]	GLIADEL [N = 110]	PLACEBO [N = 112]	GLIADEL [N = 110]	PLACEBO [N = 112]
(Continued from previous page.)									
Lomustine	1	0	0	0	0	18	11	18	11
	21-30	2	1	2	1	0	0	0	0
	31-40	0	2	0	2	0	0	0	0
	41-50	2	1	2	1	0	0	0	0
	71-80	0	1	1	1	0	0	0	0
	81-90	0	0	1	0	0	0	0	0
	>90	3	1	12	7	0	1	0	1
Procarbazine	2-5	0	0	0	0	1	0	1	0
	11-20	0	0	0	0	13	8	13	8
	21-30	0	0	0	0	0	2	0	2
	41-50	0	1	0	1	0	0	0	0
	51-60	1	1	1	1	0	0	0	0
	61-70	1	0	1	0	0	0	0	0
	>90	5	3	14	8	0	0	2	0
Tamoxifen	2-5	0	0	0	0	0	1	0	1
	31-40	0	0	0	0	1	0	1	0
	41-50	0	0	0	0	1	0	2	0
	61-70	1	1	1	1	0	0	0	0
	>90	4	0	4	0	0	0	2	0

(Continued on next page.)

TABLE 4.108: Frequency Distribution of Time to Onset of Chemotherapy and Duration of Treatment (Study 8802)

Chemotherapy	Duration (Days)	Surgery Date to Start of First Episode		Surgery Date to Start of All Episodes		Duration of All Episodes[a]		Duration of All Episodes[b]	
		GLIADEL [N = 110]	PLACEBO [N = 112]	GLIADEL [N = 110]	PLACEBO [N = 112]	GLIADEL [N = 110]	PLACEBO [N = 112]	GLIADEL [N = 110]	PLACEBO [N = 112]
(Continued from previous page.)									
Thiotepa	1	0	0	0	0	4	2	4	2
	61-70	1	0	1	0	0	0	0	0
	>90	2	1	3	2	0	0	0	0
Vincristine	1	0	0	0	0	32	35	32	35
	2-5	0	0	0	0	0	1	0	1
	11-20	1	2	1	2	1	1	1	1
	21-30	2	4	3	6	1	1	1	1
	31-40	2	1	5	4	0	1	0	1
	41-50	0	0	2	1	1	0	1	0
	51-60	1	1	2	5	0	1	0	1
	61-70	0	0	2	2	0	0	0	0
	71-80	0	0	2	1	0	0	0	0
	81-90	0	0	2	2	0	0	0	0
	>90	3	2	16	14	0	0	0	0

[a] Method 1: If end date is missing, then the episode is deleted from analysis.
[b] Method 2: If end date is missing, then use the earliest of the following dates: 11/10/95 or date of death.
Dash (--) indicates that there was no data available

Cross Reference: ATTACHMENT 1 - TABLE 33C; APPENDIX 10 - Data Listing 27

Table 2: Patients with Reoperati after Study Surgery in Study 8802

Patient ID	Trt. C or P	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants P(resent) A(bsent) U(nknown)	Duration of Survival after Study Surgery (weeks)
	P	120	lethargy, headache, left hemiparesis	bone flap re-elevated, craniotomy for tumor removal	unknown	U	42.6
	P	13	lethargy, hematemesis	wound tapped	unknown	U	9.6
	G	22	staph wound infection	bone flap removed	unknown	U	37.0
		106	recurrent GBM	craniotomy	unknown	U	
	P	252	increased tumor size on MRI	tumor debulking	unknown	U	137.9
		883	memory problems and personality changes with increased tumor size on MRI	unknown	GBM	U	
	P	55	bone flap infection	bone flap removed	unknown	U	31.4
	G	11	wound infection, seizure and increased left hemiparesis	bone flap and wafer remnants removed	unknown	P	31.9
	G	218	unknown	biopsy and resection	GBM	U	71.4
		231	headaches, nausea, vomiting, fever, with left frontal collection	collection tapped	unknown: wound cultures negative	U	
	G	561	increased frequency of seizures and increased tumor enhancement on CT scan	debulking	necrosis	U	141.0
	G	175	increase in tumor size on CT and MRI	tumor debulking	necrosis with atypical gliosis	U	123.1

Table 2: Patients with Reoper s after Study Surgery in Study 8802

Patient ID	Trt. G or P	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants P(resent) A(bsent) U(nknown)	Duration of Survival after Study Surgery (weeks)
		849	increased gait difficulty and speech deterioration	tumor debulking	malignant glioma with necrosis	U	
	P	240	neurological deterioration	tumor debulking	GBM	U	79.4
	P	108	neurological deterioration with increased tumor size on MRI	bone flap elevation, tumor debulking and temporal lobectomy	anaplastic astrocytoma with focal necrosis	U	67.3
	G	108	headache and seizure with recurrent tumor on CT scan	unknown	GBM with necrosis; small amount of wafer-like remnants	P	24.3
	P	54	neurological deterioration and seizures	debulking	tumor cyst with necros s, anaplastic astrocytoma; fragments of wafer-like remnants	P	43.4
	P	72	increased seizures and increased enhancement on CT scan	tumor debulk ng	recurrent anaplastic astrocytoma	U	26.1
	P	80	headaches, neurological deterioration, huge tumor mass on MRI with hydrocephalus	resection of mass lesion	unknown	U	19.4
	G	22	fever spikes and decline in mental status	wound exploration with debridement; removal of wafer-like remnants	extra-axial collection at craniotomy site (culture positive for staphylococcus)	P	25.9
	G	171	tumor enlargement on MRI	stereotactic biopsy	astrocytoma with no highly malignant feat res	U	42.4
	G	255	mild left hemiparesis	needle aspiration of cyst	unknown	U	96.4

Table 2: Patients with Reope. ns after Study Surgery in Study 8802

Patient ID	Trt. G or P	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants P(resent) A(bsent) U(nknown)	Duration of Survival after Study Surgery (weeks)
		311	increased left hemiparesis	debulking	unknown	U	
		470	severe headaches and syncope	debulking	unknown	U	
		540	clinical decline	debulking	unknown	U	
	G	68	increased speech difficulty and left hemiparesis, with increased tumor size on CT scan	tumor resection	unknown	U	34.9
		126	altered mental status and increased tumor size on CT scan	tumor resection	unknown	U	
	G	18	headache and fever	bone flap tapped and cultured	unknown	U	77.6
		225	tumor recurrence	tumor resection and placement of subdural shunt	unknown	U	
		284	?headaches (unknown)	shunt revision	unknown	U	
		326	left sided weakness	tumor resection	unknown	U	
	P	24	bulging bone flap	aspiration	unknown	U	20.1
		38	bulging bone flap	bone flap removal and debridement	unknown	U	
		41	CSF leak from wound	lumbar drain placed	unknown	U	
	G	91	increased tumor growth on CT scan and KPS decline	tumor resection	unknown	U	41.1

Table 2: Patients with Reoperations after Study Surgery in Study 8802

Patient ID	Trt. G or P	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants P(resent) A(bsent) U(nknown)	Duration of Survival after Study Surgery (weeks)
(cont.)		140	mental status changes, gait difficulty and hydrocephalus	subdural hematoma removed and subdural to peritoneal shunt placed	subdural hematoma	U	
		183	shunt malfunction	shunt revision	unknown		
	G	20	nausea, vomiting, headaches (hydrocephalus)	V-P shunt placed	unknown	U	37.7
		93	seizures and aphasia	debulking and Ommaya reservoir placement	unknown	U	
		101	nausea, vomiting, headaches, urinary incontinence	twist-drill craniotomy	postoperative pneumocephalus	U	
	G	225	hydrocephalus	V-P shunt placed	unknown	U	56.3
	G	108	unknown	shunt placed	unknown	U	98.6
	G	31	fluid collection over bone flap	epidural drain placed	unknown	U	94.0
		272	repetitive motions, urinary incontinence, increased enhancement on CT	biopsy and V-P shunt placement	malignant astrocytoma	U	
	G	25	infected bone flap (pre-existing condition)	bone flap removal	unknown	U	25.6

Table 2: Patients with Reoper... as after Study Surgery in Study 8802

Patient ID	Trt. G or P	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants P(resent) A(bsent) U(nknown)	Duration of Survival after Study Surgery (weeks)
	P	24	prevalent discharge from scalp wound	bone flap removal, polymer wafer fragment removed	necrotic fibrous tissue, inflammatory exudate and numerous gram-positive cocci; portions of bone with acute inflamation, fibrous tissue with reactive changes, infected bone fragments and debrided tissue	P	9.4
	G	65	drainage and swelling in area of incision, edema with ventricular system compression	bone flap removed, 3-4 wafer remnants removed	unknown, culture revealed gram-positive organisms	P	26.3
		81	significant increase in tumor size	debridement of necrotic tissue	unknown	U	
	G	3	declining mental status, hydrocephalus	elevation of bone flap, ventricular drain inserted	clot removed, "bubbling CSF" noted, CSF grew gram-negative rods culture grew Klebsiella		5.4
		4	"polymer wafers were a source of concern"	removal of polymer wafers	"sterilization report confirmed wafers were not contaminated"	P	
	G	37	CSF leak	insertion of a spinal drain	unknown	U	30.7
		71	CSF leak	transmastoid repair of a CSF fistula with abdominal fat grafting	unknown	U	
	G	22	cystic tumor cavity	tapping of cystic collection with removal of 30 cc of CSF	unknown	U	30.1

Table 2: Patients with Reopera[illegible]s after Study Surgery in Study 8802

Patient ID	Trt. G or P	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants P(resent) A(bsent) U(nknown)	Duration of Survival after Study Surgery (weeks)
(cont.)		34	craniotomy wound dehiscence	spinal drain placed	unknown	U	
	P	62	tumor cyst	drainage of cyst with reservoir placement	unknown	U	22.1
		77	unknown	reservoir tapped	unknown	U	
		116	decreased neurological status	cyst tapped	unknown	U	
	G	42	CSF leak	wound revision	unknown	U	42.6
	G	154	progression of tumor and hydrocephalus	right frontal craniotomy for tumor	pathological report indicated viable tumor	U	39.4
		156	unknown	conversion of reservoir into ventriculo-peritoneal shunt	unknown	U	
	P	148	unknown	tumor debulking and placement of an external catheter	unknown	U	27.1
	G	16	CSF leak with subgaleal fluid collection, fever	effusion tapped, CSF studies negative	unknown	U	16.1
		87	lethargy and shunt malfunction with blocked ventricular catheter	ventricular catheter replaced	unknown	U	
	P	12	fever spikes	"repeat tap from the VP shunt"	unknown	U	96.6
		34	fluid leak from incisional area with necrotic edges around wound	bone flap removed and wound revision	wound culture positive for staphylococcus	U	

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Table 2: Patients with Reopera after Study Surgery in Study 8802

Patient ID	Tx G or P	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants P(resent) A(bsent) U(nknown)	Duration of Survival after Study Surgery (weeks)
(cont.)		35	unknown	placement of external ventricular drain	drainage of large amount of cherry colored CSF	U	
		75	unknown	removal of external ventricular drain	unknown	U	
		68	unknown	wound revision and resuturing	unknown	U	
		161	problems with wound healing	wound revision, placement of external ventricular drain, repair of dural fistula	unknown	U	
		358	problems with wound healing	wound debrided	unknown	U	
	P	15	intracranial hemorrhage	exploration, removal of bone flap, removal of clot, removal of 8 wafer remnants	necrotic white matter with macrophages and recent hemorrhage; no viable tumor	?	21.6
		45	wound leakage	wound revision, external ventricular drain converted to ventriculo-peritoneal shunt	unknown	A (previously removed)	
	G	16	scalp wound red, swollen and tender	bone flap removal, wound revision, and placement of a subgaleal external ventricular drain	unknown	U	12.7
		19	unknown	removal of external ventricular drain	unknown	U	

Table 2: Patients with Reopera s after Study Surgery in Study 8802

Patient ID	Trt. G or P	Study Day	Reason for Reoperat on	Procedure Performed	Findings at Surgery	Wafer-Like Remnants P(resent) A(bsent) U(nknown)	Duration of Survival after Study Surgery (weeks)
	G	233	massive increase in tumor size	tumor debulking	GBM with tumor cell necrosis	U	43.4
		234	moderate effusion, large cystic area on CT scan	placement of reservoir to drain cystic area	unknown	U	
	G	127	increasing mass with shift	removal of necrotic debris, wafer remnants, and viable tumor, drainage of cystic lesion, placement of Selker reservoir	necrotic debris, wafer remnants and viable tumor	P	39.9
	G	176	tumor on MRI	placement of catheters for direct brachytherapy	unknown	U	79.3
		180	to remove catheters	removal of catheters	unknown	U	
		297	unknown	debulking	unknown	U	
	P	46	increased headache, vomiting and drowsiness	aspiration of tumor cyst via burrhole; insertion of Ommaya reservoir	unknown	U	8.3
	P	5	CSF draining	lumbar drain	unknown	U	108.1
	P	36	headaches, blurred vision and increased mass effect on CT	excision of right temporal GBM	GBM; small wafer-like fragments of soft brown material that showed necrotic debris, and an amorphous material	P	40.9
	G	68	deterioration due to meningitis	debridement of tumor cavity; abscess drained and wafer-like remnants removed	abscess	P	12.3
	P	1	tension pneumocephalus	burr hole to tap air off	unknown	U	21.3

Table 2: Patients with Reoperations after Study Surgery in Study 8802

Patient ID	Trt. G or P	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants P(resent) A(bsent) U(nknown)	Duration of Survival after Study Surgery (weeks)
	P	297	tumor recurrence	debulking of tumor	unknown	U	53.4
	P	12	coma, high fever, Enterobacter sepsis	removal of bone flap for infection	unknown	U	5.9
		18	lethargy, midline shift on CT	removal of necrotic tissue, wafer remnants removed	unknown	P	
	G	139	enhancing lesion and cyst in right temporal occipital region	drainage	unknown	U	32.4
		197	wound infection	bone flap removal	unknown	U	
		213	mass lesion with solid and cystic components, midline shift, enlargement of left lateral ventricle	occipito-temporal lobectomy, debridement of skin edge, ventriculostomy placement	malignant mixed astrocytoma/ oligodendroglioma	U	
	G	131	left hemiparesis and encephalopathy	brain biopsy	malignant glioma	U	56.1
	P	21	subgaleal bacterial infection	wound debridement and removal of bone plate	unknown	U	28.4
	G	47	cerebral hemorrhage	evacuation of hematoma	unknown	U	19.7
	P	195	right posterior fossa enhancement and multiple cystic areas on CT scan with shift of ventricle to the left	resection of right cerebellar hemisphere and vermis	recurrent malignant astrocytoma	U	79.6
		281	unknown	proximal shunt revision with replacement	unknown	U	
		433	gait difficulties, shunt erosion	shunt revision	unknown	U	
	P	20	CSF leak	single stitch was placed	unknown	U	32.4

Table 2: Patients with Reopera[illegible] after Study Surgery in Study 8802

Patient ID	Trt. G or P	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants P(resent) A(bsent) U(nknown)	Duration of Survival after Study Surgery (weeks)
		39	unknown	ventriculo-peritoneal shunt placed	unknown	U	
		90	incisional drainage	5 stitches placed along incision	unknown	U	
		97	unknown	shunt revision	unknown	U	
		120	left sided loss of control	right temporal lobectomy	unknown	U	
	P	56	hydrocephalus	ventriculo-peritoneal shunt placed	unknown	U	123
	P	74	left parietal abscess	drainage of abscess	unknown	U	28.0
		152	headaches and recurrent tumor, increased mass effect and edema on CT	reoperation	unknown	U	
		166	bone plate infected	bone plate removed	unknown	U	
	C	127	cystic mass in left hemisphere with enhancement in right frontotemporal region	tumor debulking	GBM	U	47.0
		175	unknown	"wound repair"	unknown	U	
		176	unknown	excisional biopsy of left temporal lesion; debridement and closure of draining right temporal incision line	GBM	U	
		25	wound dehiscence with serosanguineous fluid	wound sutures placed	wound dehiscence with serosanguineous fluid	U	7.3

Table 2: Patients with Reoper ns after Study Surgery in Study 8802

Patient ID	Tr: G or P	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants P(resent) A(bsent) U(nknown)	Duration of Survival after Study Surgery (weeks)
(cont.)		51	rigor to left shift, fixed and dilated pupils	resection cavity enlarged	thick proteinaceous fluid under pressure	U	

TABLE 4.2.4 Six-Month Life Table Summary by Treatment Group and Age (Study 8802)

	Age ≥65				Age <65			
	GLIADEL 3.85% (N = 104)		PLACEBO (N = [illegible])		GLIADEL 3.85% (N = 106)		PLACEBO (N = 102)	
Timepoint	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths
1 month	0.0	[illegible]	[illegible]	[illegible]	1.1	1	2.9	3
2 months	0.0	[illegible]	10.3	3	9.1	9	8.8	9
3 months	10.6	[illegible]	[illegible]	[illegible]	17.1	17	22.5	23
4 months	10.6	[illegible]	[illegible]	[illegible]	28.1	28	34.3	35
5 months	30.0	8	[illegible]	8	35.1	35	45.1	46
6 months	50.0	5	--	--	36.1	36	50.0	51
	Age ≥65 P-value				Age <65 P-value			
Log-Rank	[illegible]18				[illegible]28			
Wilcoxon	[illegible]23				[illegible]155			
Cox Model:								
Treatment:	P = [illegible]65							
Age	P = [illegible]72							
Treatment-by-age interaction	P = 0.501							

Dash (--) indicates that there was no data available

Cross-Reference: ATTACHMENT I - TABLE [illegible] - Data Listings 2.24 and 2.9

TABLE # 34 Overall Life Table Summary by Treatment Group and Age (Study [illegible])

	Age ≥65				Age <65			
	GLIADEL 3.85% [N = 10]		PLACEBO [N = 11]		GLIADEL 3.85% [N = 140]		PLACEBO [N = 112]	
Timepoint	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths
3 months	10.0	1	[illegible]	3	[illegible]	17	22.5	27
6 months	50.0	5	[illegible]	8	[illegible]	39	50.0	61
9 months	70.0	7	[illegible]	9	[illegible]	51	68.5	79
12 months	100.0	10	[illegible]	10	[illegible]	76	78.4	89
15 months	--	--	--	--	[illegible]	85	[illegible]	92
[illegible] months	--	--	--	--	[illegible]	88	[illegible]	96
21 [illegible] months	--	--	--	--	[illegible]	95	[illegible]	98
24 months	--	--	--	--	[illegible]	98	[illegible]	[illegible]
27 [illegible] months	--	--	--	--	[illegible]	[illegible]	[illegible]	[illegible]
30 months	--	--	--	--	[illegible]	[illegible]	[illegible]	[illegible]
33 months	--	--	--	--	[illegible]	[illegible]	[illegible]	[illegible]
36 months	--	--	--	--	[illegible]	[illegible]	[illegible]	[illegible]
39 months	--	--	--	--	[illegible]	[illegible]	[illegible]	[illegible]
42 months	--	--	--	--	[illegible]	[illegible]	[illegible]	[illegible]
45 months	--	--	--	--	[illegible]	[illegible]	[illegible]	[illegible]
48 months	--	--	--	--	[illegible]	[illegible]	--	--
51 months	--	--	--	--	[illegible]	[illegible]	--	--

	Age ≥65 P-Value	Age <65 P-Value
Log-Rank	[illegible]	[illegible]
Wilcoxon	[illegible]	[illegible]

Cox Model

Treatment	[illegible]
Age	[illegible]
Treatment-by-age interaction	[illegible]

Dash (—) indicates that there was no data available.

Cross-Reference: ATTACHMENT [illegible] TABLE OF CONTENTS

Overall Kaplan-Meier survival curves by treatment group and age are shown in Figure 9.

FIGURE 9 Overall Kaplan-Meier Survival Curves by Treatment Group and Age (Study 8802)

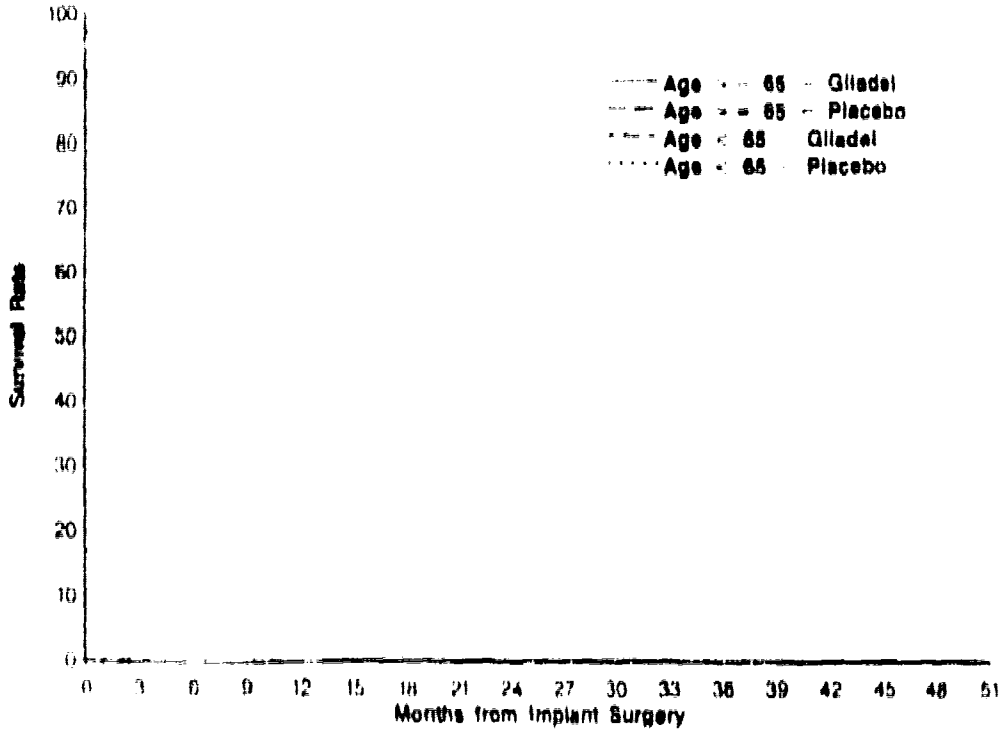


TABLE 4.25 Six-Month Life Table Summary by Treatment Group and Gender: Study 88-2

	Male				Female			
	[redacted] [N = 74]		[redacted] [N = 49]		[redacted] [N = 56]		[redacted] [N = 42]	
Timepoint	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths
1 month	0.0	0	2.4	1	2.8	1	2.7	1
2 months	8.1	6	10.2	4	8.2	3	2.3	1
3 months	16.2	12	22.5	9	16.7	6	4.7	2
4 months	25.7	19	30.8	12	25.6	9	7.2	3
5 months	33.8	25	37.8	15	33.3	12	44.2	19
6 months	37.8	28	42.2	16	44.4	16	53.3	23

	Male [redacted] value	Female [redacted] value
Log-Rank	[redacted]	[redacted]
Wilcoxon	[redacted]	0.548

Cox Model

Treatment	[redacted]
Gender	[redacted]
Treatment-by-gender interaction	[redacted]

Cross-Reference ATTACHMENT 1 - TABLE 19C; APPENDIX 10 - Data Listings 2.24, and 2.28

TABLE 4.35 Overall Life Table Summary by Treatment Group and Gender (Study 88-02)

	Male				Female			
	GLIADEL 3.85% (N = 74)		PLACEBO (N = 65)		GLIADEL 3.85% (N = 36)		PLACEBO (N = 31)	
Timepoint	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths
3 months	16.2	12	27.5	18	8.3	3	16.1	5
6 months	37.8	28	52.2	34	22.2	8	41.9	13
9 months	60.8	45	68.1	44	33.3	12	71.0	22
12 months	75.7	56	78.5	51	44.5	16	83.7	26
15 months	78.4	58	81.2	53	47.2	17	87.1	27
18 months	82.4	61	82.9	54	47.2	17	90.3	28
21 months	82.4	61	84.5	55	47.2	17	93.5	29
24 months	86.5	64	86.2	56	47.2	17	93.5	29
27 months	87.8	65	86.2	56	47.2	17	93.5	29
30 months	87.8	65	86.2	56	47.2	17	93.5	29
33 months	90.5	67	86.2	56	47.2	17	93.5	29
36 months	90.5	67	86.2	56	47.2	17	--	--
39 months	90.5	67	91.3	59	47.2	17	--	--
42 months	90.5	67	92.8	60	47.2	17	--	--
45 months	91.9	68	94.2	61	--	--	--	--
48 months	91.9	68	--	--	--	--	--	--
51 months	93.2	69	--	--	--	--	--	--

	Male P-Value	Female P-Value
Log-Rank	0.372	0.764
Wilcoxon	0.156	0.438

Cox Model:

Treatment	P = 0.351
Gender	P = 0.138
Treatment-by-gender interaction	P = 0.760

Dash (--) indicates that there was no data available.

Cross-Reference ATTACHMENT 1 - TABLE 1.8(C) APPENDIX 16.1.9 (Data Listings 2, 24, and 28)

Overall Kaplan Meier survival curves by treatment and gender are shown in Figure 10

FIGURE 10 Overall Kaplan Meier Survival Curves by Treatment and Gender (Study 8802)

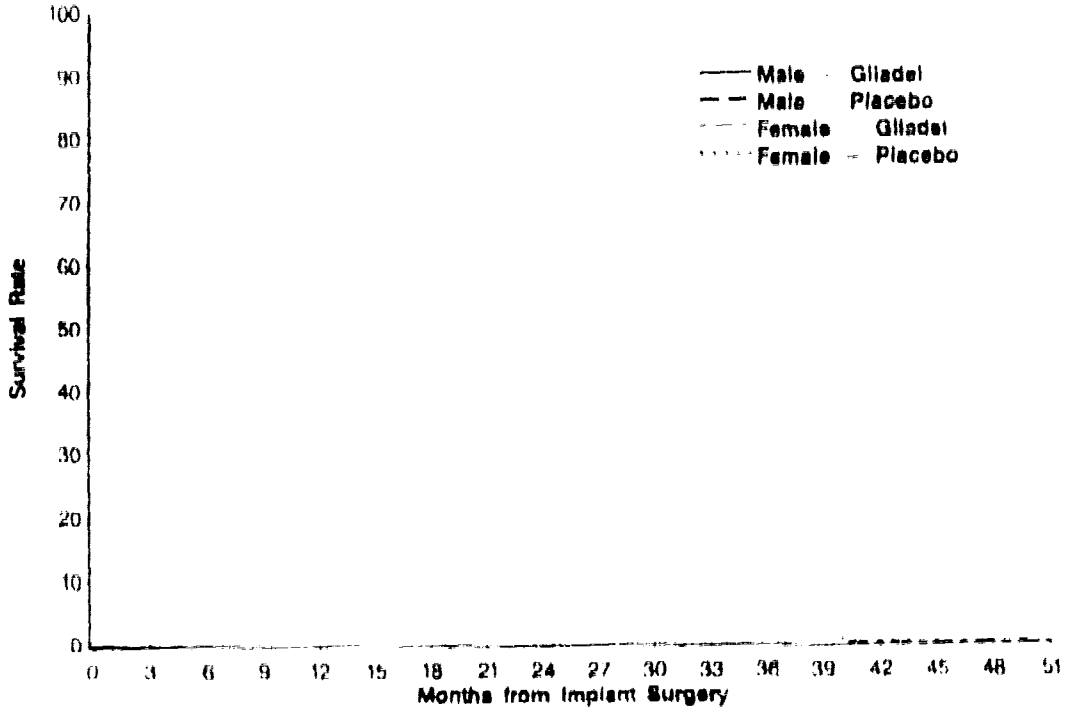


TABLE 4.26: Six-Month Life Table Summary by Treatment Group and Race (Study 880...

	White				Non-White			
	GLIADEL 3.85% [N = 100]		[illegible] [N = ...]		[illegible] 3.85% [N = 36]		[illegible] [N = 8]	
Timepoint	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths
1 month	1.0	1	2.+	3	...		...	
2 months	9.0	9	...	...	...		...	
3 months	18.1	...	25.1	...				
4 months	29.1	...	...	...			12.5	1
5 months	36.0	...	...	...	...	1	...	...
6 months	42.0	42	55.8	58	2	2	...	...

	White P-Value	Non-White P-Value
Log-Rank	...02	.732
Wilcoxon	...88	.784

Cox Model:

Treatment:	P = ...074
Race	P = 0.905
Treatment-by-race interaction	P = 0.524

Dash (—) indicates that there was no data available.

Cross-Reference: ATTACHMENT 1 - TABLE ... APPENDIX ... Data ... 2.24 ... 4.28

TABLE 4.36 Overall Life Table Summary by Treatment Group and Race (Study 88-2)

	White				Non-White			
	GLIADEL 3.85% [N = 1[illegible]]		PLACEBO [N = 1[illegible]]		GLIADEL 3.85% [N = 2[illegible]]		PLACEBO [N = 8[illegible]]	
Timepoint	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths	Cumulative Death Rate	Cumulative # of Deaths
3 months	18.0	18	25.[illegible]	2[illegible]	[illegible]	[illegible]	0.0	
6 months	42.[illegible]	42	55.6	5[illegible]	2	2	12.5	1
9 months	61.0	[illegible]	75.[illegible]	7[illegible]	7[illegible]	7	12.5	1
12 months	78.[illegible]	78	84.[illegible]	8[illegible]	8[illegible]	8	25.[illegible]	2
15 months	83.[illegible]	83	86.5	8[illegible]	8[illegible]	8	25	2
18 months	85.0	85	88.5	8[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
21 months	85.0	85	90.[illegible]	9[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
24 months	88.[illegible]	88	90.4	9[illegible]	--	--	42.5	3
27 months	89.[illegible]	89	92.3	9[illegible]	--	--	42.5	3
30 months	90.[illegible]	[illegible]	92.3	9[illegible]	--	--	42.5	3
33 months	92.[illegible]	92	92.3	9[illegible]	--	--	75.[illegible]	[illegible]
36 months	92.[illegible]	92	92.3	9[illegible]		--	75.[illegible]	
39 months	92.0	92	95.2	9[illegible]	--	--	75.[illegible]	[illegible]
42 months	93.0	93	95.2	9[illegible]	--	--	87.5	[illegible]
45 months	94.0	94	96.2	[illegible]0	--	--	--	
48 months	94.0	94	--	--	--	--	--	--
51 months	95.0	95	--	--	--	--	--	--

	White P-Value	Non-White P-Value
Log-Rank	[illegible].082	0.0[illegible]6
Wilcoxon	[illegible].049	[illegible].018
Cox Model		
Treatment	[illegible].[illegible]34	
Race	[illegible].[illegible]33	
Treatment-by-race interaction	[illegible].[illegible]33	

Dash (--) indicates that there was no information available.

Cross-Reference: [illegible]

Overall Kaplan-Meier survival curves by treatment and race are shown in Figure 11.

FIGURE 11: Overall Kaplan-Meier Survival Curves by Treatment and Race (Study 8802)

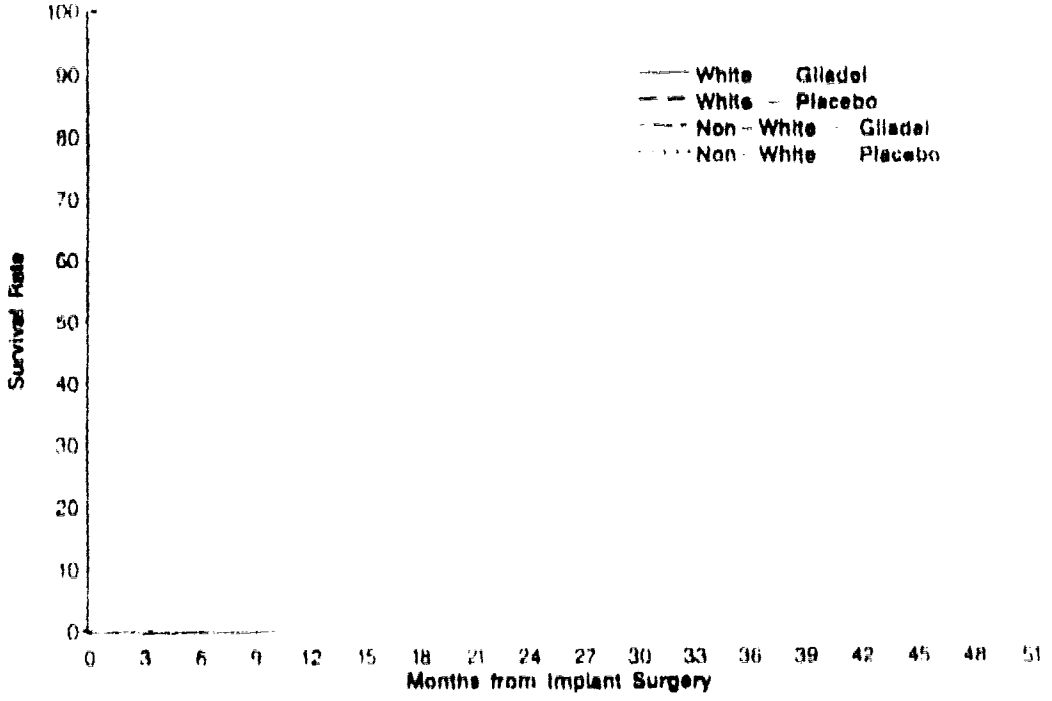


TABLE 4 SO presents severe treatment-emergent adverse events by treatment group and by COSTART term that were reported during the clinical study.

TABLE 4 SO Severe Treatment-Emergent Adverse Events by Treatment Group and Summarized by Body System and COSTART Term (Study 850[illegible])

	[illegible]ADEL [illegible]ESS[illegible] (N = 130)	PLACEBO (N = 112)
Body System / COSTART Term[a]	Number (Percentage) of Patients	
Body as a Whole	TOTAL	TOTAL
Abdominal pain	0 (0)	1 (1)
Asthenia	1 (1)	0 (0)
Back pain	2 (2)	0 (0)
Infection	2 (2)	1 (1)
Sepsis	2 (2) / 7	0 (0) / 2
Cardiovascular		
Deep thrombophlebitis	1 (1)	2 (2)
Heart arrest	0 (0)	1 (1)
Hypertension	1 (1)	0 (0)
Pulmonary embolus	1 (1)	6 (5)
Shock	1 (1)	0 (0)
Tachycardia	1 (1) / 6	0 (0) / 9
Digestive		
Anorexia	0 (0)	1 (1)
Dysphagia	0 (0)	1 (1)
Gastrointestinal hemorrhage	1 (1)	0 (0)
Nausea and vomiting	2 (2)	2 (2)
Sigmoid tumor[b]	1 (1) / 4	0 (0) / 4
Metabolic and Nutritional		
Cachexia anorexia[b, c]	0 (0)	1 (1)
Dehydration	1 (1)	0 (0)
Healing abnormal	1 (1) / 2	0 (0) / 1
Musculoskeletal		
Bone metastases[b]	0 (0) / 0	1 (1) / 2
Nervous		
Abnormal gait	1 (1)	0 (0)
Abscess	0 (0)	1 (1)
Aphasia	3 (3)	3 (3)
Cerebral hemorrhage	1 (1)	2 (2)
Cerebral infarct	0 (0)	2 (2)
Cerebrovascular accident	0 (0)	1 (1)
CNS neoplasia	0 (0)	1 (1)
Coma	2 (2)	5 (4)
Confusion	2 (2)	0 (0)
Convulsion	5 (5)	5 (4)
Dementia	1 (1)	0 (0)
Diplopia	0 (0)	1 (1)
Extramedular palsy	1 (1)	0 (0)
Grand mal convulsion	0 (0)	1 (1)
Headache	7 (6)	4 (4)
Hemiplegia	6 (5)	8 (7)
Hydrocephalus	1 (1)	0 (0)
Increased ICP culminating in brain stem herniation[b, c]	0 (0)	1 (1)
Insomnia	1 (1)	0 (0)
Intracranial hypertension	2 (2)	2 (2)
Meningitis	1 (1)	0 (0)
Monoplegia	0 (0)	1 (1)
Mute[b]	1 (1)	0 (0)
Neuro status deterioration[b]	1 (1)	0 (0)
Neurologic deterioration[b]	1 (1)	0 (0)
Somnolence	1 (1)	3 (3)
Speech disorder	1 (1)	1 (1)
Stupor	3 (3)	2 (2)
Thinking abnormal	0 (0) / 42	1 (1) / 45
Respiratory		
Apnea	0 (0)	1 (1)
Dyspnea	1 (1)	0 (0)
Pneumonia	2 (2) / 3	1 (1) / 2
Skin and Appendages		
Skin ulcer	0 (0)	1 (1)
Special Senses		
Blindness	1 (1)	1 (1)
Visual field defect	0 (0) / 1	1 (1) / 2
Urogenital		
Urinary tract infection	0 (0) / 0	1 (1) / 1
TOTAL	64 severe treatment-emergent events were reported by 43 of	68 severe treatment-emergent events were reported by 47

TABLE 4.5.2 presents the treatment-emergent adverse events by treatment group that were, in the opinion of the investigator, definitely, probably, or possibly related to study drug.

TABLE 4.5.2 Treatment-Emergent Adverse Events that Were Considered to be Definitely, Probably or Possibly Related to Study Drug by Treatment Group, Summarized by Body System and COSTART Term (Study 888-3)

	GUARDIAN™ (N = 110)	PLACEBO (N = 112)
Body System / COSTART Term*	Number (Percentage) of Patients	
Body as a Whole	TOTALS	TOTALS
Back pain	1 (1)	0 (0)
Face edema	0 (0)	1 (1)
Fever	1 (1)	1 (1)
Infection	0 (0) / 4	2 (2) / 4
Cardiovascular		
Deep thrombophlebitis	0 (0)	1 (1)
Hypertension	2 (2) / 2	0 (0) / 1
Digestive		
Guaiac positive fecal tube drainage†	1 (1)	0 (0)
Nausea	0 (0)	2 (2)
Nausea and vomiting	1 (1)	2 (2)
Rectal hemorrhage	1 (1)	0 (0)
Vomiting	1 (1) / 4	0 (0) / 4
Hemic and Lymphatic		
Anemia	0 (0)	2 (2)
Leukopenia	1 (1)	0 (0)
Thrombocytopenia	1 (1) / 2	0 (0) / 2
Metabolic and Nutritional		
Amylase increased	0 (0)	1 (1)
Healing abnormal	1 (1)	2 (2)
Weight decrease	1 (1) / 4	0 (0) / 5
Nervous		
Brain edema	2 (2)	0 (0)
Confusion	0 (0)	1 (1)
Change in [illegible]	1 (1)	0 (0)
Coma	0 (0)	1 (1)
Confusion	1 (1)	1 (1)
Convulsion	1 (1)	1 (1)
Decreased consciousness†	1 (1)	0 (0)
Diplopia	0 (0)	1 (1)
Emotional lability	0 (0)	1 (1)
Extrapyramidal syndrome	1 (1)	0 (0)
Headache	7 (6)	1 (1)
Hemiplegia	1 (1)	1 (1)
Hydrocephalus	1 (1)	1 (1)
Increased ICP (intracranial pressure)†		
Brainstem herniation†	0 (0)	1 (1)
Intracranial hypertension	1 (1)	2 (2)
Meningism	1 (1)	0 (0)
Mild left arm drift†	0 (0)	1 (1)
Monoplegia	1 (1)	1 (1)
Somnolence	2 (2)	1 (1)
Stupor	1 (1)	1 (1)
Thinking abnormal	1 (1)	0 (0)
Tumor cavity evacuated on CT†	1 (1) / 29	0 (0) / 23
Respiratory		
Dyspnea	1 (1) / 1	0 (0) / 0
Special Senses		
Blindness	0 (0)	1 (1) → IA DDP
Optic Atrophy	0 (0)	1 (1)
Partial Permanent Deafness	0 (0)	1 (1)
Visual Field Defect	0 (0) / 0	1 (1) / 4
Urogenital		
Urinary Retention	0 (0)	1 (1)
TOTAL	46 treatment-emergent adverse events judged to be treatment-related were experienced by 21 of 110 (11%) patients	42 treatment-emergent adverse events judged to be treatment-related were experienced by 20 of 112 (10%) patients

* The investigator verbatim term was used in place of a COSTART preferred term when the verbatim term was so nonspecific that assignment to an appropriate COSTART preferred term could not be made unambiguously or when the most appropriate COSTART preferred term was either misleading or so general as to be uninformative.

† To capture all available information from this investigator verbatim term, multiple coded COSTART terms have been assigned to it and are listed under the investigator verbatim term in the data listings.

TABLE 4.55 presents a by-patient listing of those patients who experienced abnormal healing.

TABLE 4.55 Treatment-Emergent Abnormal Healing Adverse Events (Study 8802)

Patient No	Treatment-Emergent Adverse Event (Verbatim)	Study Day Onset	Severity	Relationship to Study Drug
GLIADEL Treatment Group				
	Fluid collection under flap	97	Mild	Not Related
	Spinal fluid collection over bone flap	1	Moderate	Possible
	Wound dehiscence	18	Moderate	Possible
	Subdural fluid collection	29	Moderate	Not Related
	CSF leak	33	Moderate	Unknown
	Craniotomy wound dehiscence	34	Moderate	Not Related
	CSF leak from cranial incision	42	Moderate	Unknown
	Wound effusion	52	Moderate	Not Related
	Subgaleal effusion		Moderate	Possible
	Subgaleal collection		Moderate	Unknown
	Yellow discharge incision	10	Moderate	Unknown
	Spinal fluid leak	2	Mild	Unknown
	CSF leak at ventric drain site	16	Mild	Not Related
	Cyst fluid reaccumulation	134	Moderate	Not Related
	Wound breakdown	175	Severe	Unknown
PLACEBO Treatment Group				
	Bone flap bulging	6	Moderate	Unknown
	CSF leak	7	Moderate	Not Related
	Wound leak and staph infection	14	Moderate	Possible
	Wound effusion	3	Mild	Possible
	CSF drainage from wound	7	Moderate	Not Related
	Cerebral spinal fluid leak from wound	29	Moderate	Unknown

Cross Reference APPENDIX 10 - Data Listing 22

TABLE 4.69 Treatment-Emergent Infections by Treatment Group, Body System and COSTART Term (Study 8802)

	GLIADEL 3.85% [N = 110]	PLACEBO [N = 112]	Fisher's Exact Test
Body System / COSTART Term*	Number (Percentage) of Patients		P-Value
Body as a Whole			
Abscess	1 (1)	0 (0)	0.495
Cellulitis	0 (0)	4 (4)	0.122
Flu syndrome	1 (1)	0 (0)	0.495
Infection	8 (7)	9 (8)	1.000
Sepsis	2 (2)	2 (2)	1.000
Digestive			
Hepatitis	0 (0)	1 (1)	1.000
Infection	2 (2)	3 (3)	1.000
Oral moniliasis	6 (6)	6 (5)	1.000
Periodontitis	0 (0)	1 (1)	1.000
Musculoskeletal			
Infection	2 (2)	2 (2)	1.000
Nervous			
Abscess	0 (0)	1 (1)	1.000
Meningitis	1 (1)	0 (0)	0.059
Respiratory			
Bronchitis	0 (0)	2 (2)	0.498
Infection	5 (5)	1 (1)	0.117
Pharyngitis	1 (1)	2 (2)	1.000
Pneumonia	7 (6)	7 (6)	1.000
Special Senses			
Chronic ear infection and perforated right ear drum*	1 (1)	0 (0)	0.495
Conjunctivitis	1 (1)	1 (1)	1.000
Eye Infection*	1 (1)	0 (0)	0.495
Eye Infection O.S. *Klebsiella**	0 (0)	1 (1)	1.000
Otitis media	0 (0)	1 (1)	1.000
Sore throat and ear infection*	0 (0)	1 (1)	1.000
Urogenital			
Urinary tract infection	23 (21)	19 (17)	0.496
TOTAL	**65 treatment-emergent infections were reported**	**64 treatment-emergent infections were reported**	**0.924**

*The investigator verbatim term was used in place of a COSTART preferred term when the verbatim term was so nonspecific that assignment to an appropriate COSTART preferred term could not be made unambiguously, or when the most appropriate COSTART preferred term was either misleading or so general as to be uninformative

Cross-Reference: ATTACHMENT 1 - TABLE 25A, APPENDIX 10 - Data Listings 4 and 22

TABLE 4.24 Frequently Reported[a] Treatment-Emergent Adverse Events Summarized by Body System and COSTART Term (Study 8701)

	Treatment Group 1 GLIADEL 1.925% [N = 5]	Treatment Group 2 GLIADEL 3.85% [N = 5]	Treatment Group 3 GLIADEL 6.35% [N = 11]	All Patients Enrolled [N = 21]
Body System/ COSTART Term	Number (Percentage) of Patients			
Body as a Whole				
Drug level decreased	1 (20)	0 (0)	1 (9)	2 (10)
Drug level increased	1 (20)	1 (20)	0 (0)	2 (10)
Fever	1 (20)	0 (0)	2 (18)	3 (14)
Infection	1 (20)	0 (0)	1 (9)	2 (10)
Infection Prophylaxis	3 (60)	0 (0)	0 (0)	3 (14)
Neck Pain	0 (0)	0 (0)	2 (18)	2 (10)
Pain	2 (40)	0 (0)	0 (0)	2 (10)
Cardiovascular				
Hypertension	1 (20)	0 (0)	1 (9)	2 (10)
Digestive				
Nausea	1 (20)	0 (0)	2 (18)	3 (14)
Constipation	1 (20)	0 (0)	2 (18)	3 (14)
Metabolic/Nutritional Disorders				
Abnormal healing[b]	1 (20)	0 (0)	3 (27)	4 (19)
Hyperglycemia	1 (20)	0 (0)	2 (18)	3 (14)
Hypokalemia	1 (20)	0 (0)	1 (9)	2 (10)
Hypomagnesmia	2 (40)	0 (0)	0 (0)	2 (10)
Nervous System				
Brain Edema	1 (20)	1 (20)	1 (9)	3 (14)
Convulsions	1 (20)	1 (20)	3 (27)	5 (24)
Dizziness	0 (0)	0 (0)	2 (18)	2 (10)
Headache	1 (20)	1 (20)	4 (36)	6 (29)
Intracranial hypertension	1 (20)	0 (0)	2 (18)	3 (14)
Urogenital System				
Urinary tract infection	2 (40)	0 (0)	1 (9)	3 (14)

[a] Two or more patients

[b] Includes: CSF leaks, subgaleal collection, and fluid at the surgical site

Cross-Reference: ATTACHMENT 1 - TABLE 17A, APPENDIX 13 - Data Listing 21

TABLE 4.27 Treatment-Related (Possibly) Treatment-Emergent Adverse Events Summarized by Body System and COSTART Term (Study 8701)

	Treatment Group 1 GLIADEL 1.925% [N = 5]	Treatment Group 2 GLIADEL 3.85% [N = 5]	Treatment Group 3 GLIADEL 6.45% [N = 11]	All Patients Enrolled [N = 21]
Body System COSTART Term[1]	Number (Percentage) of Patients			
Body as a Whole				
Neck Pain	0 (0)	0 (0)	1 (9)	1 (5)
Digestive System				
Nausea	0 (0)	0 (0)	1 (9)	1 (5)
Musculoskeletal System				
Infection	0 (0)	0 (0)	1 (9)	1 (5)
Nervous System				
Aphasia	0 (0)	0 (0)	1 (9)	1 (5)
Brain edema	1 (20)	1 (20)	0 (0)	2 (10)
Change in brain edema*	1 (20)	0 (0)	0 (0)	1 (5)
Convulsion	0 (0)	1 (20)	2 (18)	3 (14)
Headache	1 (20)	1 (20)	1 (9)	3 (14)
Insomnia	0 (0)	0 (0)	1 (9)	1 (5)
Intracranial hypertension	1 (20)	0 (0)	1 (9)	2 (10)
Meningitis	0 (0)	0 (0)	1 (9)	1 (5)
Progression of decreased level of consciousness*	0 (0)	0 (0)	1 (9)	1 (5)
Special Senses				
Eye pain	0 (0)	0 (0)	1 (9)	1 (5)
Infection	0 (0)	0 (0)	1 (9)	1 (5)

[1] The investigator verbatim term was used in place of a COSTART preferred term when the verbatim text* was so nonspecific that assignment to an appropriate COSTART preferred term could not be made unambiguously, or when the most appropriate COSTART preferred term was either misleading or so general as to be uninformative

Cross-Reference: ATTACHMENT - TABLE 12B APPENDIX 13 - Data Listing 21

Table 1: Patients with Reoperations after Study Surgery in Study 8701

Patient ID	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants Present/ Absent/ Unknown	Duration of Survival after Study Surgery (weeks)
	918	headache, projectile vomiting	removal of tumor, necrosis, and blood clot	tumor and necrosis, blood clot	U	176
	unknown	tumor in contralateral hemisphere	unknown	unknown	U	65.4
	475	progressive symptoms	biopsy of tumor	tumor	U	92.3
	558	increased intracranial pressure and headaches	debulking, wound revision, external ventricle drainage	GBM	U	
	573	unknown	ventriculo-peritoneal shunt placed	unknown	U	
	86	unknown	craniotomy for removal of necrotic tissue	necrotic tissue	U	47.1
	189	unknown	removal of cyst fluid at tumor site	unknown	U	45.4
	281	unknown	debulking	cyst and tumor	U	
	91	growing tumor on scan, declining clinical status, seizures, ? positive thallium scan	removal of necrotic material	necrotic material	U	42.0
	119	deteriorating condition with increased right-sided weakness and positive thallium scan	removal of necrotic tissue, placement of Hickman reservoir into cystic cavity	necrotic tissue	U	
	274	enlarging tumor on CT scan	"very large resection"	unknown	A	133.6
	833	cerebral edema	reservoir placement	unknown	U	
	91	difficulty in titrating steroid doses and declining clinical status	removal of necrotic tumorous tissue and 8 wafer-like remnants	necrotic tumorous tissue	P	23.4

Table 1: Patients with Reoperations after Study Surgery in Study 8701

Patient ID	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants (Present) Absent) Unknown)	Duration of Survival after Study Surgery (weeks)
	148	clinical status deterioration confirmed by CT scan	unknown, some wafer-like remnants removed	unknown	P	20.1
	interval of 3 - 11	worsening CSF leak	CSF drain placement	unknown	U	5.7
	49	frequent headaches and prolonged seizure, with increasing edema on MRI	placement of ^{125}I interstitial seeds	unknown	U	67.6
	162	increasing headaches	occipital lobectomy and removal of 8 wafer-like remnants	unknown	P	
	51	cyst at operative site	percutaneous drainage of cyst	unknown	U	7.4
	189	tumor enhancement, unable to taper steroids	[illegible] resection	tumor in a new area adjacent to surgery location	U	52.7

Table 3: Patients with Reoper n after Study Surgery in Study 9003

Patient ID	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-like Remnants Present (Present, Absent, Unknown)	Duration of Survival after Study Surgery (weeks)
	86	seizures, mutism, hemiparesis cystic lesion on CT scan	decompression of cystic lesion and biopsy of wall	recurrent GBM, mostly necrotic; polymer wafers, blood and foamy macrophages, necrotic debris with acute inflammation and negative stains for bacteria and fungi	P	31.0
	3	severe lethargy, impassive aphasia, shift, small increase in ventricle size, hematoma on CT scan	craniotomy for evacuation of intracerebral hematoma and removal of wafer-like remnants	GBM, hematoma and foreign material, consistent with polymer wafer	P	58.7
	204	enlargement of enhancing lesion on MRI, with increased edema and mass effect	craniotomy for exploration	recurrent glioma with necrotic tissue and polymer fragments	P	40.4
	204	unknown	"debulking of necrosis"	active glioma and fragments of necrotic tissue	U	40.0
	199	increasing left-sided weakness and speech deterioration	unknown	GBM and necrotic tissue	U	55.4
	282	unknown	"reoperation for recurrent GBM"	tumor recurrence at the margin outside of the cyst from prior resection; GBM with areas of [brain] parenchymal necrosis and florid mesenchymal response	U	54.0

Table 3: Patients with Reoper n after Study Surgery in Study 9003

Patient ID	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants Present (Absent) Unknown	Duration of Survival after Study Surgery (weeks)
	112	increase in tumor size, with large amount of surrounding edema	resection	extensively necrotic tumor with microscopic foci of viable GBM, foreign material consistent with wafer material	P	38.6
	209	tumor necrosis	"surgery"	unknown	U	92.1
	228	tumor necrosis	unknown	diagnosis 1. almost entirely necrotic tumor with rare viable tumor cells, brain with gliosis and necrosis diagnosis 2. brain and brain tumor with large areas of geographic coagulation necrosis consistent with radiation effect, "glossy" [?poorly] to moderately cellular astrocytic neoplasm	U	
	325	enhancement and edema on CT scan	stereotactic biopsy	brain with necrosis and vascular changes consistent with therapy [radiation] effect, atypical gliosis that may be therapy radiated or may be irradiated glioma in "quiescence"	U	

Table 3: Patients with Reoper. n after Study Surgery in Study 9003

Patient ID	Study Day	Reason for Reoperation	Procedure Performed	Findings at Surgery	Wafer-Like Remnants (Present/Absent/Unknown)	Duration of Survival after Study Surgery (weeks)
	403	tumor recurrence	tumor resection	treated astrocytoma, including regions of pure necrosis	U	230.5

TABLE 6. All Adverse Events Entered into the Database Summarized by Body System and Comparison with Prior GLIADEL Trials

Body system	Number of Occurrences in Treatment Protocol[1]	Number (Percentage) of Patients in Treatment Protocol[2] (N=50)	Number (Percentage) of GLIADEL Patients in Uncontrolled Trials (N=83)	Number (Percentage) of GLIADEL Patients in Placebo-Controlled Trials (N=126)	Number (Percentage) of All GLIADEL Patients (N=209)
Body as a Whole	14	10 (20%)	35 (42%)	46 (37%)	81 (39%)
Cardiovascular System	3	2 (4%)	16 (19%)	28 (22%)	44 (21%)
Digestive System	9	6 (12%)	18 (22%)	34 (27%)	52 (25%)
Endocrine System	0	0 (0%)	2 (2%)	3 (2%)	5 (2%)
Hemic and Lymphatic System	6	4 (8%)	5(6%)	11 (9%)	16 (8%)
Metabolic and Nutritional Disorders	9	7 (14%)	20 (24%)	21 (17%)	41 (20%)
Musculoskeletal System	0	0 (0%)	6 (7%)	8 (6%)	14 (7%)
Nervous System	17	7 (14%)	60 (72%)	90 (71%)	150 (72%)
Respiratory System	4	2 (4%)	8 (10%)	16 (13%)	24 (11%)
Skin and Appendages	1	1 (2%)	1 (1%)	10 (8%)	11 (5%)
Special Senses	1	1 (2%)	7 (8%)	10 (8%)	17 (8%)
Uncertain	1	1 (2%)	3 (4%)	0 (0%)	3 (1%)
Urogenital System	1	1 (2%)	10 (12%)	29 (23%)	39 (19%)
Total	66	16 (32%)	77 (93%)	112 (89%)	189 (90%)

[1] Multiple episodes of the same adverse event in the same patient were treated as one occurrence

[2] Patients with at least one occurrence of at least one adverse event in that body system

[Cross Reference Appendix II - Table 7, NDA Volume 1.14 - Table 4.47, Volume 1.25 - Table 4.35, Volume 1.28 - Table 4.23, Volume 1.31- Table 4.30, Volume 1.34 - Table 4.24]

TABLE 7. Adverse Events Occurring in Greater Than 5% of the Patients in the Treatment Protocol and/or in all Other GLIADEL Clinical Trials Summarized by Body System and COSTART Term[1]

Body system\COSTART Term	Number (Percentage) of Patients in Treatment (ND) (N=80)	Prior Studies of GLIADEL		
		Number (Percentage) of Patients in Uncontrolled Studies (N=83)	Number (Percentage) of Patients in Placebo-Controlled Studies (N=126)	Number (Percentage) of Patients in All Studies (N=209)
Body as a Whole\Fever	8 (10%)	9 (11%)	14 (11%)	23 (11%)
Body as a Whole\Infection	2 (4%)	5 (6%)	9 (7%)	14 (7%)
Cardiovascular System\Deep Thrombophlebitis	1 (2%)	5 (6%)	11 (9%)	16 (8%)
Cardiovascular System\Pulmonary Embolus	2 (4%)	4 (5%)	7 (6%)	11 (5%)
Digestive System\ Nausea	1 (2%)	6 (7%)	6 (5%)	12 (6%)
Digestive System\Nausea and Vomiting	0 (0%)	4 (4%)	9 (7%)	12 (6%)
Digestive System\Vomiting	3 (6%)	1 (1%)	4 (3%)	5 (3%)
Metabolic and Nutritional Disorder\Healing Abnormal	5 (10%)	11 (13%)	15 (12%)	26 (12%)
Nervous System\Aphasia	2 (4%)	5 (6%)	12 (10%)	17 (8%)
Nervous System\Brain Edema	1 (2%)	9 (11%)	5 (4%)	14 (7%)
Nervous System\Confusion	0 (0%)	4 (5%)	11 (9%)	15 (7%)
Nervous System\Convulsion	1 (2%)	22 (27%)	24 (19%)	46 (22%)
Nervous System\Hemiplegia	2 (4%)	7 (8%)	27 (21%)	34 (16%)
Nervous System\Headache	4 (8%)	12 (14%)	17 (13%)	29 (14%)
Nervous System\Intracranial Hypertension	1 (2%)	7 (8%)	4 (3%)	11 (5%)
Nervous System\Somnolence	1 (2%)	2 (2%)	15 (12%)	17 (8%)
Respiratory System\Pneumonia	0 (0%)	5 (6%)	7 (6%)	12 (6%)
Urogenital System\Urinary Tract Infection	0 (0%)	8 (10%)	23 (18%)	31(15%)

[1]The entries are the numbers (percentages) of patients with each given adverse event
[Cross References: Appendix III - Listing 3, NDA: Volume 1.38 - Theme 4 - Table 1]

TABLE 8. Severity of All Adverse Events, and Comparison with Prior GLIADEL Trials

Severity	Number (Percentage) of Adverse Events for patients in Treatment Protocol*	Number (Percentage) of Adverse Events in Prior GLIADEL Trials		
		GLIADEL Patients in Uncontrolled Studies	GLIADEL Patients in Placebo-Controlled Studies	All GLIADEL Patients in All Studies
Severe	12 (18.5%)	69 (23%)	81 (18%)	150 (20%)
Moderate	24 (36.9%)	134 (46%)	254 (56%)	388 (52%)
Mild	29 (44.6%)	91 (31%)	122 (27%)	213 (28%)
Total	65 (100%)	294 (100%)	457 (100%)	751 (100%)

* Only 65 adverse events are classified because severity has not yet been determined for one adverse event.

[Cross Reference: APPENDIX II - TABLE 5, APPENDIX III - LISTING 3; NDA: Volume 1.14 - Table 4.49, Volume 1.25 - Table 4.37, Volume 1.28 - Table 4.25, Volume 1.31- Table 4.32, Volume 1.34 - Table 4.26]

Four Month Safety Update

The Safety Update provides further information only on patients currently being accrued to the Treatment IND. A total of 64 patients with recurrent GBM have been entered (safety data on 50 of these patients had previously been reported in a prior correspondence dated May 7, 1996. The following serious A.E. represents the first case of brain herniation associated with Gliadel, although cerebral edema has previously been reported.

Patient had a brain herniation judged by the investigator as probably related to study medication two months after wafer implantation. The patient underwent craniotomy and placement of Gliadel wafers on 1/29/96. On 4/1/96, the patient developed brain herniation during which she became unresponsive with a dilated right pupil and was intubated, hyperventilated and given mannitol. The CT revealed a left parieto-occipital mass with significant edema and midline shift. She underwent decompressive craniotomy with temporal lobectomy. The number of wafers initially implanted, 7 3/4, were visualized and removed. Proprionobacterium was cultured from the brain tissue. One week later, the patient again developed edema and herniation, requiring an occipital lobectomy. The investigator felt that the initial cause of cerebral edema was wafer-related necrosis. There was no associated cerebritis or abscess. Final pathology revealed tissue necrosis primarily, with only minimal tumor at the center of the lesion. The investigator attributes the second case of cerebral edema to "leaky blood vessels".

The following are serious A.E.s that have occurred on the Treatment IND possibly related to study medication:

SERIOUS ADVERSE EVENT	RELATIONSHIP TO GLIADEL
Cerebral edema/abscess (no evidence of tumor; 3 1/2 wafer remnants removed	Probably related
Cerebral edema	Possible related
Necrosis (associated with tumor)	Possibly related
1 PE	Possibly related
Meningitis/abscess 21 days post-op	Possibly Related
Urticaria	Probably related to phenytoin
CSF rhinorrhea (2)	Possibly related (2)
Fluid collection in the tumor bed requiring surgery	Possibly related
Cyst/CSF leak requiring surgery/antibiotics/meningitis	Possibly related
Meningitis/Abscess	Possibly related
Seizure	Possibly related
Post-operative hemorrhage	Possibly related

In summary, there were 4/64 (6%) of patients reported to have meningitis or abscess. The Safety Update is consistent with the data reported in the NDA with the one exception of the case of herniation described above.

LABELING REVIEW

NDA 20-637 **Submission Date:** July 31, 1996

August 13, 1996

Drug Name, Dose and Formulation: Polifeprosan 20 with Carmustine, 7.7mg/m^2

Carmustine/ wafer

Brand Name: Gliadel® Wafer

Sponsor: Guilford Pharmaceuticals, Baltimore, Maryland 21224

Reviewer: N.A.M. Atiqur Rahman

Type of Submission: New Drug Application

The submission includes the revised package insert from the sponsor. The revised package insert has included human pharmacokinetic information in the Clinical Pharmacology section as suggested by the Biopharmaceutics reviewer in the original NDA review.

Note: Comment 1 provided below was composed after consultation with the Pharmacology reviewer, Dr. Lee-Ham and Medical officer, Dr. Martin.

COMMENTS

1. The **Clinical Pharmacology** section should be revised as follows.

2. In Therapeutic Interactions under Precautions the statement

Recommendation

The comments describing the proposed revisions for the package insert should be conveyed to the sponsor.

N.A.M. Atiqur Rahman, Ph. D. 08/16/96
Division of Pharmaceutical Evaluation I

Mehul U. Mehta, Ph.D. 8/19/96
Division of Pharmaceutical Evaluation I

cc:
NDA 20-637 (original)
HFD-150 /Division file, Pzimmerman
HFD-150/AMartin, Lee Ham
HFD-860 /HMalinowski, MMehta, ARahman
HFD-870 /Drug file (Clarence Bott, PKLN 13B 31)
HFD-870/Chron file (Clarence Bott, PKLN 13B 31)
HFD-870/Reviewer's file (Clarence Bott, PKLN 13B 31)

Pharmacologist Review

MEMORANDUM

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

DATE: March 20, 1996

FROM: Acting Director
Division of Oncology Drug Products, HFD-150

TO: Director, Division of Scientific
Investigations, HFD-340

SUBJECT: Request for Study Oriented Audits for NDA 20-637 for
Gliadel (polifeprosan 20 with carmustine) Wafer

We have identified the following studies as being pivotal to the approval of this application. We recommend that the indicated sites be audited.

Study 8802

Center 001:	Henry Brem, M.D. Johns Hopkins Hospital 725 North Wolfe Street Baltimore, MD 21205	35 patients
Center 016:	Robert Selker, M.D. Western Pennsylvania Hospital 4800 Friendship Avenue Pittsburgh, PA 15224	26 patients
Center 005:	Nicholas Vick, M.D. Evanston Hospital 2650 Ridge Avenue Evanston, IL 60201	20 patients
Center 003:	Keith Black, M.D. UCLA 10833 Le Conte Avenue Los Angeles, CA 90024-6901	16 patients

GliaDel
Centers For . IT — Given to G. Trout
Jan

Coversheet for Audit of Electronic Database NDA#: 20-637 Drug: GLIADEL

Center# 901 Investigator: BREM

INTRODUCTION:

After review of the protocol and of the case report form structure, the reviewing medical officer selected data elements most central to the approval of this drug. The selected data was extracted from the database using MS ACCESS 2.0.

Validation of these data to the source documents will determine that the electronic data which forms the basis of FDA and Company analyses, has been accurately transcribed.

In addition to the validation of the individual patient data printouts which are attached, the Oncology Division is also interested in an examination of the following points:

1. Is the list of all patients treated by the investigator with the study drugs the same as the following list of patients extracted from the database?

2. Can the Randomization process be verified for this site? If so, how was it verified?

3. Adverse Reaction Data validation: While verifying the validity of adverse reaction data is relatively important, especially on the control arm of studies, unreported adverse reactions are of more interest. Please make special effort to search for serious adverse events not included in attached printouts.

List of Patients for Center# 901 Investigator: BREM

Patient#	Patient ID	Date enrolled	Birthday	Treatment Arm
		3/27/90		1 : Gliadel
		4/25/89		2 : Placebo
		3/27/90		2 : Placebo
		6/13/89		1 : Gliadel
		5/1/90		2 : Placebo
		6/18/89		2 : Placebo
		5/9/90		1 : Gliadel
		6/20/89		1 : Gliadel
		5/22/90		2 : Placebo
		6/18/90		2 : Placebo
		7/19/89		2 : Placebo
		6/20/90		1 : Gliadel
		7/26/89		1 : Gliadel
		2/13/91		1 : Gliadel
		8/23/89		2 : Placebo
		8/23/89		2 : Placebo
		3/5/91		1 : Gliadel
		5/8/91		2 : Placebo
		8/30/89		2 : Placebo
		6/6/91		2 : Placebo
		9/13/89		1 : Gliadel
		6/24/91		2 : Placebo
		10/24/89		1 : Gliadel
		8/6/91		2 : Placebo
		11/12/89		2 : Placebo
		11/14/89		1 : Gliadel
		9/17/91		1 : Gliadel
		12/3/91		1 : Gliadel
		12/19/89		1 : Gliadel
		12/3/91		1 : Gliadel
		12/20/89		2 : Placebo

Coversheet for Audit of Electronic Database **NDA#: 20-637 Drug: GLIADEL**

Center# 001 Investigator: BREM

12/22/89	2 Placebo
1/30/90	1 Gliadel
2/28/90	2 Placebo
3/20/90	1 Gliadel

If you have any questions about this data printout, please contact Grant Williams, M.D., Division of Oncology Drug Products (301-594-5779).

Coversheet for Audit of Electronic Database

NDA#: 20-637 Drug: GLIADEL

Center# 003 Investigator: BLACK

INTRODUCTION:

After review of the protocol and of the case report form structure, the reviewing medical officer selected data elements most central to the approval of this drug. The selected data was extracted from the database using MS ACCESS 2.0.

Validation of these data to the source documents will determine that the electronic data which forms the basis of FDA and Company analyses, has been accurately transcribed.

In addition to the validation of the individual patient data printouts which are attached, the Oncology Division is also interested in an examination of the following points:

1. Is the list of all patients treated by the investigator with the study drugs the same as the following list of patients extracted from the database?

2. Can the Randomization process be verified for this site? If so, how was it verified?

3. Adverse Reaction Data validation: While verifying the validity of adverse reaction data is relatively important, especially on the control arm of studies, unreported adverse reactions are of more interest. Please make special effort to search for serious adverse events not included in attached printouts.

List of Patients for Center# 003 Investigator: BLACK

Patient#	Patient ID	Date enrolled	Birthday	Treatment Arm
		9/17/89		1 Gliadel
		12/21/89		1 Gliadel
		3/4/90		2 Placebo
		3/16/90		2 Placebo
		7/17/90		1 Gliadel
		8/19/90		2 Placebo
		9/10/90		2 Placebo
		9/10/90		1 Gliadel
		11/11/90		2 Placebo
		12/11/90		2 Placebo
		3/27/91		1 Gliadel
		4/29/91		1 Gliadel
		5/19/91		1 Gliadel
		6/2/91		1 Gliadel
		6/2/91		2 Placebo
		11/17/91		2 Placebo

Coversheet for Audit of Electronic Database NDA#: 20-637 Drug: GLIADEL

Center# 003 Investigator: BLACK

If you have any questions about this data printout, please contact Grant Williams, M.D., Division of Oncology Drug Products (301-594-5779).

Coversheet for Audit of Electronic Database NDA#: 20-637 Drug: GLIADEL

Center# 005 Investigator: VICK

INTRODUCTION:

After review of the protocol and of the case report form structure, the reviewing medical officer selected data elements most central to the approval of this drug. The selected data was extracted from the database using MS ACCESS 2.0.

Validation of these data to the source documents will determine that the electronic data which forms the basis of FDA and Company analyses, has been accurately transcribed.

In addition to the validation of the individual patient data printouts which are attached, the Oncology Division is also interested in an examination of the following points:

1. Is the list of all patients treated by the investigator with the study drugs the same as the following list of patients extracted from the database?

2. Can the Randomization process be verified for this site? If so, how was it verified?

3. Adverse Reaction Data validation: While verifying the validity of adverse reaction data is relatively important, especially on the control arm of studies, unreported adverse reactions are of more interest. Please make special effort to search for serious adverse events not included in attached printouts.

List of Patients for Center# 005 Investigator: VICK

Patient#	Patient ID	Date enrolled	Birthday	Treatment Arm
		4/12/89		1 Gliadel
		7/5/89		2 Placebo
		11/14/89		2 Placebo
		11/20/89		1 Gliadel
		12/12/89		1 Gliadel
		3/28/90		1 Gliadel
		8/26/90		2 Placebo
		9/5/90		2 Placebo
		10/22/90		1 Gliadel
		1/13/91		2 Placebo
		2/1/91		2 Placebo
		3/10/91		1 Gliadel
		3/10/91		1 Gliadel
		4/29/91		2 Placebo
		6/6/91		1 Gliadel
		6/12/91		2 Placebo
		6/27/91		1 Gliadel
		7/21/91		2 Placebo
		8/19/91		2 Placebo
		8/27/91		1 Gliadel

Coversheet for Audit of Electronic Database **NDA#: 20-637** **Drug: GLIADEL**

Center# 005 **Investigator: VICK**

If you have any questions about this data printout, please contact Grant Williams, M.D., Division of Oncology Drug Products (301-594-5779).

Coversheet for Audit of Electronic Database NDA#: 20 637 Drug: GLIADEL

Center# 016 Investigator: SELKER

INTRODUCTION:

After review of the protocol and of the case report form structure, the reviewing medical officer selected data elements *most central to the approval of this drug.* The selected data was extracted from the database using MS ACCESS 2.0.

Validation of these data to the source documents will determine that the electronic data which forms the basis of FDA and Company analyses, has been accurately transcribed.

In addition to the validation of the individual patient data printouts which are attached, the Oncology Division is also interested in an examination of the following points:

1. Is the list of all patients treated by the investigator with the study drugs the same as the following list of patients extracted from the database?

2. Can the Randomization process be verified for this site? If so, how was it verified?

3. Adverse Reaction Data validation: While verifying the validity of adverse reaction data is relatively important, especially on the control arm of studies, unreported adverse reactions are of more interest. Please make special effort to search for serious adverse events not included in attached printouts.

List of Patients for Center# 016 Investigator: SELKER

Patient#	Patient ID	Date enrolled	Birthday	Treatment Arm
		2/28/89		2 : Placebo
		3/21/89		1 : Gliadel
		3/27/89		2 : Placebo
		3/28/89		1 : Gliadel
		4/27/89		2 : Placebo
		5/23/89		1 : Gliadel
		6/5/89		1 : Gliadel
		8/31/89		2 : Placebo
		9/15/89		2 : Placebo
		10/12/89		1 : Gliadel
		11/12/89		1 : Gliadel
		11/15/89		2 : Placebo
		1/19/90		2 : Placebo
		1/22/90		1 : Gliadel
		2/21/90		1 : Gliadel
		7/11/90		2 : Placebo
		9/16/90		1 : Gliadel
		11/25/90		2 : Placebo
		1/6/91		2 : Placebo
		3/5/91		1 : Gliadel
		5/9/91		2 : Placebo
		6/20/91		1 : Gliadel
		8/19/91		2 : Placebo
		9/16/91		1 : Gliadel
		9/30/91		2 : Placebo
		1/6/92		1 : Gliadel

Coversheet for Audit of Electronic Database NDA#: 20-637 Drug: GLIADEL

Center# 016 Investigator: SELKER

If you have any questions about this data printout, please contact Grant Williams, M.D., Division of Oncology Drug Products (301-594-5779).

JUL 22 1996

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-637 **Submission Date:** February 06, 1996
February 20, 1996
March 12, 1996

Drug Name, Dose and Formulation: Polifeprosan 20 with Carmustine, 7.7mg/m^2
Carmustine/ wafer

Brand Name: Gliadel® Wafer

Sponsor: Guilford Pharmaceuticals, Baltimore, Maryland 21224

Reviewer: N.A.M. Atiqur Rahman

Type of Submission: New Drug Application

SYNOPSIS

Carmustine is currently approved for palliative therapy as a single agent or with other chemotherapeutic agents in the treatment of brain tumors, multiple myeloma, Hodgkin's Disease, and Non-Hodgkin's lymphomas. Gliadel is a sterile wafer containing 192.3 mg of a biodegradable polyanhydride copolymer (polifeprosan 20) and 7.7mg of carmustine. Gliadel is indicated for use as an adjunct to surgery to prolong survival in patients with malignant glioma. Gliadel received orphan drug designation for localized placement in the brain in the treatment of recurrent malignant glioma. In the NDA submission, the sponsor have requested a waiver of the requirements for human pharmacokinetics and bioavailability studies.

Waiver Justification

The sponsor have requested that a waiver be granted of the requirements for information under Section 6 (21CFR 314.50(d)(3)), Human Pharmacokinetics and Bioavailability, for NDA 20-637.

Justifications for waiver request are as follows:

1. Gliadel wafers are implanted into the brain cavity resulting from surgical resection of a malignant glioma.

2. Because Gliadel is designed to release BCNU at the site of the tumor resection, and because there is no direct contact between the BCNU release from the wafers and the vascular compartments, the expected systemic exposure and the associated systemic toxicities of the chemotherapeutic agent should be low.

3. No measurable BCNU detected in blood samples from a subset of patients studied under I 8701 (data not provided to the Agency).

4. Maximum dose of Gliadel, 8 wafers, 61.6 mg of BCNU, is almost 6 times less than the highest recommended single intravenous dose, 200 mg/m^2, 346 mg of BCNU.

5. Possible toxicity associated with the local exposure to BCNU is accounted for in the safety assessment of the NDA.

In-vitro Release Test

In the amendment submission, dated March 12, 1996, the sponsor has provided information regarding in-vitro release testing of Gliadel Wafers using a flow-through system. Report of in-vitro release testing results obtained for lots (original manufacturer of wafers) and Guilford lots tested using Guilford system is submitted (appendix). In the report, two Guilford lots, 5C002 and 5C003, have lower percent BCNU release at 36 hour time point compared to the remaining six lots tested. The performance of these two lots were not taken into consideration in setting the interim In-vitro Release Test specifications for the drug product presented below. The sponsor should submit the results of the in-vitro release test of three consecutive production lots of Gliadel using the interim test specifications. After evaluation of the data generated from the three production lots, a proper in vitro release test specifications will be set for the drug product.

In-vitro Release Test Specifications (Interim):

Methodology :	Flow-Through System Guilford Method No. AC-2029
Units:	6 individual units

Percent BCNU released:	Time(h)	% released (Range)

6

Labeling

There is no information regarding the pharmacokinetics or brain exposure to carmustine after Gliadel implant in humans in the package insert.

Comments

1. The sponsor should conduct in vitro release test of three consecutive production lots following the interim test specifications set below, and submit the data to the Agency to set proper in vitro release test specifications.

In-vitro Release Test Specifications (Interim):

Methodology :	Flow-Through System Guilford Method No. AC-2029
Units:	6 individual units

Percent BCNU released: Time(h) % released (Range)

2. The sponsor should provide information on the pharmacokinetics of carmustine after intravenous administration in the package insert.

3. The sponsor stated CFR code for waiver 21 CFR314.50(d)(3) is incorrect. The section of the code describes the content and format of an application. A waiver request should have followed procedure described in 21 CFR 320.22.

Recommendation

A biowaiver for the NDA 20-637 is justified based on the nature of the site of application for the drug product and on the available knowledge about the systemic exposure to the active drug carmustine. The comments should be forwarded to the sponsor.

N.A.M. Atiqur Rahman, Ph. D. 07/18/96
Division of Pharmaceutical Evaluation I

Mehul U. Mehta, Ph.D. 7/22/96
Division of Pharmaceutical Evaluation I

cc:
NDA 20-637 (original)
HFD-150/ Division File

HFD-150/PZimmerman/[illegible]
HFD-150/AMartin
HFD-850/LLesko
HFD-860/ HMalinowski, MMehta, ARahman
HFD-870/ Drug File (Clarence Bott, PKLN RM. 13B-31)
HFD-870/Chron File (Clarence Bott, PKLN RM. 13B-31)
HFD-870/Reviewer's File (Clarence Bott, PKLN RM. 13B-31)
HFD-205/FOI
HFD-340/Vishwanathan

Division of Oncology Drug Products
Review of Pharmacology and Toxicology Data
Labeling Review #2

NDA: 20-637

Date of Submission: February 7, 1996
Received by Reviewer: February 13, 1996
Amendment Dates: May 17, June 27, July 29, July 30, August 13, & August 26, 1996

Information to be conveyed to sponsor: Yes(x), No( )

Reviewer: Doo Y. Lee Ham, Ph. D.

Date Labeling Review Completed: August 5, 1996

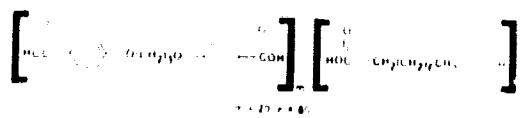
Applicant: Guilford Pharmaceuticals Inc.
Baltimore, MD 21224

Drug Name: Primary: Gliadel® Wafer
Other Names: Polifeprosan 20 with carmustine; NPC 702

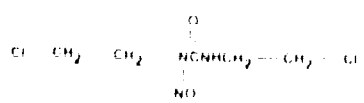
Chemical Name: Poly[bis(p-carboxyphenoxy)propane:sebacic acid 20:80] with 1,3-bis(2-chloroethyl)-1-nitrosourea

Structure:

- The structural formula for polifeprosan 20 is



- The structural formula for carmustine is



Molecular Formula: $C_5H_9Cl_2N_3O_2$

Molecular Weight: 214.06

Related IND & NDA: and NDA 17-422 (BiCNU, Carmustine) by Bristol

Class: Antineoplastic agent

Indication: Gliadel is indicated for use as an adjunct to surgery to prolong survival in patients with malignant glioma.

Clinical Formulation: Each Gliadel wafer consists of a copolymer of polycarboxyphenoxypropane (PCPP) and sebacic acid (SA) with 7.7 mg (3.85% by weight) carmustine (BCNU) incorporated into polymer matrix (PCPP:SA 20:80).

Route of Administration: Brain implant

Labeling Comments:

Labeling conforms to the format specified under CFR21, Part 201, Subpart B dated April 1, 1994. The proposed labeling accurately describes the preclinical observations for the most part. However, the following revisions are requested:

Recommendation:

This NDA is approvable from the pharmacologic toxicologic aspect of the application pending the labeling will be revised as requested.

Doo Y. Lee Ham, Ph. D.

cc: Orig. NDA 20-637
HFD-150/Division File
/LeeHam
/DeGeoerge
/Martin
/CSO
DYLH/WP
Revised on 8/11/96
Revised on 8/15/96
Revised on 8/27/96

8/28/96

Division of Oncology Drug Products
Review of Pharmacology and Toxicology Data
Original Review

NDA: 20-637

Date of Submission: February 7, 1996
Received by Reviewer: February 13, 1996
Amendment Dates: June 3, & July 1, 1996

Information to be conveyed to sponsor: Yes(x), No( )

Reviewer: Doo Y. Lee Ham, Ph. D.

Date Review Completed: June 10, 1996

Applicant: Guilford Pharmaceuticals Inc.
Baltimore, MD 21224

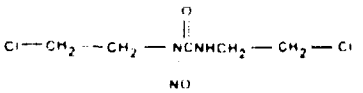
Drug Name: Primary: Gliadel[R] Wafer
Other Names: Polifeprosan 20 with carmustine; NPC 7)2

Chemical Name: Poly[bis(p-carboxyphenoxy)propane:sebacic acid 20:80] with 1,3-bis(2-chloroethyl)-1-nitrosourea

Structure:

- The structural formula for polifeprosan 20 is

- The structural formula for carmustine is



Molecular Formula: $C_5H_9Cl_2N_3O_2$

Molecular Weight: 214.06

Related IND & NDA: and NDA 17-422 (BiCNU, Carmustine) by Bristol

Class: Antineoplastic agent

Indication: Gliadel is indicated for use as an adjunct to surgery to prolong survival in patients with malignant glioma.

Clinical Formulation: Each Gliadel wafer consists of a copolymer of polycarboxyphenoxypropane (PCPP) and sebacic acid (SA) with 7.7 mg (3.85% by weight) carmustine (BCNU) incorporated into polymer matrix (PCPP:SA 20:80).

Route of Administration: Brain implant

Previous Reviews, Dates and Reviewers:

Original Review	7/27/87	AWCoulter
Review #2	3/25/96	DYLeeHam
Biopharm Review	2/9/96	PZannikos

Studies Reviewed Previous Submissions:

Biocompatibility Studies:

Biocompatibility of NPC 702 with rat brain, protocol #86-001
Biocompatibility and release kinetics of NPC 702 in rabbit brain, protocol #86-002
Biocompatibility of NPC 702 with the monkey brain, protocol #86-003
Biocompatibility of NPC 702 subcutaneously in the rat, protocol #86-004
Biocompatibility and efficacy of NPC 702 in the rat brain, protocol #86-005

Pharmacokinetics and Drug Metabolism in Animals:

Toxicology:

28 week brain implantation study in rats
Chronic brain implantation study in monkeys

Studies Reviewed with this Submission:

I. Pharmacology:
   - A. A Safety Tolerance Study (28 day) in Rat
   - B. 26 Week Efficacy Study
   - C. Tamargo, RJ, Myseros, JS, Epstein, JI et al (1993) Interstitial Chemotherapy of the 9L Gliosarcoma: Controlled Release Polymers for Drug Delivery in the Brain. Cancer Res 53: 329-333

II. Pharmacokinetics: rat and rabbit

III. Toxicology:
   - A. Subchronic Toxicity Studies:
     One month brain implantation study in rabbits
   - B. Chronic Toxicity Studies:
     10-month brain implantation study in rabbits
     10 week brain implantation study in monkeys
     26 week brain implantation study in monkeys

IV. Special Toxicity Studies:
   In vitro BCNU toxicity

V. Mutagenicity: Ames assay

* Portions of this review were excerpted directly from the sponsor's submission

Overall Summary and Evaluation:

Carmustine (BCNU), chloroethylnitrosourea, is commonly used for the treatment of brain tumors for its ability to cross the blood-brain barrier. In order to minimize systemic toxicities (myelosuppression, hepatic, renal and pulmonary) and maximize local drug concentration within brain tumors, interstitial BCNU therapy with implantable biodegradable polymer, a Gliadel wafer, is being developed for the new treatment for malignant gliomas by Guilford Pharmaceuticals Inc.

Gliadel (BCNU-loaded polymer) consists of a biodegradable polyanhydride polymer incorporating BCNU into the polymer matrix [carboxyphenoxypropane (CPP) copolymerized with sebacic acid (SA) 20:80 molar ratio]. The hydrophobic matrix protects BCNU from hydrolysis. Preclinical results have demonstrated that Gliadel has been shown to increase the therapeutic efficacy of the BCNU by producing high local tissue concentrations directly at the tumor site over extended periods of time. Drug is released over a two to three weeks period primarily by polymer degradation or wafer erosion. A number of factors influence drug release kinetics including CPP:SA content and the loading dose of BCNU. Radiolabeled BCNU (Gliadel 1-2.5%), PCPP, and SA biodistribution studies in rat and rabbit indicated >80% of the radiolabeled BCNU were released from the wafer within 7 days of implantation, and >60% of the radiolabeled polymer components is released from the wafer by day 21 post-implantation.

In vivo efficacy studies of Gliadel were performed using escalating doses of BCNU in rat brain tumor model. Fischer 344 rats bearing ic 9L gliosarcoma were surgically implanted with different concentrations of BCNU in Gliadel ranging 10-40% (correspond to 1.15-4.6 mg BCNU). Gliadel 30% (containing 3.45 mg BCNU) was determined to be effective in increasing the mean survival of 13.5 days for untreated tumor to 122.5 days for treated rats. The efficacy was observed as a dose-related increase in mean survival time when compared to the untreated tumor bearing rats.

Pharmacokinetic studies were performed with radiolabeled Gliadel (^{14}C- or ^{3}H-) in rats and in rabbits to determine the in vivo release of ^{14}C-BCNU from a PCPP:SA 20:80 wafer. In SD rats implanted with Gliadel 3.85% (0.36 mg BCNU), brain tissue analyses indicate only trace amounts of BCNU present on days 1, 5 and 10 after implantation. The wafer contained about 50% of the initial BCNU concentration after 24 hrs and less than 1% of BCNU after 5 or 10 days of implantation. The local concentration and distribution of BCNU were evaluated following implantation of Gliadel doses ranging from 2.5% to 10% (300 to 1200 ug BCNU) or direct ic injection of ^{3}H-BCNU into rabbit brain. The local delivery of BCNU to brain tissue with Gliadel wafer resulted in a more sustained high local concentration of BCNU than direct ic injection.

Subchronic and chronic toxicity studies were conducted by brain implantation to evaluate biocompatibility of Gliadel wafer or PCPP:SA 20:80 (copolymer, or blank) polymer wafer in rat, rabbit, and monkey brain. In rat studies, the ic implantation of PCPP:SA 20:80 wafers and Gliadel wafers 4, 8, 12, 20 or 32%(containing 0.44, 0.88, 1.32, 2.2, or 3.52 mg BCNU) have been evaluated. Two of eight rats treated with Gliadel wafers 32% died before day 200 and all other animals survived for 200 days after implantation. Rats in the 32% Gliadel group gained less weight than did control animals. Mean weight gain in other groups were comparable to those of the blank wafer group. Mild gliotic reactions were observed around surgical sites of both implants and no toxicity was reported from other organs of the rat.

In a one month subchronic study with Albino rabbits, PCPP:SA 20:80 wafer and Gliadel wafer 3.85% (0.46 mg BCNU) were implanted in the brain ventricle. Both wafers (Gliadel 3.85%, blank)

produced no deaths, clinical or neurological/behavioral signs. Both implants resulted in a region of local necrosis, which was limited to the implantation sites, and increased with Gliadel wafer. The necrosis was not present 28 days after implantation.

The biocompatibility of the two polymer components was evaluated in vivo. PCPP:SA was evaluated for local tissue response for six weeks following corneal implantation in the NZW rabbit and for six months following subcutaneous injection in the SD rat. Overall, the results indicated that PCPP:SA is biocompatible.

Studies were performed in two species (rabbit, monkey) to evaluate whether the brain implantation of Gliadel or PCPP:SA 20:80 without BCNU, and subsequent external beam brain irradiation, resulted in more toxicity than is observed with Gliadel, the polymer alone, or irradiation alone. In a ten-month rabbit study, after a surgical recovery of 5 days after wafer implantation (Gliadel 4%, or blank wafer) into NZW rabbits, half the rabbits received radiation treatment of 97.6 centigrays/minutes (~3820 rads). At one month, implant- and radiation-related brain necrosis with mononuclear cell infiltrate was observed. In the non-radiated groups at ten months, the effects of Gliadel 4% or PCPP:SA 20:80 were comparable to the sham control. In the radiated groups, brain necrosis was still present in all of the treatment groups with comparable incidence and severity. In the ten week cynomolgus monkey study, monkeys received 5 daily/week for 6 weeks conventional external beam radiation treatment (the total dose was 6000 cGy). In the 26 week study, two monkeys were irradiated for a period of 42 days. No meaningful toxicological, neurological or histological findings were observed in either study except for localized brain necrosis around the implanted wafer. Radiation treatment in the monkeys implanted Gliadel 3.85% and sacrificed at 10 weeks did not produce greater severity of brain necrosis than was observed in the non-radiated monkeys implanted with Gliadel 1.9% wafers in the ten month study. The studies indicate brain radiation treatment of Gliadel implanted monkeys did not result in a greater toxicity than was expected with radiation treatment alone.

The mutation potential of copolymer alone, PCPP:SA 45:55, was tested on S. typhimurium using 8-azaguanine resistance as a genetic marker. At 1 mg/ml concentration with or without metabolic activation, the degradation products of the polymer, PCPP:SA 45:55 were non-mutagenic. However, BCNU is known to be teratogenic and genotoxic, thus Gliadel also is considered genotoxic and teratogenic.

Doo Y. Lee Ham, Ph. D.

cc: Orig NDA 20637
HFD-150/Division File
/LeeHam
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Revised on 7/9/96
Revised on 7/22/96
Revised on 7/24/96

7/27/96

A. 28 Day Intracerebral Range Finding Study (Safety Tolerance Study) and Efficacy Study of Gliadel in Rat, NOVA Study Report 86-005:

A 28 day range finding study was conducted with intracerebral Gliadel in normal rats to determine the highest tolerated dose of BCNU. A second study was performed to determine the efficacy of Gliadel with escalating doses of BCNU in tumor bearing rats.

1.. 28 Day Intracerebral Range Finding Study:

Fischer 344 normal male rats (n=5 rats/group) were implanted with intracerebral (ic) Gliadel 10, 20, 30, and 40% (correspond to 1.15, 2.3, 3.45, 4.60 mg BCNU), or PCPP:SA 20:80 (control) as in the Table 6. The implanted wafer was placed surgically in the dorsum of the brainstem between the superior colliculus and the posterior thalamus. Animals were observed daily for survival and body weight changes for 14 days.

Table 6: Gliadel 10, 20, 30 and 40% and PCPP:SA 20:80: 28 Day Intracerebral Dose range Finding Study in Rats

Species Strain	Group Description (BCNU)	Results		
		Initial Wt loss	Initial Wt Recovery	Survival
Fischer rats 5 males/group	0% (PCPP:SA)			
	10%	3%	7-10 days	4/5*
	20%	8%	12-14 days	4/5
	30%	15%	14-16 days	4/5
	40%	20%	14 days(1/3 rats)	3/5

* One death in each group occurred due to water deprivation.

Results:

One of 5 rats each treatment group died due to dehydration in each cage (the time of these deaths are not given). No treatment-related deaths were observed. One rat death in the 40% BCNU occurred during the study (no date) and appeared to be treatment-related. Body weight loss was dose-related across all dose groups. Moderate decreases in body weights (~ 15- 20%) were observed at 30% and 40% BCNU treated groups compared to control group. Based on these results, Gliadel 30% BCNU was selected as the highest tolerated dose in a follow-up study.

2. 150 Day Efficacy Study of Gliadel 30% in 9L Gliosarcoma bearing rats:

A second study (150 Day) was conducted to evaluate the efficacy of intracerebral Gliadel 30% for the treatment of 9L gliosarcoma tumor in adult male Fischer 344 rats.

Sixty rats (n=10 rats/group) were divided into 6 groups (4 treatment and 2 controls) as shown in the Table 7. NineL gliosarcoma tumor cells were implanted intracerebrally. On the 4th day after tumor implantation, rats underwent implantation of Gliadel 30% (3.45 mg BCNU). Animals were observed for survival, clinical signs/behavioral signs, and histopathologic changes for 150 days.

Table 7: Survival Study of Gliadel 30% in 9L gliosarcoma bearing Fischer 344 male rats for 150 days

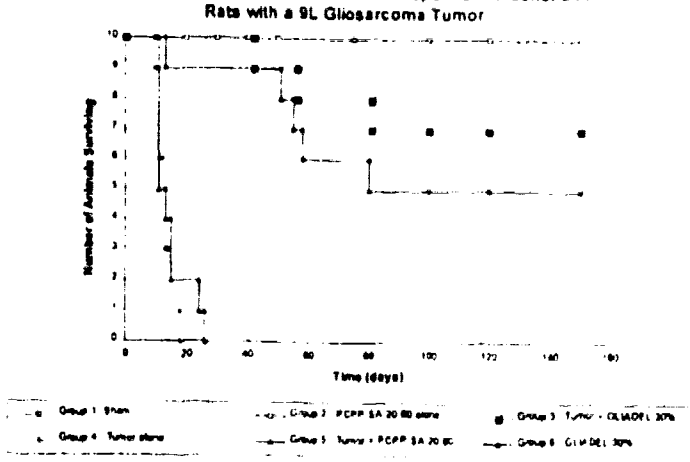
Species Strain	Treatment Groups	Results Mean Survival	Histopathology
Rat, Fischer 344 10 males/group	1) Sham control 2) PCPP:SA 20:80 3) Tumor + Gliadel 30%* 4) Tumor alone 5) Tumor + PCPP:SA 20:80* 6) Gliadel 30%	1) 150 days 2) 150 days 3) 122.9 days 4) 13.5 days 5) 14.8 days 6) 100.7 days	In Gliadel 30% groups, 50% of the hepatic specimens showed single or multiple areas of coagulation necrosis with/ without mixed cell infiltrates and/or microabscess formation

* Tumor and Gliadel implantation were performed during the same surgery

Results:

Mean survival time increased about 10-fold in the Gliadel 30% treated group (122.9 days) compared to the untreated tumor alone (13.5 days) and tumor + polymer (14.8 days). Mean survival of non-tumor bearing rats was decreased to 100.7 days (about 22%) by Gliadel 30% alone probably due to BCNU systemic toxicity. Histopathologic findings in the Gliadel 30% treatment groups induced in ~50% of animals with single or multiple foci of coagulation necrosis in the liver (likely due to BCNU toxicity).

FIGURE 2: GLIADEL 30%: Survival Response in Fischer 344 Rats with a 9L Gliosarcoma Tumor



B. 28 Week Efficacy Study of Gliadel in Rat:

Forty-eight adult male Fischer 344 rats were implanted with a 9L gliosarcoma in a dorsal brainstem cortical defect. On the 5th day following tumor implantation, the rats were randomized into six groups of 8 rats/group and implanted with PCPP:SA 20:80, or Gliadel 4, 8, 12, 20, or 32% (correspond to 0.44, 0.88, 1.32, 2.2, 3.52 mg BCNU). These wafers weighed approximately 10-12 mg. Animals were observed for survival, clinical/behavioral signs, and histopathologic evaluation for 200 days.

Table 9: Comparison of PCPP:SA 20:80 and different concentrations of Gliadel in 9L gliosarcoma bearing male rats for 200 days

Species/Strain # of rat	Treatment Groups	Results	
		Efficacy	Toxicity
Rat Fischer 344 8 males/group	1) PCPP:SA 20:80 2) Gliadel 4% 3) Gliadel 8% 4) Gliadel 12% 5) Gliadel 20% 6) Gliadel 32% Groups 1-6 were duplicated. One set had 9L gliosarcoma cells implanted with treatment following 5 days after tumor implant (efficacy). The other set was given treatment only (toxicity)	Gliadel groups had extended survival. In Gliadel 20 and 32% groups, survival was increased as compared to lower dose.	Gliadel 32% was systemically toxic causing decreased weight gain

Results:

Two rats implanted with Gliadel 32% died on days 82 and 97. Prior to death, a significant weight loss (69 and 59%, respectively) was observed in these rats. A dose-related decrease in mean body weight gain was seen in the Gliadel groups treated at doses >20% compared to control animals with blank polymers.

A dose-related increase in mean survival time was noted in treated animals when compared to the non-treated tumor-bearing rat group. Gliadel 4, 8, or 12% BCNU was effective in increasing survival (no survival was observed beyond 20 days in untreated rats) in 10- 25% of the animals. With Gliadel 20 or 32%, survival was extended to 200 days for 50-60% of the rats as shown in the Figure 4 below.

At autopsy, gliosis was observed in all treated rats and was most pronounced around the surgical sites of rats treated with 32% BCNU loaded polymers. Other significant pathologic findings in the treated and control animals were age-related myocardial and renal changes. No other drug-related toxicities were seen in these animals.

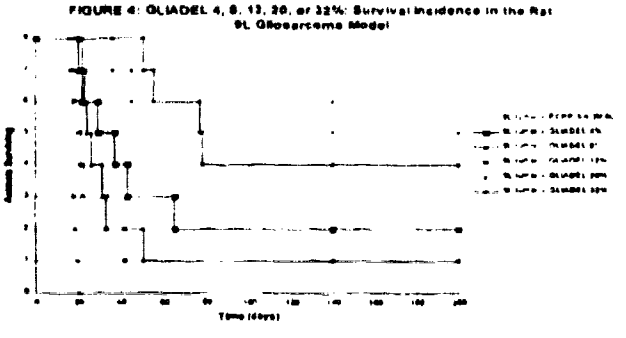


FIGURE 4: GLIADEL 4, 8, 12, 20, or 32%: Survival Incidence in the Rat 9L Gliosarcoma Model

These findings indicate that higher doses of BCNU (20-32%) may be more effective in the treatment of the 9L gliosarcoma in a rat model than doses of 12% or less

C. Tamargo, RJ et al (1993) Interstitial Chemotherapy of the 9L Gliosarcoma: Controlled Release Polymers for Drug Delivery in the Brain. Cancer Res. 53: 329-333.

Ninety-six adult male Fischer rats underwent a craniectomy. Sixty rats were implanted with a 9L gliosarcoma tumor in the left parietal area. The remaining 36 rats were assigned to one of three experimental groups to assess the toxicity of the i.c. and systemic i.p. BCNU. Four days after surgery, rats were randomized into one of eight experimental groups (Table 2) for the treatment and reoperated for the insertion of either 30% (BCNU 3.54 mg) BCNU-EVAc discs (3 mm in diameter, weighed 11.5 mg) or similar EVAc discs without BCNU through the craniotomy defect into the cerebral cortex. A systemic i.p. injection of BCNU (14 mg) was administered within 5 minutes to the 9L/i.p. BCNU and i.p. BCNU and the same volume of the vehicle was administered to the other six groups. The wound was reclosed with surgical clips and animals were returned to the cages. Animals were observed twice daily during the first few weeks and daily thereafter for 125 days for survival, behavioral changes and pathologic changes.

Table 2 *Study design: intracranial experimental groups*

Each group had 12 rats. Survival values are presented as mean ± SEM. Two rats that died perioperatively were excluded from the study (one from an i.c. hemorrhage and the other from an i.c. abscess).

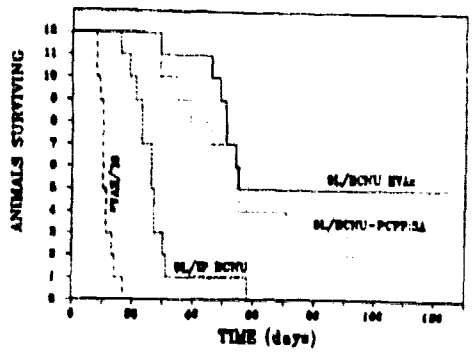
Group label	9L* glioma	Intracranial polymer implant	i.p. injection	Survival (days)
9L/I.VAc	Yes	Empty EVAc	Vehicle	10.9 ± 0.8
9L/PCPP:SA	Yes	Empty PCPP:SA	Vehicle	11.6 ± 0.7
9L/i.p. BCNU	Yes	Empty EVAc	BCNU	27.3 ± 3.1
9L/BCNU-EVAc	Yes	BCNU in EVAc	Vehicle	80.0 ± 11.6
9L/BCNU-PCPP:SA	Yes	BCNU in PCPP:SA	Vehicle	62.3 ± 9.9
Control	No	Empty EVAc	Vehicle	(125)
i.p. BCNU	No	Empty EVAc	BCNU	63.3 ± 8.0
i.c. BCNU	No	BCNU in EVAc	Vehicle	92.7 ± 8.9

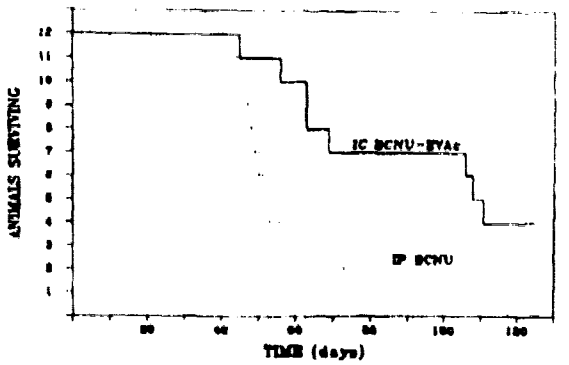
* 9L, i.c. implantation of the 9L gliosarcoma at first operation; empty EVAc, i.c. implantation at second operation of an 11.5-mg EVAc disc, vehicle, i.p. injection at second operation of 0.1 ml of ethyl alcohol and 0.1 ml of normal saline; empty PCPP:SA, i.c. implantation at second operation of an 11.5-mg PCPP:SA disc; BCNU, i.p. injection at second operation of 3.5 mg of BCNU in 0.1 ml of ethyl alcohol and 0.1 ml of normal saline; BCNU in EVAc, i.c. implantation at second operation of an 11.5-mg EVAc disc containing 3.5 mg of BCNU (30% loading of BCNU); BCNU in PCPP:SA, i.c. implantation at second operation of an 11.5-mg PCPP:SA disc containing 3.5 mg of BCNU.

Results:

The i.c. delivery of Gliadel 30% via EVAc (9L/BCNU-EVAc group) or PCPP:SA polymer (9L/BCNU-PCPP:SA) significantly increased mean survival (about 5.4- and 7.3 fold; $p < 0.05$) in rats bearing the 9L gliosarcoma compared to the systemic i.p. injection of BCNU (9L/i.p. BCNU; 2.3-fold). Five of 12 rats (42%) in the 9L/BCNU-EVAc group and two of 12 rats (17%) in the 9L/BCNU-PCPP:SA group survived to the end of the experiment (125 days); no viable tumor was found in any of these long-term survivors (Figure 2). All the rats in the control group without BCNU survived to the end of the experiment at 125 days. By contrast, 10/12 rats died prematurely after the i.p. BCNU group and 8/12 died after the i.c. BCNU group. The mean survival of the i.c. BCNU group was higher than that of the i.p. BCNU group (Figure 3), but the difference was not significant.

Histopathological changes in all rats treated with BCNU showed pulmonary changes (e.g., interstitial pneumonitis, fibrosis) and hepatic changes (small scattered micro abscesses). These lesions were not detected in untreated control animals.





Summary of Pharmacology:

The efficacy of Gliadel depends on delivery of BCNU to the tumor for its cytotoxicity. Efficacy studies of Gliadel were performed using escalating doses of BCNU in a rat brain tumor models.

In a 150 day study, 9L gliosarcoma bearing male rats were implanted with i.c. Gliadel 30% containing 3.45 mg BCNU. Mean survival of rats treated with Gliadel 30% wafer increased (8-fold and 9-fold) compared to untreated tumor (13.5 days) and untreated tumor with polymers (14.8 days). In this group about 50% of survivors had single or multiple foci of coagulation necrosis in the liver.

In a 125 day study, the i.c. implant of Gliadel 30% via EVAc (9L/BCNU-EVAc group) or PCPP:SA polymers (9L/BCNU-PCPP:SA group) significantly increased the mean survival time (5-fold and 7-fold) compared to i.p.BCNU (9L/i.p. BCNU group) or i.c. BCNU (BCNU/EVAc). All animals treated with i.p. or i.c. BCNU exhibited multiple scattered areas of coagulation necrosis in the liver.

In a 28 week study, 9L gliosarcoma bearing rats were implanted Gliadel with escalating doses of BCNU. A dose-related increase in mean survival time was noted in Gliadel 4, 8 and 12%. With Gliadel 20 or 30%, a significant increase in survival was observed for 50-60% of the rats to 200 days. However, in contrast to the 125 day study, there were no tumor-free survivors reported.

II. PHARMACOKINETICS (Vol. 1.10-12

A. In Vitro Dissolution and in Vivo Biodegradation

In Vitro Dissolution:

Method: Three different molecular weights (48,000, 72,000, and 110,000 Da) of the PCPP:SA 20:80 polymers were tested. The release characteristics of the wafers were evaluated in a 0.1 M PBS at 37° C. Sets of 3 wafers each were submerged in aqueous environment with constant shaking at 110 rpm. Wafer sets were removed from the PBS at 2, 4, 8 hr and 1, 2, 3, 5, and 7 days. The water soluble sebacic acid and carboxyphenoxypropane levels in PBS were determined by HPLC.

Results: During the initial 8 hrs, <5% weight loss occurred. During the next 7 days, almost 80% of the original weight had been lost. The exponential decay in wafer mass suggests a pseudo-first-order erosion kinetics. Even though wafer molecular weight (MW) varied widely, wafer mass loss was independent of its initial MW. During the initial 10 hrs of incubation, the wafer MW decrease was rapid and slowed thereafter. Depolymerization occurred more rapidly than did wafer erosion and mass loss.

The release of the water soluble SA was very rapid, with almost 80% released by day 7. During this same period, only 5% of the less soluble PCPP was released. The differences in initial wafer MW did not affect the release rates for SA and PCPP.

In Vivo Biodegradation:

Method: Four wafers containing different concentrations of BCNU (3.6-3.9%, 0.47-0.59 mg) with different PCPP:SA molecular weights (20, 29, 47, or 56 kDa) were implanted into four male rat brains (one wafer in each rat). The wafers were ~3 mm in diameter and weighed 13-15 mg. One male rat each was sacrificed at 2 hrs, 1, and 5 days after wafer implantation. The wafers were immediately frozen on dry ice and then lyophilized. The molecular weight of the retrieved wafer was determined by gel permeation chromatography (GPC). BCNU remaining in the wafer was determined by HPLC. The wafer morphology was evaluated at each time point using a scanning electron microscopy (SEM).

Results: By 24 hrs post-implantation, approx. 50-80% of the BCNU was released from the wafer. Wafer MW decreased exponentially as a function of implantation time during the first 10 hrs following implantation in the rat brain (first erosion phase), which was followed by a reduction in weight decrease thereafter. The decrease in MW was slower in the rat brain than in vitro in the PBS.

Morphological Study:

By scanning electron microscopy (SEM), examination of Gliadel wafers before and after implantation demonstrated morphological changes due to polymer erosion and release of BCNU in the rat brain. Before implantation, the surface of the wafer is very firm, with microspheres densely packed next each other. At two hrs post-implantation, the surface layer of the wafer has eroded exposing the next layer of compressed microspheres which were clearly identifiable. At 24 hrs post-implant, the surface become very porous and no individual microspheres could be identified. When cross sections of the degrading wafer were examined, the dynamic process of water penetration from the surface into the interior was apparent. The portion of the wafer immediately beneath the surface is as porous as the surface. However, farther down from the wafer surface, the wafer is less porous. By 5 day post-implantation, the entire cross-section of the wafer displayed a uniformly high porosity with no individual microspheres identifiable, indicating that water has penetrated throughout the whole wafer and degraded the interior as well as the exterior of the wafer.

B. **Intracerebral Distribution Studies in Rabbit.**

The local concentration and distribution of BCNU within normal brain tissue were studied following surgical implantation of Gliadel 2.5%, 5%, or 10% (correspond to 300, 600, or 1200 ug BCNU).

Fifty-six NZW male rabbits (8 rabbits/group) were divided into 6 groups and surgically implanted with 12 mg wafers (or discs) containing Gliadel 2.5, 5, or 10% [^{3}H]-BCNU by either trituration or solution method, and control group was implanted with [^{3}H]-inulin wafer (0.2 mg, 40 uCi) into the brain. Another group of eight rabbits were injected with [^{3}H]-BCNU directly into the brains. Two rabbits/group were sacrificed on 3, 7, 14, and 21 days. The brains were removed, frozen, and prepared for quantitative autoradiography. All rabbit brains were evaluated histopathologically.

The quantitative autographic findings indicated that 30-59% of the brain was exposed to the [^{3}H]-BCNU radiolabel on day 3; 5-20% on day 7; and 2-7% on days 14 and 21 as in Table 1. In contrast, the exposure of the brain to the radiolabel [^{3}H]-inulin was relatively constant at 30% for two weeks before decreasing.

After the direct ic injection of [^{3}H]-BCNU, labeled tracer was rapidly distributed throughout the exposed area of the brain. At 24 hrs after injection, only 15% of the area of the brain was exposed to free drug and by 72 hr, drug concentration was undetectable. In contrast, 72 hrs after implantation of polymer prepared by either method, ~40% of the area of the brain was exposed to the tracer and a decrease to 15% level did not occur until 180 to 350 hrs. The BCNU polymer discs made by either trituration or solution methods were not significantly different as shown in Figure 2.

TABLE 1

*Distribution and concentration of [^{3}H]-BCNU administered in polymer in normal rabbit brain**

Time Postimplant	% Brain Section Exposed	Average Concentration (mM BCNU)
300-μg BCNU polymer		
day 3	14.0	1.9
day 7	5.2	5.8
day 14	4.1	5.4
day 21	2.4	7.3
600-μg BCNU polymer		
day 3	30.0	2.5
day 7	20.2	5.1
day 14	4.8	7.1
day 21	4.2	7.1
1200-μg BCNU polymer		
day 3	58.5	7.5
day 7	18.0	6.6
day 14	7.0	7.6
day 21	4.5	7.1

* BCNU-loaded polymer prepared by trituration method. Values are average data for two animals sacrificed at each time point.

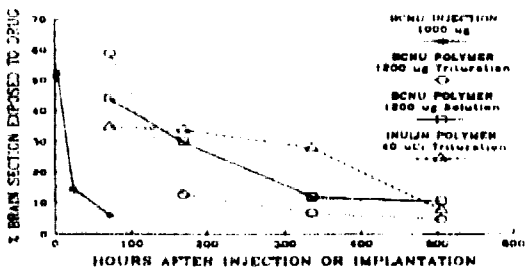


FIG. 2. Graph showing distribution of [^{3}H]-BCNU and inulin delivered by polymer and [^{3}H]-BCNU by direct injection into rabbit brain. The percentage of the area of brain sections exposed to the radiolabeled compound in animals is given following administration of 1200 μg trituration *(circles)* and solution *(squares)* polymers, triturated inulin polymer *(triangles)*, and direct injection of [^{3}H]-BCNU *(stars)*. These data are displayed as a function of time following implantation or injection for two rabbits per time point. Each animal received 40 μCi tritium.

A profile of concentrations as a function of distance from the implanted polymer was studied in each animal. At 3 days after implantation as in Table 2, the area of activity extended 12 mm from the polymer-loaded with 300 ug BCNU with average BCNU concentration of 3 mM within this region. The 600 ug BCNU disc generated a region of activity with a 6 mM concentration that extended about 10 mm from the polymer. The 1200 ug BCNU discs generated a 12 mm zone of activity with concentrations in 8 mM range. The diameter of activity was 5mm at 7 and at 14 days following polymer implantation, and at 21 days measured 3 mm.

TABLE 2

*Results 72 hours after implantation of BCNU-loaded polymer in rabbit brain**

BCNU Dose	Diameter of Tracer Surrounding Polymer (mm)	Concentration at Edge of Tracer Region (mM BCNU)	Average Concentration within Tracer Region (mM BCNU)
300-μg BCNU polymer	12	0.55	3
600-μg BCNU polymer	10	0.62	6
1200-μg BCNU polymer	12	0.70	8

* BCNU-loaded polymer prepared by trituration method. Values are averages of two animals each.

Histopathological findings indicated that direct injections of [^{3}H]-BCNU resulted in some local necrosis and edema at the site. These findings were more prominent at early time points. The edema and necrosis in animals with BCNU-containing polymer discs were most prominent adjacent to the 1200 ug loaded discs and least prominent adjacent to those loaded with 300 ug of the drug. These histologic findings closely paralleled the regions of the brain that contained the highest concentrations of [^{3}H]-BCNU demonstrated by quantitative autoradiography.

C. Metabolic Disposition and Excretion Studies in Rats and Rabbits:

A metabolic disposition study was performed to evaluate distribution and clearance of Gliadel components (BCNU, PCPP:SA 20:80) in adult SD rat and NZW rabbit. Three types of Gliadel wafers with BCNU were prepared containing a different ^{14}C-label (^{14}C-CPP,^{14}C-SA, and ^{14}C-BCNU) and surgically implanted into the rat and rabbit brain. The wafers were approximately 3 mm in diameter and 1 mm in thickness and ranged in weight 11-17 mg. The concentration of BCNU varied from 0.18- 0.27 mg (1-2.5%). In the rat, one wafer was implanted into right hemisphere in an area posterior to the coronal suture and lateral to the sagittal suture. Rats were housed individually in glass metabolism cages to collect expired CO_2, urine, and feces. In experiments not requiring CO_2 collection, the rats were housed in Nalgene metabolic cages which allowed separate collection of urine and feces

In the rabbit, two wafers, one each side of the sagittal suture, were implanted in each animal. Rabbit cages were modified to collect urine and feces separately. Animals were observed once/twice daily for mortality and toxicity. Wafer remnants were collected from the animals and analyzed. Samples of expired CO_2, urine and feces were collected on days 1, 4, and 7 and processed and analyzed by HPLC.

The percent of radiolabeled BCNU, PCPP and SA in brain, wafer remnant, and urine and feces were followed by radioactivity measurements for 7 days after implantation in rat and rabbit are summarized in Table 17.

TABLE 17 Selected Radiolabelled Biodistribution of BCNU, PCPP, and SA (%)

^{14}C-labeled Component (Assay Days)	Urine		Feces		Expired CO_2		Brain*		Wafer Remnant	
	Rat	Rabbit	Rat	Rabbit	Rat	Rabbit	Rat	Rabbit	Rat	Rabbit
BCNU										
Day 7	62	56	4.7	1.9	4.6	-	1	2	3.4	11.6
PCPP										
Day 1	0.1	-	<0.1	-	-	-	0.2	-	101.8	-
Day 4	0.5	-	1.6	-	-	-	0.2	-	96.8	-
Day 7	1.3	-	2.8	-	-	-	0.8	-	96.6	-
Day 21	-	62	-	2	-	-	-	2.2	-	28.8
SA										
Day 1	1.2	-	<0.1	-	2	-	1.0	-	97.0	-
Day 4	7.9	-	0.7	-	-	-	1.4	-	49.9	-
Day 7	10	9.3	2	1.2	40	-	<1	1.8	8	14

* not including implantation site
- not assayed
[SRI Study No. LSC 2047-D01-91]

With ^{14}C-SA-labeled wafers, expired CO_2 was the major route of elimination of radioactivity. About 40% of the dose was measured as expired CO_2, 10% as urinary excretion and 2% in fecal excretion over a 7 day period in rats. For the same 7 day period, about same amount of radioactivity was excreted in urine and feces of rabbit. The wafer recovered after 7 days of implantation contained about 8% (rat) and 14% (rabbit) of the original radioactivity.

The radioactivity level in the rat brain was highest on day 4 (1.4%) and ~ 1% on day 7. The percentage of radioactivity remaining in the recovered ^{14}C-SA wafers loaded with BCNU were 97% after 1 day, 49.9% after 4 days and 8.3% after 7 days. The ^{14}C-SA levels in the spleen, kidney, lung and plasma did not exceed a total of 1% of the administered dose as shown in Table 4.

Table 4 Seven day disposition of ^{14}C after brain implantation of ^{14}C radiolabelled polymer–BCNU wafers in rats

Organ	[^{14}C]SA* (% dose)	[^{14}C]CPP† (% dose)	[^{14}C]BCNU‡ (% dose)
Urine	11.20	1.28	61.77
Faeces	1.00	2.58	4.68
CO_2	43.62	0.00	4.60
Brain	1.03	0.62	0.97
Kidney	0.89	0.03	—
Liver	1.09	0.10	0.48
Spleen	0.04	0.01	—
Lung	0.09	0.01	—
Fat	0.68	0.09	0.17
Carcass	5.19	1.48	3.53
Plasma	0.24	0.01	0.08
Wafer	8.30	96.61	3.43
Total recovered	84.8	93.09	80.02

Single ^{14}C-labelled wafers implanted in rat brains, radioactivity followed for 7 d; results are an average of four rats.
*Dose implanted, wafer of p(CPP:[^{14}C]SA)20:80, 9.38 μCi, 13.5 mg.
†Dose implanted, wafer of p([^{14}C]CPP-SA)20:80, 17.34 μCi, 15 mg.

With ^{14}C-CPP-labeled wafers, the radioactivity was very slowly released from the wafer because of its limited solubility. As shown in Table 17, more than 96% of the administered radioactive dose still resided in the recovered BCNU-loaded wafers after 4 and 7 days. The brain tissue contained < 1% of the radioactivity after 4 and 7 days in rats and 2.2% after 21 days in rabbits. In rabbits, about 62% of the radioactivity was excreted in the urine by 21 days. In rat, radioactivity was excreted slightly more in the feces (2.8%) than in the urine (1.3%). The total excretion (urine, feces) after 7 days was less than 5%.

With [^{14}C]-BCNU-labeled wafers, urine was the major route of elimination of radioactivity ([^{14}C]-BCNU-labeled wafers). About 60% (rat) and 56% (rabbit) of the radioactive dose was excreted in the urine over a 7 day period. Expired CO_2 contained less than 5% of the radioactive dose. After 2 and 5 days, the radioactivity levels remaining in the wafers were 60.5 and 11.5% in rat, respectively. The wafers recovered 7 days after implantation had only 3.4% of the original radioactivity in rat and 12% in rabbit. The radioactivity in brain tissue after 7 days was 1% in rat and 2% in rabbit.

Summary of Pharmacokinetics:

Intracerebral BCNU dose delivery is dependent on polymer degradation following Gliadel wafer implantation. The studies were carried out with radiolabeled Gliadel (^{14}C- or ^{3}H-) in rats and in rabbits to determine the in vivo release of ^{14}C-BCNU from a PCPP:SA 20:80 wafer. In Fischer 344 rats, an i.c. study with Gliadel 20% reported ^{14}C-BCNU levels on day 1 of post-implant to be 1900 uM at 4.7 mm

distance from the wafer surface, and days 3, 7 and 14 to be 700-900 uM at 1.0-1.6 mm distance. Within two days, 50% of the ^{14}C-BCNU in the wafer was released into the surrounding brain tissue.

Local concentration and distribution of BCNU within normal brain tissue were evaluated following implantation of Gliadel 2.5, 5, or 10% [^{3}H]-BCNU (correspond to 300, 600, and 1200 ug BCNU). Quantitative autoradiographic findings indicated about 60% of the brain sections was exposed to radiolabeled compounds 3 days after BCNU-polymer implantation, 15% at 7 days, and the BCNU levels less than 10% at 14 and 21 days. The concentration of BCNU in the exposed areas increased with time- at day 3 it was calculated at 3 nmol/mg and at day 14 it was 7.6 nmol/mg. Adjacent to the polymer the high dose wafer was calculated to produce a BCNU concentration of 8 mM at day 3 and 3 mM by day 21. Tracer was calculated to travel ~12 mm by day 3. The ^{14}C- or ^{3}H-BCNU levels released from Gliadel implant into surrounding brain tissue are summarized as in the Table below.

In Vivo Release of BCNU Levels (mM) from Gliadel into Surrounding Brain Tissue in the Rat and Rabbit				
Species	Rat	Rabbit		
Dose % (BCNU mg)	Gliadel 20% (4.2 mg BCNU)	Gliadel 2.5% (300 ug BCNU)	Gliadel 5% (600 ug BCNU)	Gliadel 10% (1200 ug BCNU)
Day 1	1.9	ND	ND	ND
Day 3	0.9	1.9	2.5	2.9
Day 7	0.8	5.8	5.3	6.3
Day 14	0.7	5.4	7.7	7.6
Day 21	ND	7.4	7.1	7.3

*BCNU mM levels are average data for two animals sacrificed at each time point
ND- not determined

The wafer release and metabolic excretion of radiolabeled Gliadel wafer components ([^{14}C]-SA, [^{14}C]-CPP, and [^{14}C]-BCNU) have been studied. The concentration of BCNU varied from 0.18-0.27 mg (1-2.5%). Biodistribution studies of radiolabeled BCNU, PCPP, and SA in rats and rabbits indicated that the major excretory route of radioactivity from the ^{14}C-SA labeled wafer was CO_2 (40%) and that from the ^{14}C-BCNU-labeled wafers was urine (62%). The percentages of the administered dose remaining in the wafers recovered after 7 days of implantation were 8, 97 and 3%, respectively, for SA-, CPP-, and BCNU-labeled wafers in rats. In rabbits, the percentages of the administered dose remaining in the wafers after 7 days were 14 and 12 % for SA- and BCNU-labeled wafers, respectively. After 21 days of implantation, 29% of the dose administered in ^{14}C-CPP-labeled was still in the recovered wafers. The drug-loaded polymer degraded faster than the blank polymer.

BCNU levels in whole blood or plasma and cerebrospinal fluid over a 5 or 28 day period following implantation of Gliadel 3.8% (0.46 mg BCNU) were evaluated in rabbit brain. The bio-analytical method (not specified) indicates that no BCNU was detected in the tissues exclusive of implantation site.

BCNU concentrations delivered by Gliadel wafer have not been determined in human brain tissue.

III. TOXICOLOGY (Vol. 1.10-12)

A. Subchronic Toxicity Studies:

1. One month brain implantation study in rabbits

1. One-Month Brain Implantation Study in Rabbits:

Fifteen Albino male rabbits (1.43- 2.27 kg, 11 weeks old, n=3) were surgically implanted in the right ventricle with one 3 mm diameter, 1 mm in thickness and weighing ~12 mg Gliadel 3,85% (0.46 mg BCNU, Lot #SR042-45-24E-3mm-15; SR042-45-24E-3mm-12) or PCPP:SA 20:80 (Lot#SRO42-45-24C-3mm-26; SRO42-45-24C-3mm-22) as shown in Table 10. On days 1, 3, 5, 14, and 28 after implantation, 3 rabbits/group were sacrificed for pathological evaluation. The remaining animals were observed for survival, clinical signs, neurological behavioral and pathological changes for 28 days.

Table 10: A 28 days subchronic toxicity study of Gliadel 3,85% in NZW rabbit

Species/Strain # of Animals	Treatment Groups	Results
Rabbit NZW n= 3 males/group	1) PCPP:SA 20:80 2) Gliadel 3.85%	Mortality: No deaths Clinical Signs: No treatment related clinical signs Body wt./food intake: No change Pathology: Limited necrosis was observed at implantation site Severity of necrosis: Days 1, 3, 5 > Day 14 > Day 28 (no necrosis)

Results:

Mortality: None

Clinical signs: Several animals in both groups exhibited occasional episodes of clonus jaw and intermittent twitching on days 1-6. No body weight or other behavioral changes were noted.

Gross and Histopathology:

Gross pathology evaluation was limited to the head, the skin over the head, the cranial bones, meninges and brain. The polymer consisted of a brown/yellow amorphous material. Wafer limits were partly or wholly defined by a thin red margin. Polymer implants in animals killed at 14 and 28 days after surgical implantation were generally decreased in size compared to in animals killed at 1, 3, or 5 days after implantation. A slightly greater amount of necrosis was observed around Gliadel 3.85% wafer than around empty polymer (PCPP:SA 20:80). No necrosis was seen 28 days after implantation. No other degenerative changes were observed in the ventricular system.

B. Chronic Toxicity Studies:

1. 10 Week brain implantation study to evaluate Biocompatibility in monkeys
2. 10-month brain implantation study in rabbits
3. 26 week brain implantation study to evaluate Biocompatibility in monkeys

1. 10 Week brain implantation study: Biodegradable polymers for controlled delivery of chemotherapy with and without radiation therapy in the monkey brain:

This study determined the effects on the monkey brain of interstitial BCNU delivered by the PCPP:SA in 20:80 formulation with radiation (Non GLP study).

Eighteen adult male cynomolgus monkeys (3 or 5/group, 3.5-4.5 kg) were assigned to one of four groups as in the Table 1. Group 1 (control) underwent a right-sided frontal lobectomy without implant. Group 2 animals received a frontal lobectomy followed by implantation of 2.5 cm wafers of PCPP:SA. Group 3 animals underwent a frontal lobectomy followed by implantation of Gliadel 1.9%. In Group 4, bilateral frontal lobectomies were performed with placement of Gliadel in the bed of the left lobectomy and PCPP:SA wafers without BCNU in the bed of the right lobectomy, followed by whole-brain radiation therapy. The PCPP:SA wafers (or disks) measured 2.5 cm in diameter and 1 mm in thickness and weight about 660 mg. Two types of disks were used: an empty polymer and Gliadel (polymer with 12.5 mg BCNU (1.9% loaded by weight). Beginning on day 21 after polymer implantation, the monkeys in Group 4 received conventional external beam radiation treatment to the entire brain, with a total dose equal to the standard course given to patients with high-grade gliomas. The total midsagittal plane dose was 6000 cGy (200 cGy/day x 5/week).

Animals were observed for systemic and neurological effects of the implants. In this monkey study, the effect of the polymer on normal brain was assessed by computerized tomography (CT) and magnetic resonance (MR) imaging at specified intervals after implantation, and at autopsy.

Table 1: Experimental design: number of monkeys and times of evaluation

Treatment Group	# of monkeys	Computerized Tomography			Magnetic Resonance Imaging		Autopsy		
		Day 14	Day 42	Day 72	Day 14	Day 28	Day 16	Day 72	Day 196
1. Control	5	5		1	3	1	3	2	
2. Empty polymer	5	5		1	3	1	3	2	
3. BCNU-loaded polymer	5	5		2	3	1	3	2	
4. BCNU-loaded polymer + radiation therapy	3		2					1	1

Results:

Mortality: 1/3 monkey in Group 4 died on day 2, and autopsy revealed intracerebral hemorrhage. All other animals tolerated the surgical procedures and radiological studies.

Clinical/neurologic signs:

Two surgical complications occurred because of posterior extension of the frontal

lobectomy involved the motor strip in 1/5 monkey in Group 2 (empty polymer implant). Monkey developed hemiplegia postoperatively which resolved into mild hemiparesis. The surgical procedures were modified and no further neurological complications or other systemic effects were observed in any animals throughout the study.

CT and MRI Imaging Studies:

Group 1 (Control):

-5/5 had mild edema on day 14 after surgery by CT and MRI. 2/5 had evidence of a small amount of blood at the resection site. Minimal mass effect was observed in one monkey.

- Resolution of edema and a decrease in the size of the low density area correlated with lobectomy resection on MRI at 28 days and CT scans on 72 days.

Group 2 (Empty polymer):

- The wafer was visible in all 5/5 monkeys on both CT and MRI. Polymer was surrounded by edema suggesting brain reaction to the wafer. 1/5 monkey had a small mass effect with edema.
- On day 28, brain reaction to the polymer was still present on the MRI.
- On day 72, polymer was not visible on CT and no evidence of brain reaction in the implant area was observed.

Group 3 (Gliadel 1.9%-polymer):

- The results of CT and MRI on day 14 were similar to those of the Group 2. The polymer wafer was visible on both CT (opaque area) and MRI (dark area).
- The area surrounding the polymer showed brain edema.
- 4/5 monkeys had minimal shift of intracranial structure across the midline.
- On day 28, brain reaction to the polymer was still present on MRI.
- On day 72, one monkey had no evidence of the polymer while 4/5 had an opaque area that was consistent with blood or dissolved wafer. Brain reaction edema to the polymer had improved and one monkey had an area of residual low density on CT at the site of the implant.

Group 4 (Gliadel-polymer + irradiation)

- CT revealed the bilateral craniotomies, but was otherwise normal.
- No difference was detected between the hemisphere implanted with the empty polymer and hemisphere implanted with Gliadel 1.9%-loaded polymer.

Gross pathology:

Groups 1, 2, and 3:

- No gross evidence of the effect of treatment on the brain except at the implant site.
- In animals implanted with empty polymer (Group 2) or BCNU-loaded polymer (Group 3), fragments of polymer were present on both days 16 and 72. Necrosis and gliosis were present in animals with Gliadel + irradiation (Group 4).

Histopathology:

Autopsies with histopathological evaluation were performed on all animals. In Groups 1, 2, and 3 three animals were sacrificed around day 16 and two on day 72. In Group 4, one surviving animal each 4 was sacrificed on day 72 and day 196.

Groups 1, 2 and 3 showed:

On day 16, a narrow zone of necrosis was not present in the Group 1 but necrosis with inflammatory response in the brain parenchyma was observed in Groups 2 and 3. The width of the necrosis was

0.5 to 1.0 mm in Group 2 and 2.0 to 3.0 mm in Group 3. A cellular inflammatory response was seen on day 16 in both groups, with a greater response in Group 3. A zone of gliosis and neovascularization formed around the residual polymer not seen in the control animals. Histopathologic changes were greater in group 3 (Gliadel 1.9%) than group 2 (PCPP:SA 20:80).

On day 72, the tissue reaction had evolved into a chronic inflammatory response. A narrow zone of gliosis, neovascularization, and hemosiderin-laden macrophages was present at the polymer-brain interface. In the group 3, one monkey had only mild gliosis of the brain adjacent to the polymer, while the second continued to have a zone of neovascularization, mild gliosis, and necrotic parenchyma with hemosiderin and polymer-filled glial macrophages.

Group 4:

On day 72, the BCNU-polymer implantation area was surrounded by a 6-mm region of necrosis, which was not present around empty polymer. A narrow zone of intense histiocyte infiltration measuring ~1 mm was found around both polymers. Outside the zone of histiocyte, a perivascular lymphocytic infiltration was observed.

With radiation effects, vascular changes, wall thickening, and hyalinization were observed in several vessels at the edge of the hemisphere implanted with BCNU-loaded polymer. At both implantation sites the area of reaction was less than 1 cm in diameter, and outside this area the brain appeared normal.

On day 196, the abnormal zone was measured 1.2 cm in diameter was severe at the empty polymer implantation site. This zone comprised a 4-mm area of dense fibrosis with hemosiderin-laden macrophages, thick-walled vessels, and recent hemorrhage. The remaining 8 mm of the reaction consisted of edema, perivascular lymphocytes, and gliosis.

The reaction in the hemisphere implanted with BCNU polymer measured 1.5 mm in diameter, showed mild gliosis and edema. No inflammatory infiltrate or abnormal vessels were found. In both hemisphere, the brain beyond the reaction zone was normal. Material consistent with degraded polymer was found on day 72 at the empty polymer implantation site. No polarizable polymer was seen on day 196.

2. 10-Month brain implantation study in rabbits:

This study was conducted to determine the effects of Gliadel 4% or PCPP:SA 20:80 with subsequent irradiation, or irradiation alone (A GLP study).

Sixty adult SPF NZW male rabbits were randomly assigned into six groups (n = 10 rabbits/group). Rabbits in Groups of 3, and 4 were implanted with Gliadel 4% (0.45 mg BCNU) and rabbits in Group 2 were implanted with PCPP:SA 20:80 (wafer weighed ~12 mg) into the brain, and rabbits in Group 1 served as sham (untreated) controls. Group 5 had sham surgery and Group 6 were implanted with PCPP:SA 20:80 wafer. After a surgical recovery of five days post-implantation, each rabbits in Group 4, 5, and 6 were irradiated at a single dose of ~3820 rads (based on results of dosimetry) using a Theraton 780 cobalt unit with ^{60}Co gamma rays. The radiation dose (97.6 centigrays/min) was delivered laterally to the cerebral cortex using parallel opposite fields. The duration of irradiation to each side of the cerebral cortex was 19.6 minutes.

Measurement and Observation:

Daily:	survival, clinical or behavioral signs
Biweekly:	neurobehavioral signs (gnawing reflex, gait, corneal reflex, righting reflex)
Weekly:	body weight
Gross/Histo.	4 rabbits/group were sacrificed at 4 week interim, the remainder rabbits/group at 40 week

Table 11: Ten-Month brain implantation and subsequent irradiation study in NZW male rabbits

Species Strain	Group/Identification	Treatment Wafer Diameter	Treatment Average Wt%BCNU	Single Radiation Dose
Rabbit NZW n=10 males	1) Sham Control	None	None	None
	2) PCPP:SA 20:80	3 mm	None	None
	3) Gliadel 4%	3 mm	4.09	None
	4) Gliadel 4% + irradiation	3 mm	4.09	3250 rads*
	5) Sham Control + irradiation	None	None	3250 rads*
	6) PCPP:SA 20:80 + irradiation	3 mm	None	3250 rads*

*Target radiation dose

Results:

Mortality:

4 week interim: No mortality

40 week: -2/6 rabbits in group 5 (sham surgery + irradiation) and 1/6 rabbits in group 6 (PCPP:SA 20:80 + irradiation) were found dead after 33 weeks (days 235, 273, and 279, respectively)
-2/6 rabbits in group 6 were sacrificed after 31 weeks on study because of Clinical deterioration.

Clinical signs:

4 week interim: 2/4 rabbits in groups 4 (Gliadel 4% + irradiation), and 2/4 rabbits in group 5 showed chewing of left hind foot. This finding was first observed ~2 weeks following surgery.

40 week: 2/6 rabbits in group 4 and 2/6 in group 6 showed chewing of the foot
One animal in group 6 showed aggressive and exaggerated reaction to the skin sensitivity.

Gross/Histopathology:

4 week Interim: Brain necrosis was observed in 1/4 rabbits in group 2 (PCPP:SA 20:80), 3/4 rabbits in group 3 (Gliadel 4%), 4/4 rabbits in group 4 (Gliadel + irradiation), and 2/4 rabbits in group 6 (PCPP:SA + irradiation). Slight to moderate mononuclear cell infiltration was present in the brain in 4/4 rabbits in groups 2, 3

and 4, and 1/4 rabbits in group 5 and 3/4 in group 6.

40 week: Brain necrosis was observed in 14/18 rabbits that received radiation. Necrotic changes were comparable whether the rabbits received irradiation with sham surgery, with the PCPP:SA 20:80 wafer, or with the Gliadel 4% wafer. No necrosis was present in groups that were not irradiated (groups 1, 2, and 3).

3. **26 week brain implantation study to evaluate biocompatibility in monkeys:**

This study was conducted to evaluate the effects of brain irradiation in the male monkey following a bilateral brain implant of either Gliadel 3.85% or PCPP:SA 20:80 wafers (Non GLP Study).

Three monkeys (B-8, B-9, B-10) underwent a small bilateral frontal pole lobectomy and implantation with a 200 mg PCPP:SA 20:80 wafer (1.4 cm diameter) in the right hemisphere and a 200 mg Gliadel 3.85% (7.7 mg BCNU) wafer in the left hemisphere. After a surgical recovery period of 20-21 days, the two monkeys (B-8, B-10) received irradiation (total 60 Gy given in 30 fractions over a period of 42 days). Animals were observed for survival, clinical and neurological signs, and CT scans were performed 1-2 months post surgery. At 10 weeks, one monkey (B-10) was sacrificed and at 26 weeks, the second monkey was sacrificed. Complete necropsies were performed and the brain was prepared for histopathological evaluations.

Table 13: Twenty-six week brain implantation of Gliadel 3.85% and subsequent irradiation study in monkey

Species/Strain	Treatment Group	Results
Monkey Cynomolgus 3 males	All 3 monkeys underwent bilateral frontal lobectomy Right side:200 mg PCPP:SA 20:80 Left side: 200 mg Gliadel 3.85%	Mortality: 1/3 died on the second postoperative day Clinical signs: No abnormalities were observed Gross pathology: At 10 week: Residual wafer seen bilaterally. Mild blurring of the grey-white matter at the level of frontal lobe. At 26 week: No residual wafer or abnormalities were seen. Histopathology: At 10 week: Moderate gliosis and necrosis. At 26 week:Edema and gliosis

Results:

Mortality: 1/3 of monkeys died of unknown cause on the second postoperative day

Clinical signs: No neurological effects were observed in the remaining two monkeys. CT scans at 10 weeks revealed no abnormal findings.

Gross and Histopathology:

At 10 week: Right side of the brain with blank polymer contained some residual wafer surrounded by histiocytes and a moderate gliotic response with lymphocytic infiltration. Mild blurring of the grey-white matter was noted at the level of the frontal lobe. On the left side of the brain with Gliadel, some necrosis, and histiocytes infiltration was observed at the implantation site. Residual wafer were seen.

At 26 week: Right side: dense fibrosis, hemosiderin-laden macrophages, some thick-walled vessels, scattered lymphocytic infiltrate were observed at the implantation site. Reaction was 1.2 cm in diameter.

Left side: edema, mild gliosis, necrosis nor inflammatory infiltrates were seen. Reaction was 1.5 cm in diameter. No residual wafer were seen.

Summary of Toxicology:

Gliadel wafer (a polymer loaded BCNU) with different doses (%) of BCNU or the copolymer (PCPP:SA 20:80 formulation (copolymer; :SA 20:80 formulation; blank or empty polymer) were evaluated by brain implantation in the rat, raboit, and monkey. In an one-month study, Albino male rabbits were implanted with Gliadel 3.85% (0.46 mg BCNU) or PCPP:SA 20:80 polymers into the right ventricle of brain cerebrum. Gliadel 3.85% produced no treatment-related death, clinical sign, or changes in body weights, food intake or behavior(neurological). In histopathology, slightly greater amount of focal necrosis was present around Gliadel wafer implanted sites than the blank polymer. These findings were resolved at day 28.

Studies were performed to evaluate the possible interaction of Gliadel with radiation treatment in rabbit and monkey. In ten-month rabbit study, brain implantation of wafer (Gliadel 4% or polymer), and subsequent irradiation were evaluated. Rabbit exhibited brain nerosis with mononuclear cell infiltration at one month but delayed deaths (5 rabbits) due to delayed brain necrosis were observed at ten month in the irradiated groups. Necrotic changes were comparable among treatment groups with irradiation (sham, polymer, or Gliadel 4% BCNU). From these results, radiation treatment toxicity was not additive or synergistic with implanted Gliadel wafer toxicity.

Monkey studies (with Gliadel 1.9% + radiation) were performed using CT and MRI for brain imaging to identify the polymer implants and the surrounding local reaction. A zone of focal brain parenchymal necrosis with inflammatory tissue response was observed on day 16 during the course of biodegradation. By day 72, the inflammatory response was reduced and more chronic in appearance (with gradual biodegradation of the implant). Stacked fragments of wafer were still present.

In 26 week monkey study, 3 monkeys were implanted with Gliadel 3.85% (7.7 mg BCNU) and 21 days later, 2/3 monkeys received irradiation treatment of 60 grays given in 30 fractions over a period of 42 days. One of three monkey died due to surgical stress on day 2. At 10 week, all tissue reaction occurred within one cm of the implant sites (Gliadel 3.85%, PCPP:SA 20:80). The implantation site for the Gliadel 3.85% wafer exhibited a localized tissue necrosis. Residual wafer was seen bilaterally. At 26 weeks, an edema and mild gliosis with Gliadel 3.85% but the tissue necrosis observed at 10 weeks were not present. No residual wafers were seen at 26 weeks.

The brain implantation of Gliadel in rat, rabbit and monkey produced no systemic toxicity (mortality, clinical or neurological) or behavioral changes in these animals except consistant pathological findings of focal brain necrosis, gliosis, and edema with or without inflammatory responses. Brain radiation treatment did not result in a significant change in the pathology associated with Gliadel or PCPP:SA 20:80.

Summary of Histopathological Findings with various Gliadel doses in rat, rabbit, and monkey

Species # of Animals	Duration (Days)	Dosages Gliadel or PCPP:SA 20:80	Results
Rat n=8/group	28 Week 200 Days	Gliadel 4, 8, 12, 20, or 32% (0.44,0.88, 1.32, 2.2,& 3.52 mg BCNU) PCPP:SA 20:80(Empty polymer)	Most pronounced gliosis around the implant sites with Gliadel 32% BCNU. Mild to moderate necrosis was observed at implanted site.
Rabbit n=3/group	28 Day	Gliadel 3.85%(0.46) PCPP:SA 20:80	Limited necrosis at the implanted sites Mild necrosis
Rabbit n=10/group	10 Month 28 300	Group 1 Sham control (without polymer) Group 2 PCPP:SA20:80 Group 3 Gliadel 4% Group 4 Gliadel + irradiation Group 5 Sham control + irradiation Group 6 PCPP:SA + irradiation	At one month, brain necrosis was observed in 25% of the animals in the Group 2, 75% in Group 3, 100% in group 4, and 75% in group 6. A slight to moderate mononuclear cell infiltration was observed in 4/4 rabbits in groups 2, 3 and 4, with 1/4 rabbits in group 5 and 3/4 rabbits in group 6. At ten month, in non-radiated groups (1, 2, and 3), brain necrosis was not present. In radiated groups (4, 5, & 6), brain necrosis persisted in 14/18 rabbits that received radiation. Necrotic changes were comparable whether the rabbits received irradiation with sham surgery, with the PCPP:SA 20:80 wafer, or with Gliadel 4% wafer.
Monkey n=3-5/group	10 Week 16 Days 72 196	Group 1 Control (without polymer) Group 2 PCPP:SA20:80 Group 3 Gliadel 1.9% Group 4 Gliadel 1.9% + irradiation	Groups 1, 2, and 3, no gross evidence was observed on the brain except implant site. A zone of necrosis was not present in the Group 1 but the width of necrosis was 0.5-1mm in the Group 2, and 2-3 mm in the Group 3. Early cellular response was seen on day 16 in both groups, with a greater response in the Group 3. A zone of gliosis and neovascularization formed around polymer was not seen in the controls but was wider in the Group 3 than Group 2 on day 16. The tissue reaction had evolved into a chronic inflammatory response by day 72. A zone of gliosis, vascularization and hemosiderin-laden macrophages were present at the polymer-brain interface both in the Group 2 and 3. On day 72, a zone of intense histiocytosis measuring 5 mm and moderate gliosis was found around polymers in the Group 4. Radiation effects as vascular changes, wall thickening and hyalinization were found in several vessels at the edge of the reaction with BCNU-loaded polymer. Polymer fragments were present in animals in Groups 2 & 3 on both day 16 and 72. On day 196, abnormal zone consisted of dense fibrosis with hemosiderin-laden macrophages, thick-walled vessels and hemorrhage at the empty polymer implanted site. The reaction with BCNU polymer showed mild gliosis and edema with no inflammatory infiltrate or abnormal vessels. No polymer was seen in hemisphere on day 196.
Monkey n=3 1/3 died on day 2	26 Week 70 182	Gliadel 3.85% Implanted in left hemisphere PCPP:SA 20:80 Implanted in right hemisphere	At 10 weeks: Gliosis, necrosis, thick-walled vessels with hyalinization and lymphocytes were observed At 26 weeks: Mild gliosis and edema but necrosis was not present At 10 weeks: Gliosis, histiocytes and perivascular lymphocytes were seen. At 26 weeks: Dense, fibrosis, hemosiderin-laden macrophages, thick-walled vessels and scattered lymphocytes were observed.

IV. SPECIAL TOXICITY: (Vol. 1.11)

A. In Vitro BCNU Toxicity:

Method: An in vitro study evaluated the effects of BCNU on B6C3F1 mouse peritoneal macrophage cells. Two types of peritoneal macrophages were used: 1) resident macrophage from untreated mice, and 2) thioglycollate-treated macrophages which were obtained from mice injected with 10% thioglycollate 3 days prior to collection. Cultures were incubated with BCNU concentrations ranging from 10^{-4} to 10^{-7} M in 0.01% ethanol vehicle for 1 and 24 hrs. The response of macrophages to BCNU was determined by their ability to adhere to glass, phagocytize latex spheres, and adhere to and phagocytize chicken erythrocytes.

Results: BCNU produced macrophage toxicity at very low concentrations (5 uM to 0.1 mM) as determined by an inability to adhere to glass slides, reduced number of macrophages pesent following incubation, and reduced phagocytic ability of chicken erythrocytes as in the Table ES-1. From these studies, BCNU is cytotoxic to peritoneal macrophages (resident and thioglycollate).

Table ES-1

Peritoneal Macrophage Status in the Presence of BCNU

Parameter	Cell Type	Incubation Period Hours	No Effect Concentration	Low Effect Concentration
Cells/Field	Resident	1	5×10^{-4} M	10^{-4} M
Cells/Field	Resident	24	5×10^{-7} M	10^{-6} M
Cells/Field	Thioglycollate Recruited	1	10^{-5} M	10^{-4} M
Cells/Field	Thioglycollate Recruited	24	10^{-5} M	10^{-4} M
Phagocytosis Latex Particles	Resident	1	5×10^{-5} M	10^{-5} M
Phagocytosis Latex Particles	Resident	24	10^{-5} M	10^{-4} M
Phagocytosis Latex Particles	Thioglycollate Recruited	1	$< 10^{-4}$ M	$< 10^{-4}$ M
Phagocytosis Latex Particles	Thioglycollate Recruited	24	10^{-5} M	10^{-4} M
Phagocytosis Chicken Erythrocytes	Resident	1	10^{-5} M	10^{-4} M
Phagocytosis Chicken Erythrocytes	Resident	24	10^{-6} M	5×10^{-6} M
Phagocytosis Chicken Erythrocytes	Thioglycollate Recruited	1	10^{-5} M	10^{-4} M
Phagocytosis Chicken Erythrocytes	Thioglycollate Recruited	24	10^{-5} M	10^{-4} M
Adherence Chicken Erythrocytes	Resident	1	$< 10^{-4}$ M	$< 10^{-4}$ M
Adherence Chicken Erythrocytes	Resident	24	5×10^{-6} M	10^{-5} M
Adherence Chicken Erythrocytes	Thioglycollate Recruited	1	$< 10^{-4}$ M	$< 10^{-4}$ M
Adherence Chicken Erythrocytes	Thioglycollate Recruited	24	10^{-5} M	10^{-4} M

V. MUTAGENICITY: (Vol. 1.10)

Ames Assay:

Method: Forward mutation potential of PCPP:SA 45:55 was examined on Salmonella typhimurium using 8-azaguanine resistance as a genetic marker. Samples were tested at 1 mg/mL both with and without metabolic activation. Positive controls were benzopyrene for assays with metabolizing enzyme and 4-nitroquinoline-N-oxide for assays without metabolizing enzyme.

Results: The degradation products of the polymer, PCPP:SA 45:55, were non-mutagenic either with or without metabolizing enzyme. The induced mutant fraction was essentially zero. The positive controls in both cases were 20 times higher in mutant counts.

PHARMACOLOGY CONSULT

NDA: 20-637

Consult Date: March 21, 1996
Date Received: March 27, 1996
Response Date: March 28, 1996

From: Doo Y. Lee Ham
To: Paul Dietze and Donald Klein
Subject: Residual Methylene Chloride level in Gliadel wafers

Paul,

You have stated concern over the residual levels of methylene chloride (< 0.1%) in each Gliadel wafer. Each 200 mg wafer contains 3.85 mg BCNU. The clinical doses of Gliadel are 200 mg/wafer or up to 1600 mg/8 wafers.

Comments:

Let us assume,

1. Highest dose level to man = 1600 mg/8 wafers
2. < 0.1% MC in 200 mg/wafer,
   200000 ug x 0.001 = 200 ug, or 200 ug x 8 = 1600 ug
3. The calculated level of methylene chloride is 200 ug/wafer or 1600 ug/8 wafers.

Animal studies have shown that Gliadel wafer delivers BCNU in a sustained manner and that levels in the brain are detectable up to 21 days post implant. With the 21 days decomposition time in rats assumging a constant rate of release the average daily exposure to methylene chloride is 1600 ug/21 days or < 76.2 ug/day. The maximum allowable daily dose of methylene chloride is 140 ug/day for long term use in non-life threatening disease. Therefore, these levels are well below the daily maximum allowable dose.

cc: Orig. NDA 20637
HFD-150/Division File
/LeeHam
/DeGeorge
/Tolpvesi
/CSO
DYLH/WP

Statistical Review

Statistical Review and Evaluation

NDA#:	20-637	JUL 1 2 1996
Applicant:	Guilford Pharmaceuticals	
Name of Drug:	GLIADEL WAFER	
Indication:	As an adjunct to surgery to prolong survival in patients with a malignant glioma	
Documents Reviewed:	Vols. 1.43 - 1.59 dated on 02/06/96. Additional submissions dated on 03/29/96, 05/10/96, and 05/20/96.	
Medical Officer:	Alison Martin, M.D.	

Major Statistical Issues:

(i) discrepancy in results by nonparametric survival analysis and Cox model
(ii) a correlation issue and a missing mechanism in a longitudinal analysis
(iii) a measurement error problem in a linear regression setting

I. Background

Two controlled clinical trials (Studies 8802 and CL-0190) will be evaluated in this review. The rationale of the trials is described as follows: "The standard treatment of malignant gliomas consists of surgery followed by cranial irradiation and, at times, systemic chemotherapy. Clinical studies have determined that maximal tumor resection improves survival. A correlation between the extent of tumor resection and subsequent survival has been noted. ... Though total resection of a malignant glioma should be the total goal of surgical treatment for malignant gliomas, this outcome is usually not possible because these tumors are locally invasive and wide resection margins are impossible. Thus, additional treatment modalities are necessary. Radiation therapy is used as an adjunct to surgery to kill remaining tumor cells and delay recurrence. Subsequent research ... has not resulted in any substantial survival benefit. ... Systemic chemotherapy is also used to kill tumor cells remaining after surgery. A variety of drugs have been used, including nitrosoureas, procarbazine, carboplatin, and vincristine. ... Treatment of recurrent malignant gliomas is more problematic: surgery is of benefit but radiation therapy cannot be used because these patients receive a maximal dose at the time of their initial therapy. Systematic chemotherapy is often used because there is nothing else to offer but this approach has not been demonstrated to prolong survival. ... Recurrence of malignant gliomas occurs at the original tumor site in 90% of cases, therefore, local control of tumor recurrence is a major therapeutic objective. ... Approach has been the use of polymer-implants containing chemotherapeutic agents. This approach allows the chemotherapy to be targeted to the tumor site in high concentration while substantially reducing the exposure of the rest of the body to the potential adverse effects of the chemotherapeutic agent. Use of polymer implants is particularly appealing for those chemotherapeutic agents that do not otherwise cross the blood-brain barrier."

The treatment effect of polymer wafer (GLIADEL wafer) surgical implantation after maximal tumor removal surgery was investigated in the two phase III trials. Study 8802 was conducted in the U.S.A. and Study CL-0190 was conducted in Finland and Norway. The targeted populations

of the two clinical trials were different: 8802 study targeted a population of adult patients with recurrent malignant glioma and CL-0190 targeted a population of patients newly diagnosed with malignant glioma.

The efficacy variables of the two studies were survival rates, duration of survival, and Quality of Life (QOL) measurements.

In this review three main statistical issues; discrepancy in results by nonparametric survival analysis and Cox regression, a missing mechanism in a longitudinal analysis, and a measurement error problem in a linear regression setting, will be discussed.

First, this reviewer will summarize the reported results of each clinical study, 8802 and CL-0190, and will discuss the issue of discrepancy of a nonparametric approach (logrank or Wilcoxon test) and Cox regression in a survival analysis. A missing mechanism in a longitudinal analysis and a measurement error problem in an independent variable will be discussed in the analysis of Quality of Life data.

II. Study 8802 (Summary of the Sponsor's Results and Reviewer's Comments)

Study 8802 was a Phase III, multicenter, randomized, double-blind, placebo controlled trial with 222 total patients, 110 on Gliadel arm and 112 on Placebo arm. Patients with **recurrent** malignant gliomas were eligible for this trial and enrolled into the study from March 1, 1989 to January 17, 1992.

The patients were randomly assigned either to Gliadel or to Placebo groups at the time of surgery. "Twenty seven centers in North America (25 in the United States and 2 in Canada) participated in the trial." Randomization was stratified by these centers.

In this study the primary efficacy variables were six month survival rates and patient survival through six months. Note that in the six month survival analysis, patients who survived more than six months were considered to be censored at six months. The secondary efficacy variables were overall patient survival and an evaluation of Quality of Life measurements by Karnofsky Performance Status (KPS) and Mini-Mental State Examination (MMSE) scores.

First this reviewer will summarize and confirm the reported results by the sponsor through the submitted data.

II.1 Survival Analyses:

In this section the results from survival analyses (survival rates at six months, over the entire study period, and patient survival through the first six months and over the entire study period) will be discussed.

(i) Survival Rates:

Table 2.1 summarizes six-month and overall survival rates. 44 subjects of the 110 subjects on Gliadel and 59 subjects of the 112 subjects on Placebo died before six months after wafer implantation surgery (p=0.061 by Fisher's exact test). 5 subjects in each treatment group were alive at the end of the post-surgery observation period (up to 71 months). The overall survival rates were not statistically significant between the two treatments.

REVIEWER'S TABLE 2.1 Survival Rates

	6 month		Overall	
	Gliadel	Placebo	Gliadel	Placebo
Death	44	59	105	107
Alive	66	53	5	5
Total	110	112	110	112
	p=0.061 (Fisher's Exact)		p=1.000 (Fisher's Exact)	

(ii) Survival Duration:

According to Table 2.1, 66 patients of the 110 patients on Gliadel and 53 patients of the 112 patients on Placebo were censored for the six-month survival analysis. 5 patients of the 110 patients on Gliadel and 5 patients of the 112 patients on Placebo were censored for the overall survival analysis. Note that in the six-month survival analysis, the maximum observed time for each subject was a six months, which means that all censored subjects have a six month survival time and that in the overall survival analysis, the maximum follow-up time was 71 months.

Table 2.2 shows the results of the six month survival and the overall survival analyses: the logrank test and Gehan's generalized Wilcoxon test show a statistically marginal survival difference with p=0.063 and p=0.077 in the six month survival analysis, respectively and show non-significant result in the overall survival analysis (p=0.297 and p=0.106, respectively). Figure 1 shows an overall Kaplan-Meier survival curve indicating that the survival difference between the two arms occurred around six months and thereafter the two survival curves were almost superimposable. This suggests that the logrank test has more power to detect a late survival difference than the Wilcoxon test and that the Wilcoxon test has more power to pick up an early survival differences than the logrank test. Reviewer's Table 2.2 shows these indications.

The median survival time was 7.24 months with 95% C.I. (6.05 - 8.54 months) for Gliadel treated patients and 5.42 months with 95% C.I. (4.73 - 6.44 months) for Placebo treated patients.

REVIEWER'S TABLE 2.2 Survival Duration

6 month		Overall (up-to 71 month)	
logrank	Wilcoxon	logrank	Wilcoxon
p=0.063	p=0.077	p=0.297	p=0.106
Median Survival			
Gliadel		Placebo	
7.24 months (95% CI: 6.05 - 8.54 months)		5.42 months (95% CI: 4.73 - 6.44 months)	

(iii) Cox Proportional Hazards Regression

A Cox proportional hazard regression model was applied to adjust for the effect of strong

prognostic factors at baseline on survival outcome due to chance imbalances in the treatment groups. The sponsor identified 15 factors as being potentially clinically important. This was done by applying univariate Cox regression without treatment effect in the model for each of the possible factors. "Of the 15 factors evaluated, 9 were found to be statistically important [p<0.15] in six month survival". These nine selected covariates were as follows: tumor type, KPS Score, race, percentage of tumor resection, age, history of prior chemotherapy, time from first surgery to index surgery, median MMSE score, and number of wafers implanted. By a backward elimination method of multiple regression in the Cox proportional hazards model, seven covariates were found to be statistically significant.

Reviewer's Table 2.3.A. shows the results from the stepwise regression procedure in Cox model for six month survival. As noted in Table 2.3.A., if the selected seven covariates were fit in Cox model directly, we obtained a slightly different estimates of parameter coefficients and its associated standard errors. Comparing the result from the logrank test, p-value was reduced from p=0.063 to p=0.009 for the effect of treatment.

REVIEWER's TABLE 2.3.A The Results From Cox Regression Model for the 6 Month Survival Endpoint

Treatment Effect in Six-Month Survival (All Patients)*			
Parameter	Estimate	Standard Error	P-value
Treatment	-0.537	0.206	**0.009**
GBM vs NonGBM	0.522	0.244	0.032
Karnofsky Score	-0.429	0.214	0.045
Radiation	-0.563	0.236	0.017
Age (per decade)	0.173	0.085	0.043
Prior Chemotherapy	0.496	0.213	0.020
Years to Index Surg	-0.135	0.069	0.050
Number of Wafers	-1.135	0.518	0.028

Note that these Cox results were obtained by forcing all of these covariates into the model simultaneously.
Note* that results from the stepwise procedure (backward) are different from those obtained directly with the selected covariates in parameter estimates and their associated standard errors.

Reviewer's Table 2.3.B. shows the results from the stepwise regression procedure in the Cox model for overall survival. The same criterion regarding the selection of possible covariates employed in the six month survival analysis was applied in the overall analysis. Six covariates instead of seven were selected in this overall survival analysis. As noted in Reviewer's Table 2.3.B., the results presented here were slightly different from those reported in Sponsor's Table 4.30. The reason is that this reviewer did not include a certain variable, resection vs biopsy at first surgery (SURGBR), in the original working model, because the variable did not satisfy the sponsor's specified cut-off criterion, P<0.15 (Sponsor's Table 4.29 on page 75 on volume 1.43). Although six covariates were selected in this reviewer's final model, parameter coefficient estimate and associated standard error estimate of the treatment effect were slightly different from those of the sponsor.

Comparison with the result from the Wilcoxon test reveals that the p-value was reduced from p=0.106 to p=0.0301.

REVIEWER's TABLE 2.3.B The Results From Cox Regression in Overall Survival

Treatment Effect in Overall Survival (All Patients)*			
Parameter	Estimate	Standard Error	P-value
Treatment	-0.308	0.142	**0.0301**
GBM vs NonGBM	0.727	0.159	0.0001
Radiation	-0.556	0.175	0.0015
Tumor Resection	-0.663	0.164	0.0001
Age (per decade)	0.258	0.056	0.0001
Prior Chemotherapy	0.348	0.147	0.0181
Number of Wafers	-0.763	0.284	0.0072

Note* that presented results are slightly different from those reported in sponsor's Table 4.30 on page 76 in volume 1.43 because a variable, resection vs biopsy at first surgery (SURGBR), was not included in this reviewer's stepwise regression procedure as a starting model. This caused Prior Chemotherapy instead of Karnofsky Performance Score to be included in the above model.

As noted previously, the results from the stepwise regression procedure in the Cox model are very sensitive, i.e., parameter estimates depend on which covariates are included in a starting model (i.e, depending upon the prespecified p-value chosen as a cut-off point in the results of univariate Cox models without the treatment effect) and those estimates depend on whether the covariates in Cox model were forced to fit simultaneously or obtained as a result of a stepwise regression procedure.

(iv) Subgroup Analyses: (Tumor Type, Age, Gender, and Race)

Reviewer's Table 2.4.A presents subgroup analyses by tumor type, age, gender, and race for the six month survival experience.

Tumor Type: in GBM tumor type patients, there existed a statistically significant difference in patient survival between the two arms, but not in the non-GBM type of tumor patients. No treatment by tumor type interaction was detected by Cox regression (p=0.177).

In GBM patients the treatment effect result from Cox regression was p=0.0073 with AGE10 (Age per decade) as a covariate derived from a stepwise procedure with the same starting model with 8 potential covariates except for GBM vs NonGBM. In Non-GBM patients we have p=0.649 with covariates of Karnofsky Performance Status and Tumor Resection derived from the same starting model. The sponsor reported p=0.0052 in sponsor's Table 4.23 on page 83 in volume 1.43.

Age: no statistically significant difference was demonstrated in patient survival for either age category. Note that there were only 10 patients on each treatment for the at least 65 years of age category. No treatment by age interaction was detected by Cox regression (p=0.515).

Gender: a marginally statistically significant survival difference was found in the male subgroup, but not in the female subgroup. No treatment by gender interaction was detected by Cox regression (p=0.565).

Race: a marginally statistically significant survival difference was detected in the Caucasian subgroup, but not in the non-white subgroup. Note that there were only 10 patients on Gliadel arm and 8 patients on Placebo arm in the non-white subgroup. No treatment by race interaction was detected by Cox regression (p=0.517).

Reviewer's TABLE 2.4.A Subgroup Analyses for 6 Month Survival

Tumor Type				Age*			
GBM (N_g=72, N_p=73)		Non-GBM (N_g=38, N_p=39)		< 65 (N_g=100, N_p=102)		≥ 65 (N_g=10, N_p=10)	
logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon
p=0.013	p=0.015	p=0.849	p=0.775	p=0.128	p=0.155	p=0.180	p=0.231
Trt x Tumor p=0.177				Trt x Age p=0.515			
Cox Regression		Cox Regression					
p=0.0073 (Reported p=0.0052)		P=0.6491					
Gender				Race**			
Male (N_g=74, N_p=69)		Female (N_g=36, N_p=43)		White (N_g=100, N_p=104)		Non-white (N_g=10, N_p=8)	
logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon
p=0.076	p=0.074	p=0.461	p=0.548	p=0.062	p=0.088	p=0.732	p=0.784
Trt x Gender p=0.565				Trt x Race p=0.517			

Note* that the sample size in each group is 10 patients.
Note**that the sample size on Gliadel is 10 patients and 8 patients on Placebo.
Note that N_g and N_p stand for sample size of Gliadel and Placebo arms respectively.

Reviewer's Table 2.4.B shows subgroup analyses of tumor type, age, gender, and race for overall survival.

Tumor Type: in general there existed no significant survival difference between the two treatments. In GBM tumor type patients the Wilcoxon test showed a statistically significant result because an early survival difference was observed around six months in Kaplan-Meier survival curve. No treatment by tumor type interaction was detected by Cox regression (p=0.628).

Figure 2 shows an overall Kaplan-Meier survival curve by treatment group and tumor type. The median survival was 6.51 months (95% CI:5.32 - 7.49 months) on Gliadel and 4.63 months (95% CI:3.78 - 5.52 months) on Placebo in GBM tumor type subgroup. The median survival was 9.30 months (95% CI:7.46 - 13.54 months) on Gliadel and 8.67 months (95% CI:6.41 - 12.55 months)

on Placebo in non-GBM tumor type subgroup. The result from Cox regression for treatment effect was p=0.0514 with covariates of RAD, RACE, AGE10, and BETSGRY in GBM patients and p=0.6129 with covariates of KAR, AMT, and AGE10 in non-GBM patients. These results were derived from a stepwise regression procedure (backward) with the same starting covariates applied for a overall survival. *The sponsor reported p=0.013 in their Table 4.33 with different selected covariates, RAD, RACE, AMT, AGE10, BETSGRY, and SURGBR, on page 80 in volume 1.43 in GBM patients. Sponsor's Table 4.29 on page 75 of volume 1.43 indicated the possible prognostic factors selected from a univariate procedure. The table did not include the variable, SURGBR. Thus the discrepancy was derived from a different starting model.* The following table presents covariate information.

Reference 1. Abbreviation of Covariates

AGE10	Age per decade
AMT	Tumor Resection≥75% vs <75%
BETSGRY	Years from First Surgery to Index Surgery
KAR	Karnofsky Score >70 vs ≤70
RACE	White vs. Other
RAD	Local/Both vs. Whole Brain Radiation
SURGBR	Resection vs. Biopsy at First Surgery

Age: there existed no significant difference in patient survival in both age categories. Note that there were only 10 patients in each treatment in at least 65 age category. No treatment by age interaction was detected by Cox regression (p=0.436)

Gender: there existed no significantly different survival benefit in either gender. No treatment by gender interaction was detected by Cox regression (p=0.780).

Race: there existed a marginally significant survival difference in the white population, and significant survival benefit in non-white population. Note that there were only 10 patients on Gliadel arm and 8 patients on Placebo in non-white population. Treatment by race interaction was detected by Cox regression (p=0.042).

Reviewer's TABLE 2.4.B Subgroup Analyses for Overall Survival

Tumor Type				Age*			
GBM (N_g=72, N_p=73)		Non-GBM (N_g=38, N_p=39)		< 65 (N_g=100, N_p=102)		≥ 65 (N_g=10, N_p=10)	
logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon
p=0.181	p=0.021	p=0.754	p=0.864	p=0.401	p=0.196	p=0.119	p=0.184
Trt x Tumor p=0.628				Trt x Age p=0.436			
Cox Regression		Cox Regression					
p=0.0514 (Reported p=0.013)		p=0.6129					

Gender				Race**			
Male (N_g=74, N_p=69)		Female (N_g=36, N_p=43)		White (N_g=100, N_p=104)		Non-white (N_g=10, N_p=8)	
logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon
p=0.372	p=0.166	p=0.764	p=0.438	p=0.082	p=0.049	p=0.006	p=0.018
Trt x Gender p=0.780				Trt x Race p=0.042			

Note* that the sample size in each group is 10 patients.
Note**that the sample size on Gliadel is 10 patients and 8 patients on Placebo.
Note that N_g and N_p stand for a sample size of Gliadel and Placebo arms respectively.

Reviewer's Comments on Study 8802:

(I) Discrepant results among the three tests:

Reviewer's Table 2.5 summarizes the results of survival analyses for six months and for the overall study period (up to 71 months). P-values from nonparametric approaches (logrank and Gehan's generalized Wilcoxon tests) went from marginally significant (p=0.063 and p=0.077, respectively) to strongly significant (p=0.009) by Cox regression for six month survival and changed from nonsignificant (p=0.297 and p=0.106, respectively) to strongly significant (p=0.0301) by Cox regression in the overall survival analysis.

Reviewer's TABLE 2.5 Summary of Survival Analyses for Six Month and Overall Study Period in Study 8802

Six-Month Survival After Wafer Implantation Surgery		
Logrank test	Wilcoxon test	Wald's test (Cox regression)
p=0.063	p=0.077	p=0.009
Overall Survival After Wafer Implantation Surgery		
Logrank test	Wilcoxon test	Wald's test (Cox regression)
p=0.297	p=0.106	p=0.0301

In the comment section this reviewer will discuss four issues regarding this p-value difference when the alternative hypothesis is not far from the null: (i) effect of imbalance of covariates at baseline, (ii) consequences of misspecified covariates in the Cox model, (iii) stability of estimated coefficients in the Cox model.

(i) Effect of Imbalance of Prognostic Factors at Baseline:

It is reasonable that if strong prognostic factors on survival outcome are imbalanced at baseline, these factors should be adjusted for in an analysis. The sponsor identified 15 potential medically meaningful prognostic factors. By applying a univariate Cox regression for each of these factors without treatment effect, 9 factors were selected for further consideration based on a statistical criterion of $p < 0.15$. Note that there was no explanation as to why this p-value was chosen for a

cut-point and the cut-value chosen would influence the treatment effect, which will be discussed subsequently. Then, a stepwise regression procedure was applied to select seven and six prognostic factors for the six month and overall survival models, respectively.

Appendix 1 presents the distribution of eight selected prognostic factors (six dichotomous variables and two continuous variables) that were adjusted for in the six month survival and for the overall survival analysis by Cox regression. A major imbalance in the covariates at baseline does not exist in order for a Cox model to produce a large difference in p-values. This suggests that a small imbalance in each covariate might influence parameter estimates and associated p-values.

(ii) Misspecification of Cox Model (Omitting Covariates in a Model)

The theory for a Cox regression model, the partial likelihood approach, was developed on the assumption that we have a correctly specified model in terms of proportional hazards and correctly selected prognostic factors in the model (Cox, 1972, 1975). Under this **true** model, Andersen and Gill (1982) showed that estimated coefficients converge to true values in distribution to a multivariate normal with mean 0 and a covariance matrix consistently estimated by a Fisher's information matrix derived from the partial likelihood.

Unfortunately, we do not know the true Cox model. Therefore an applied Cox model can be considered as a "working" parametric model with some misspecifications. Several approaches have been suggested for handling misspecified models (e.g., Gail, et al, 1988; Huber 1967;Kent 1982;White 1982). Lin and Wei (1989) investigated the misspecified model in a Cox proportional hazard model setting and proposed a "sandwich" estimator for the covariance matrix of estimated coefficients in the misspecified Cox model for testing purposes. This "sandwich" estimator is derived from M estimation theory and these authors modified the middle part of the "sandwich" estimator for the Cox model. Since a misspecified model is estimated, estimated coefficients of the working model will not converge to the true parameter values; instead, they converge to some value, hopefully near the true value. They proved that the estimated coefficients converge to a value, β^*, where β is the true value, in distribution to a multivariate normal with mean 0 and a "sandwich" covariance matrix. Note that the same concept was applied to longitudinal analysis; This is known as the "GEE" approach proposed by Liang and Zeger (1986) to deal with a correlation problem among repeated observations per subject. The difference between the two approaches lies in the expected value of a score function evaluated at the true value $=0$ in GEE and $\neq 0$ in a "working" Cox model, which produce inconsistent estimators.

Appendices 2 and 5 show how the estimated coefficient of the treatment effect depends upon the number of covariates which were selected and reported in the submission, in six months and overall survival analyses in Study 8802, respectively. It is shown that as the number of covariates increases, the parameter estimates decrease, indicating that treatment effect increases. On the other hand, their associated standard error estimates, derived from a sort of Fisher's information from the partial likelihood, did not change along with the number of covariates employed in a "working" Cox model in six months and overall survival (Appendices 3 and 6, respectively). Therefore, taking into account these two facts, p-values derived from a Wald test depended upon an estimated coefficient of the treatment effect in both survival analyses (Appendices 4 and 7). Therefore, it is recommended that a "sandwich" estimator should be reported along with a regular estimate (naive estimate) to judge how far these two estimated values differ in order to assess how far a "working" Cox model is off from a true model. The reason is that as a "working" model approaches the true model, the difference between the two estimators, naive and "sandwich" estimators, approaches zero. This criterion may be applied for selection of a parsimonious model as a possible true model among several candidates.

(iii) Stability Issue of Two Estimated Coefficients in a Cox Model

As discussed in (ii), omitting covariates in a true Cox model affects estimation of a treatment effect even if the covariates are balanced at baseline. In addition, this reviewer observed the following: (i) the estimated treatment coefficient could vary depending upon which prognostic factors were selected initially from results of univariate Cox models with $p < 0.15$ criterion for a stepwise procedure and (ii) the estimated treatment coefficient would be different depending upon whether it was estimated in one step including all of the identified covariates or estimated through a stepwise procedure with these same covariates. Reviewer's Table 2.6 shows these discrepancies for the overall survival analysis.

Reviewer's TABLE 2.6 Different Treatment Effect Estimates for Overall Survival by Cox model

Parameter	Estimate	SE	p-value	Note
TRT	-0.308	0.142	0.0301	with $P < 0.15$ criterion as a starting model
TRT	-0.286	0.143	0.045	with $p < 0.15$ criterion + SURGBR as a starting model
TRT	-0.340	0.142	0.0166	Direct fit with the same covariates in the first model

The sponsor applied a stepwise procedure (backward) to determine a final model as a possible true Cox model. As discussed in (ii) and (iii), the derived estimates from this procedure are sensitive to the P-value criterion for selection of possible starting covariates and to the modeling method, i.e., using direct fit vs. a stepwise procedure. In addition, associated standard errors (naive estimators) were more stable, which indicates that a derived p-value from a Wald test is sensitive to the estimated parameter value. In this sense, we may not have a robust result from this procedure. At least, in this Cox procedure, the "sandwich" estimator of standard error is recommended to construct a Wald test for robust inference.

Up to this point this reviewer assumed that the key proportional hazards assumption was valid. If this assumption is violated, we do not have valid inference derived from a Cox model. The sponsor did not provide us with any information to validate the proportional hazards assumption for each Cox model such as a graph of time vs log of -log of a survival function for each treatment arm. Lagakos and Schoenfeld (1984) proved that a violation of the proportional assumption in a Cox model will cause a severe loss of efficiency, which could have occurred in the following parsimonious models.

(iv) Results from Parsimonious Models

To obtain a more robust result with fewer, yet medically meaningful covariates, this reviewer consulted with the reviewing medical officer, Alison Martin M.D., and constructed a stratified

logrank test. The suggested covariates are as follows: Tumor Type (SUB_GBM), Karnofsky Performance Status (KAR), Age (AGE*), and Years from First Surgery to Index Surgery (BETSGRY*). Note that in this stratified logrank test AGE* and BETSGRY* were dichotomized at median values of Age10 and BETSGRY, i.e., 4.86 and 1.0, respectively.

Reviewer's Table 2.7 shows the results from a stratified logrank test and a corresponding Cox model with the same dichotomized covariates and the same covariates with AGE10 and BETSGRY as continuous variables for all patients. This reviewer also applied a stratified logrank test to other two subsets of the four covariates because (i) four dichotomous covariates makes 16 cells for the subjects to fall in and to observe deaths in each cell, so that this reviewer attempted to reduce the number of the cells in order to observe more subjects and presumably more deaths in each cell and (ii) Harsh *et al* (1987) suggested AGE and KAR as strong prognostic factors and Young *et al* (1981) suggested KAR and BETSGRY as strong prognostic factors. For six months survival both a stratified logrank test and a Cox model with the two different covariates indicated a significant survival benefit of Gliadel over Placebo treatment. On the contrary, for overall survival, a stratified logrank test indicated a strong survival benefit of Gliadel over Placebo treatment, but a Cox model with both sets of covariates did not show the benefit at all. This result is opposite because for overall survival a reported Cox model with seven covariates showed a strong benefit, but no evidence from a logrank test. The results from a stratified logrank test suggested that SUB_GBM, KAR*, and AGE* are influential prognostic factors in this data for both survival analyses.

As mentioned above, this reviewer applied a Cox model with the two sets of covariates: one is with four dichotomous variables and the other is with two dichotomous variables and two continuous variables (AGE10 and BETSGRY). As Table 2.7 indicates, in this set of covariates, the two continuous variables, AGE10 and BETSGRY, did not provide influential information for either survival analysis.

Reviewer's TABLE 2.7 The Results From a Stratified Logrank and a Corresponding Cox Model For All Patients

All Patients				
	6 Months		Overall	
Covariates	Stratified Logrank	Cox	Stratified Logrank	Cox
SUB_GBM KAR AGE* BETSGRY*	P=0.0295	P=0.0316 (P=0.0341 with AGE10 and BETSGRY)	P=0.0593	P=0.3246 (P=0.2253 with AGE10 and BETSGRY)
SUB_GBM KAR AGE*	P=0.0166	P=0.0305 (P=0.0298 with AGE10)	P=0.0473	P=0.2749 (P=0.2742 with AGE10)

SUB_GBM KAR BETSGRY*	P=0.0593	P=0.0488 (P=0.0473 with BETSGRY)	P=0.1831	P=0.4251 (P=0.3004 with BETSGRY)

Reviewer's Table 2.8 shows the results from a stratified logrank test and a corresponding Cox model with the two sets of covariates for GBM patients. For six months survival both a stratified logrank and corresponding Cox models showed strong evidence of a survival benefit in Gliadel treatment over Placebo treatment. For overall survival a stratified logrank test indicated a significant benefit of Gliadel over Placebo treatment, but a Cox model with the three dichotomous covariates did not show the evidence. On the contrary, the Cox model with the set of covariates with BETSGRY treated as a continuous variable showed a marginal significance. This result contradicts the result of a Cox model with different covariates. For GBM patients, KAR and AGE* are suggested to be influential prognostic factors for survival and BETSGRY to be a potential prognostic factor.

Reviewer's TABLE 2.8 The Results From a Stratified Logrank and a Corresponding Cox Model for GBM Patients

GBM Patients				
	6 Months		Overall	
Covariates	Stratified Logrank	Cox	Stratified Logrank	Cox
KAR AGE* BETSGRY*	P=0.0083	P=0.0055 (P=0.0057 with AGE10 and BETSGRY)	P=0.0342	P=0.1821 (P=0.0737 with AGE10 and BETSGRY)
KAR AGE*	P=0.0044	P=0.0063 (P=0.0080 with AGE10)	P=0.0271	P=0.1614 (P=0.1829 with AGE10)
KAR BETSGRY*	P=0.0153	P=0.0146 (P=0.0082 with BETSGRY)	P=0.0734	P=0.2421 (P=0.0825 with BETSGRY)

Reviewer's Table 2.9 shows the results from a stratified logrank test and corresponding Cox models for non-GBM patients. Neither test showed any survival benefit of Gliadel over Placebo treatment.

Reviewer's TABLE 2.9 The Results From a Stratified Logrank and a Corresponding Cox Model for Non-GBM Patients

Non-GBM Patients				
	6 Months		Overall	
Covariates	Stratified Logrank	Cox	Stratified Logrank	Cox
KAR AGE* BETSGRY*	P=0.7857	P=0.6659 (P=0.4261 with AGE10 and BETSGRY)	P=0.8135	P=0.6928 (P=0.8363 with AGE10 and BETSGRY)
KAR AGE*	P=0.8571	P=0.7569 (P=0.7348 with AGE10)	P=0.7691	P=0.8478 (P=0.8635 with AGE10)
KAR BETSGRY*	P=0.6196	P=0.6583 (P=0.4132 with BETSGRY)	P=0.7886	P=0.6076 (P=0.7231 with BETSGRY)

The results of six months and overall survival for Non-GBM patients are robust in a sense that the results did not depend upon statistical approaches (a logrank, a stratified logrank and Cox models with various sets of covariates). The analyses indicate that there is no statistically significant treatment effect of Gliadel over Placebo treatment for non-GBM patients. Also, the results of six months survival for GBM patients is robust in the same sense indicating that there is statistically significant treatment effect of Gliadel over Placebo treatment. On the other hand, the result of a overall survival for GBM patients depends on the statistical approaches and type of covariates used, dichotomous vs continuous, eg. BETSGRY vs BETSGRY*. Logrank did not show a significant result, but a Cox model with six covariates showed a significant result. In contrast, the stratified logrank test with KAR and AGE* showed a strong treatment effect of Gliadel over Placebo treatment, but a Cox model with the same covariates did not show a treatment benefit. Lagakos and Schoenfeld (1984) showed that a violation of the proportional hazards assumption will cause a loss of efficiency in a Cox model, which might have happened in the GBM patients case. Further investigation will be needed. Combining the results of GBM and non-GBM patients, we found that there is a treatment effect of Gliadel over Placebo in six months survival, but not in overall survival.

II.2. Quality of Life (QOL)

Karnofsky Performance Status (KPS) score and Mini-Mental State Examination (MMSE) were measured as parameters of Quality of Life. Both measurements were taken at day of surgery, day of discharge from hospital, and at 2 months, 4 months, and 6 months. The sponsor applied a longitudinal analysis known as a "Generalized Estimating Equation" (GEE) approach.

In general, we have to face two challenges in an analysis of repeated measurements. These challenges are (i) a within patient correlation problem and (ii) a missing data problem. The GEE approach was developed to cope with a correlation problem among observations per subject and

was utilized because KPS and MMSE were repeatedly measured over time for each subject and, each measurement would be correlated within a subject. In a classical univariate repeated ANOVA, a particular correlation structure, known as compound symmetry structure, must be assumed for a valid F test of interaction of treatment and time, or a multivariate analysis would be applied. But in a multivariate approach, a distribution must be correctly specified with a correct mean and variance structure. In addition, we may encounter a singular covariance matrix. To deal with these problems GEE employs the idea of "working correlation" and by invoking M estimation theory, robust variance, known as a 'sandwich estimator', originally termed so by Lin and Wei (1989), is derived.

Another issue is the missing data problem. Reviewer's Table 2.10 shows the missing data pattern over time. By Visit 5 about 50% of the patients had dropped out from the study on each treatment arm.

Reviewer's TABLE 2.10 Missing Data Pattern Over the Study Period

Visit	Gliadel (N=110)	Placebo (N=112)
Visit 0 (Day of Surgery)	110	112
Visit 1 (Discharge)	109	112
Visit 3 (Month 2)	100	100
Visit 4 (Month 4)	85	74
Visit 5 (Month 6)	66	52
Visit (Month 8)	19	13
Visit 7+	5	7

The sponsor employed two analyses to cope with missing data. An observed cases (OC) analysis was employed based on the assumption that missing data would be caused by a "missing completely at random" (MCAR) missing mechanism and a last observation carried forward (LOCF) analysis was employed on the assumption that the last observed value would be frozen until the end of trial so that missing data would be replaced by the last observed data. These two missing mechanisms are very strong assumptions so that in reality it would be very difficult to justify their validity particularly in an oncology trial.

The sponsor applied GEE with the independence assumption for an ANOVA type analysis assuming these two missing mechanisms.

Reviewer's Table 2.11 summarizes the results from two analyses of KPS scores as a continuous variable: OC and LOCF analyses. Neither analysis showed a statistically significant treatment effect of Gliadel over Placebo treatment. Visit effect was found to be statistically significant in both analyses.

Reviewer's TABLE 2.11 The Results from the Two Missing Assumptions with an "Independent" Working Assumption

	OC Analysis	LOCF Analysis
Treatment Effect	p=0.571	p=0.193
Visit Effect	p <0.001	p <0.001
Trt x Visit Interaction	p=0.134	p=0.459

Reviewer's Comments on QOL Analysis for Study 8802:

This reviewer employed a growth curve analysis to deal with the correlation issue in a longitudinal analysis. This reviewer applied three types of linear model: (I) GEE with three different "working" correlation assumptions; independent, compound symmetry, and AR-1, (ii) a linear mixed effects model, known as a "Laird and Ware" model (Laird and Ware, 1982), with three random coefficients, intercept, slope, and intercept and slope, and (iii) a two stage model to obtain robust results. The details of these approaches can be found in Appendix 8.

For the missing data problem this reviewer employed the concept of a "Pattern-Mixture Model", advocated by Little (1993 and 1995) to judge whether the observed missing mechanism is ignorable or nonignorable. This reviewer did not attempt to produce one estimate or derive one p-value by modeling a missing mechanism if there was a nonignorable missing mechanism because (i) the results will be very sensitive to an assumed missing mechanism and (ii) there is no data to verify the assumed missing mechanism. The approach employed in this review is summarized in Figure 3.

This reviewer requested additional data on exact time measurement values for KPS and MMSE. These were received on 05/10/96. This reviewer noticed that there exists a measurement error problem in an independent variable, namely a time variable, in the sense that the measurements were not taken at each prespecified visit per protocol. For example, KPS measurement at visit 3 was supposed to be taken at 60 days after the surgery, but in fact some measurements were taken as late as 105 days after surgery.

It is well known in a linear regression setting that if we have measurement error in an independent variable, the estimated coefficient will be biased toward 0 in classical measurement error models but a measurement error problem will not affect parameter estimates in a Berkson model (Fuller, 1986). In general, measurement error models have an identifiability problem because there are too many parameters to estimate in such models. In our trial setting, we know the actual times when KPS was measured so that it is natural to estimate a variance of the measurement error at each visit. Even after we adjust for the measurement error, the associated confidence interval would be larger than that calculated when we do not have the measurement error problem.

In our setting we do not expect an extremely large change from baseline over time, rather we have a modest or small change over a time. If we allow a measurement error at each occasion: (1) the parameter estimate will be biased toward the null and (2) after adjustment for the measurement error we face a large confidence interval. Thus, we may not pick up the modest or small change due to the measurement error. This reviewer recommends a smaller window around each visit to minimize the measurement error problem in order to avoid bias toward the null by treating a clinical trial design as a balanced design or we can use actual time by considering the trial as an unbalanced

design.

This reviewer used reported actual time for each subject considering the trial as an unbalanced design. Therefore, this reviewer considered the trial as an unbalanced and incomplete design.

Appendix 9 shows a summary of the results of KPS measurements for all patients. On the Gliadel treatment arm we observed that as the count number of the measurements increased, the decline of KPS score was smaller, indicating that there was a relationship between KPS score and patients' survival; slow decline of KPS suggests a better survival (see Figure 6). As commented in Gliadel in Appendix 9, we found that the estimated slope among count categories was statistically significantly different. On Placebo treatment we observed the same phenomenon, but as noted in the appendix comments, the estimated slope was found to be statistically significantly different among count#>5, 5, and <5 (see Figure 7). By applying homogeneity criterion, we found that a possible missing mechanism in each treatment group is nonignorable. Therefore, statistical analysis with all observed data under an ignorable missing mechanism assumption would not be appropriate in our case.

This reviewer examined treatment effect (a slope difference) within count number. For count#< 5 and count#=5, there was not a statistically significant difference found between the two treatments. For count# >5 there might be a statistically significant difference between the two arms, depending on a statistical analysis as noted in comments for Gliadel in Appendix 9.

As we noticed in the survival analysis, tumor type is a very strong prognostic factor. Additional analyses will be required for GBM patients and for non-GBM patients.

III. Study CL-0190

Study CL-0190 was a small Phase III, multicenter, double-blind, placebo controlled trial with 32 patients, 16 patients in each arm, conducted in Finland and Norway. "Patients were enrolled into the study [from March 23, 1992 through May 14, 1993] after pathological examination of the tumor during surgery established the presence of malignant glioma. After maximum tumor resection [Study Day 1], the surgeon placed up to eight GLIADEL wafers, each containing approximately 7.7 mg BCNU or eight BIODEL (PLACEBO) wafers, into the resection cavity. About three weeks after surgery, standard radiotherapy began". The patients were newly diagnosed with malignant glioma.

The objective of this study was to evaluate the safety and efficacy of Gliadel as adjunctive treatment with surgery and external beam radiotherapy in patients **newly diagnosed with malignant glioma without prior surgical, radiotherapeutic, or chemotherapeutic treatment** .

This study was stopped after 32 patients were enrolled instead of the planned number of 100 patients because (i) "concerns about the lack of evidence that wafers from GLIADEL lot SR042-49-7 were sterile" and (ii) no GLIADEL wafers were available for
to allow the study to continue.

"The monitoring of the results was to be done after every tenth event (death) using a sequential restricted triangular stopping rule." An interim analysis was performed on a half of the patients, 16 patients, during the spring of 1994.

The primary efficacy variables were 12 month survival rates, median survival duration, and time to treatment failure. The secondary efficacy variables were KPS evaluations and MMSE Scores.

III.1 Summary of the Sponsor's Results for CL-0190

This reviewer summarized and confirmed the reported results of the sponsor through the submitted data.

III.1.1 Primary Efficacy Variables (Study CL-0190):

For All Patients:

First, this reviewer will focus on all patients in the study.

(i) Survival Rates:

Reviewer's Table 3.1 summarizes twelve months and overall survival (up-to 24 months) rates. 6 of the 16 Gliadel patients and 13 of the 16 Placebo patients died before 12 months after wafer implantation surgery (p=0.029 by Fisher's exact test). The overall survival rates were not statistically significant between the two treatments (p=0.172 by Fisher's exact test).

Reviewer's TABLE 3.1: Survival Rates

	12 month		Overall (up-to 24 month)	
	Gliadel	Placebo	Gliadel	Placebo
Death	6	13	11	15
Alive	10	3	5	1
Total	16	16	16	16
	p=0.029 (Fisher's Exact)		p=0.172 (Fisher's Exact)	

(ii) Survival Duration:

Reviewer's Table 3.2 shows 12 month and overall survival analysis results. The logrank and Gehan's generalized Wilcoxon tests show a highly statistically significant survival advantage for Gliadel with p=0.0087 and p=0.0105 in the twelve months survival comparison and p=0.012 and p=0.011 in the overall survival comparison, respectively. The median survival durations were 13.37 months (95% ci: 9.66 months to an inestimable maximum) and 9.17 months (95% ci: 8.64 - 10.33 months) for Gliadel and Placebo group patients, respectively. Reviewer's Figure 4 shows the overall Kaplan-Meier survival curve, indicating that the survival difference between the two arms occurred near the 12 month cut-point and that there existed a strong survival difference between the two treatments.

Reviewer's TABLE 3.2 Patients' Survival

12 months		Overall (up-to 24 months)	
logrank	Wilcoxon*	logrank	Wilcoxon*
p=0.0087	p=0.0105	p=0.012	p=0.011
Median Survival			
Gliadel		Placebo	
13.37 months (95% ci: 9.66 - inestimable)		9.17 months (95% ci: 8.64 - 10.33 months)	

Note that Wilcoxon* stands for a Gehan's generalized Wilcoxon test.

(iii) Cox Regression:

Cox regression was applied "to control for the effect of strong prognostic factors on survival outcome due to chance imbalances in the treatment groups". Eight factors were identified as being of potential clinical importance by the sponsor (Table 4.19 on page 43 in volume 1.54). By applying univariate regression analyses without treatment effect, three factors (tumor type, age, and Mini-Mental State Examination (MMSE) score) were identified with $p < 0.15$ criterion. A stepwise procedure (backward) was employed to identify important prognostic factors further with p=0.05 criterion. Reviewer's Tables 3.3 and 3.4 show the results for 12 month survival and overall survival with p=0.0010 and p= 0.0005, respectively for treatment effect.

Reviewer's TABLE 3.3 Cox Regression analysis for 12 Month Survival

Treatment Effect in Twelve-Month Survival (All Patients)			
Parameter	Estimate	Standard Error	P-Value
Treatment	-1.8737	0.5671	**0.0010**
Age (per decade)	0.8337	0.3817	0.0290
MMSE Score	-1.5738	0.5532	0.0044

Reviewer's TABLE 3.4 Cox Regression Analysis for Overall Survival

Treatment Effect in Overall Survival (All Patients)			
Parameter	Estimate	Standard Error	P-Value
Treatment	-1.7324	0.4961	**0.0005**
Age (per decade)	0.8100	0.3168	0.0106
MMSE Score	-1.3866	0.4683	0.0031

For GBM Patients:

In this study, 27 out of 32 patients had GBM tumor type. The following results were limited to the GBM patients.

(i) Survival Rates for GBM Patients:

Reviewer's Table 3.5 shows survival rates for the 12 month period and for the overall study period (up to 24 months). Five of 11 Gliadel patients and 13 of 16 Placebo patients died before 12 months after the implantation (p=0.097 Fisher's Exact test). 9 of the Gliadel patients and 15 of Placebo patients died during the study period (p=0.549 Fisher's Exact test).

Reviewer's TABLE 3.5 Survival Rates for GBM Patients

	12 month		Overall (up-to 24 month)	
	Gliadel	Placebo	Gliadel	Placebo
Death	5	13	9	15
Alive	6	3	2	1
Total	11	16	11	16
	p=0.097 (Fisher's Exact)		p=0.5487 (Fisher's Exact)	

(ii) Survival Duration for GBM Patients:

Reviewer's Table 3.6 shows survival analyses for 12 month and the overall study period. Figure 5 shows a overall Kaplan-Meier survival curve for GBM patients. The median survival duration after the implantation was 12.25 months (95% CI; 9.23 - 17.87 months) for Gliadel patients compared to 9.17 months (95% CI: 8.64 - 10.35 months) for Placebo patients (p=0.126 and p=0.093 by the logrank and Wilcoxon test, respectively). The Cox regression with Age and MMSE score as covariates indicated a strong statistically significant survival difference during the overall study period. During the 12 month period the logrank and Wilcoxon tests showed a borderline statistically significant survival difference and Cox regression showed a strong survival difference.

Reviewer's TABLE 3.6 Survival Analyses for 12 months and Overall Study Period for GBM Patients

12 month		Overall (up-to 24 month)	
logrank	Wilcoxon*	logrank	Wilcoxon*
p=0.0587	p=0.0702	p=0.1261	p=0.0931
Cox Regression		Cox Regression	
P=0.0072 with MMSE Score		P=0.0035 with Age and MMSE score	
Median Survival for Overall Study Period			
Gliadel		Placebo	
12.25 months (95% CI: 9.23 - 17.87 months)		9.17 months (95% CI: 8.64 - 10.35 months)	

Note that Wilcoxon* stands for a Gehan's generalized Wilcoxon test.

Subgroup Analyses: (Tumor Type, Age, and Gender)

Appendix 10 presents subgroup analyses by tumor type, age, and gender for 12 months and overall survival experience.

Tumor Type: in this study most patients had GBM tumor type (11 of 16 on Gliadel and all 16 on Placebo had GBM tumor type). There existed a marginally statistically significant survival advantage for Gliadel in 12 months survival and no statistically significant advantage for Gliadel in overall survival.

Age: most subjects in this study were under 65 years of age (15 of 16 subjects in both treatment groups were under 65 years of age). A statistically significant difference was demonstrated in patient survival in both the 12 months and overall study periods.

Gender: a statistically significant survival difference was found in the female subgroup, but not in the male subgroup in both of 12 months and overall study period.

Reviewer's Comments:

(I) **Results from survival analyses**

Reviewer's Table 3.7 summarizes the results of survival analyses (logrank, Gehan's generalized Wilcoxon and Cox model) for 12 months and for the overall study period (up to 24 months). The three approaches indicate a statistically significant survival advantage for Gliadel over Placebo.

Reviewer's Table 3.7 Summary of Survival Analyses for 12 Months and Overall Study Period in Study CL-0190

12 Months Survival After Wafer Implantation Surgery		
logrank	Wilcoxon*	Cox
P=0.0087	P=0.0105	P=0.0010
Overall Survival After Wafer Implantation Surgery		
logrank	Wilcoxon*	Cox
P=0.012	P=0.011	P=0.0005

Note that Wilcoxon* stands for a Gehan's generalized Wilcoxon test.

Previously, in the reviewer's comments for Study 8802, three issues - (i) effect of imbalance of prognostic factors at baseline, (ii) misspecification of Cox model (omitting covariates in a model), and (iii) stability issues of the estimated coefficients in a Cox model- were discussed.

For the first issue, Appendix 11 presents baseline characteristics of two covariates, MMSE score and Age (per decade). This reviewer did not find major imbalance in baseline covariates. For the second issue, this reviewer recommends a robust standard error for each estimated coefficient to produce a robust Wald's test. For the third issue, reviewer's table 3.8 shows that AGE10 (age variable treated as continuous) did not have more influential information than a dichotomous age variable, AGE*. This effect can be found by comparison with the results from Cox models with covariates between AGE* and MMSE Score and AGE10 and MMSE Score, between AGE* and AGE10, between AGE* and KAR and AGE10 and KAR in 12 months and overall study periods.

To obtain a more robust result with medically meaningful covariates, this reviewer applied a stratified logrank test after consultation with the reviewing medical officer, Alison Martin M.D.. Reviewer's table 3.8 shows the results of stratified logrank tests and corresponding Cox models with two age categories, AGE* and AGE10 for GBM patients in Study CL-0190. This reviewer focused on analyses for GBM patients because 27 of the 32 subjects had a GBM tumor type.

Age (AGE* and AGE10) and Karnofsky Performance Status (KAR) were selected from the medical point of view and Mini-Mental State Examination Score (MMSE) was selected because this variable was chosen in the sponsor's Cox models.

Reviewer's Table 3.8 The Results of Stratified Logrank Tests and Corresponding Cox Models in 12 Months and Overall Study Period for GBM Patients in Study CL-0190

GBM Patients				
	12 Months (logrank: p=0.0587)		Overall (logrank: p=0.1261)	
Covariates	Stratified Logrank	Cox	Stratified Logrank	Cox
AGE* MMSE Score	P=0.0046	P=0.0027 (P=0.0035 with AGE10 and MMSE Score)	P=0.0029	P=0.0017 (P=0.0035 with AGE10 and MMSE Score)
AGE*	P=0.0382	P=0.0326 (P=0.0291 with AGE10)	P=0.0173	P=0.0252 (P=0.0420 with AGE10)
MMSE Score	P=0.0095	P=0.0072	P=0.0190	P=0.0129
AGE* KAR	P=0.01	P=0.0057 (P=0.007 WITH AGE10 and KAR)	P=0.0063	P=0.0081 (P=0.0189 with AGE10 and KAR)
KAR	P=0.0235	P=0.0199	P=0.0773	P=0.0529

Note that AGE* is a dichotomous variable with a cut-off point=55.5 years of age.
Note that MMSE score stands for Mini-Mental State Examination Score and KAR for Karnofsky Performance Status Evaluation.
Note that imbalance of KAR at baseline was observed, i.e., more subjects with >70 KAR were in the Placebo arm.

According to reviewer's table 3.8 the results from a stratified logrank test were consistent with those obtained by a corresponding Cox model in 12 months and overall study periods to indicate a statistically significant survival advantage for Gliadel. Age, Karnofsky Performance Status score, and Mini-Mental State Examination score were shown to be a important prognostic factor in both study periods. Since we have a quite small sample size; 27 patients with 18 deaths in 12 months and 24 deaths in the overall study period, this reviewer considered a stratified logrank test with AGE* as a final model from the medical point of view and the stability point of view because we would have 4 cells with 2 covariates and 2 cells with one covariate.

Therefore, this reviewer considers that a statistically significant survival advantage for Gliadel was demonstrated for GBM patients.

III.2. Quality of Life (QOL)

Karnofsky Performance Status (KAR) and Mini-Mental State Examination Score (MMSE) were measured as parameters of Quality of Life. Both measurements were taken at Baseline, Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12. The sponsor applied a longitudinal analysis known as a "Generalized Estimating Equation" (GEE) approach advocated by Liang and Zeger (1986).

In order to deal with two challenges; the correlation issue among observations per subject and a

missing data issue, in a longitudinal analysis, the sponsor applied an "independent" correlation assumption for the correlation problem and observed case (OC) analysis and last observation carried forward (LOCF) analysis for missing data. The sponsor applied this technique to an ANOVA type analysis.

Reviewer's table 3.9 summarizes the results from two analyses of KAR score as a continuous variable: OC and LOCF analyses. Neither analyses showed a statistically significant treatment effect of Gliadel over Placebo treatment.

Reviewer's TABLE 3.9: The Results from the Two Missing Assumptions with an "Independent" Working Assumption

	OC Analysis	LOCF Analysis
Treatment Effect	P=0.808	P=0.174
Visit Effect	P=0.010	P=<0.001
Trt x Visit interaction	P=0.546	P=0.239

Reviewer's Comments on QOL Analysis for Study CL-0190:

The sponsor employed a GEE approach to a small sample of 32 subjects. The results from the GEE approach will be valid if we have a large sample size of subjects, not of observations per subject. Therefore, this reviewer is doubtful that this sample size is large enough to support asymptotic results.

For a missing data problem, the sponsor employed two approaches: observed case (OC) analysis and last observation carried forward (LOCF) analysis. As discussed in reviewer's comments on QOL analysis for Study 8802, OC analysis must assume a "missing completely at random" (MCAR) missing mechanism, which is unlikely to be realistic in our setting. LOCF analysis must assume that the last observation will be frozen until the end of trial so that missing data will be replaced by the last observed data. These two missing mechanism assumptions are too strong to be appropriate in this setting.

As discussed in reviewer's comments on QOL analysis for Study 8802, the reviewer recommends a growth curve approach employing the idea of 'pattern-mixture model' for the missing data problem. Since in this case we have a very small sample size with heavy dropouts after Visit 8, this reviewer recommends a two stage approach without any test of slope.

IV. Reviewer's Summary and Conclusions

The treatment effect of Gliadel for patients with a malignant glioma as an adjunct to surgery to prolong survival was investigated. In this review the two controlled studies, 8802 and 0190, were reviewed.

Study 8802 was a Phase III, multicenter, randomized, double-blind, placebo controlled trial with 222 total patients, 110 on Gliadel arm and 112 on Placebo arm. Patients with **recurrent** malignant gliomas were eligible for this trial. This study was conducted in North America. Study 0190 was a small Phase III, multicenter, double-blind, placebo controlled trial with 32 patients, 16

patients on each arm. Patients with **newly diagnosed malignant gliomas without prior surgical, radiotherapeutic, or chemotherapeutic treatment** were eligible for this trial. The study was conducted in Finland and Norway.

The primary efficacy variables in both studies were survival rates and patient survival. For the survival rates both studies indicated a marginally or statistically significant benefit in rates for Gliadel over Placebo treatment at early times, 6 months and 12 months, for Study 8802 and Study 0190, respectively. On the other hand, at the end of the study period, neither study showed any survival rate benefit for Gliadel over Placebo arm.

For patient survival, as discussed in reviewer's comments on Study 8802, this reviewer raised three issues regarding discrepant results among three tests (logrank, Gehan's generalized Wilcoxon, and Cox model), indicating a strong treatment effect for Gliadel with Cox modeling vs. marginal difference with a logrank test: (i) effect of imbalance of prognostic factors at baseline, (ii) misspecification of Cox model (omitting covariates in a model), and (iii) stability of estimated coefficients. For the first issue, there did not exist a major imbalance in prognostic factors at baseline to account for the large difference in p-values obtained by nonparametric approaches and a Cox model in both studies. For the second issue, this reviewer recommended a robust standard error estimate along with a naive estimate to judge how far off or how close these estimates are since we do not know a true Cox model. The third issue is related to the second issue. This reviewer recommended a robust standard error estimate to produce a robust Wald's test statistic, and pointed out the need for checking the validity of the proportional hazards assumption when a Cox model is applied.

This reviewer applied a stratified logrank test to lessen the need for the proportional hazards assumption and to control the effect of fewer, but medically meaningful prognostic factors. This analysis indicated that there existed a statistically significant survival benefit of Gliadel in both the 6 months and overall study periods in Study 8802. In this analysis, tumor type, Karnofsky Performance Status, and age are suggested to be influential prognostic factors in both study periods. For GBM patients, a stratified logrank test showed a statistically significant survival benefit for Gliadel over Placebo treatment in 6 months and overall study periods and Karnofsky Performance Status and age are suggested to be influential prognostic factors in both periods. On the other hand, there did not exist a statistically significant survival benefit for Gliadel for non-GBM patients in either period.

For Study CL-0190, a stratified logrank test indicated a statistically significant survival benefit for Gliadel over Placebo treatment in both 12 months and overall study periods for GBM patients. In this study this reviewer focused on GBM patients because 27 of the 32 patients had a GBM tumor type. Age is suggested to be an influential prognostic factor in this study.

Since there existed a statistically significant treatment benefit for Gliadel in patient survival in Study 8802 and in Study CL-0190 for GBM patients, but not for non-GBM patients in Study 8802, this reviewer recommends approval of Gliadel for the treatment of GBM patients.

The secondary efficacy variables are Quality of Life measured by Karnofsky Performance Status score and Mini-Mental State Examination score. The sponsor performed a longitudinal analysis by the GEE approach with an "independent" working assumption to cope with a correlation problem and observed case analysis and last observation carried forward analysis to deal with a missing data problem. In these analyses overall treatment effect was found not to be statistically significant in either study. This reviewer applied a growth curve analysis by the GEE method and a linear mixed effect model to cope with a correlation problem and employed the concept of a "pattern-

mixture model" to judge whether the observed missing mechanism was ignorable or nonignorable. This approach suggested that the observed missing pattern in Study 8802 was due to a nonignorable missing mechanism and that OC analysis would not be valid in this case. This reviewer found a relationship between Karnofsky Performance Status score and survival time, i.e., the longer a patient survival time is, the slower the decline in Karnofsky Performance Status. This relationship was observed in both Gliadel and placebo arms, but there existed no statistically significant QOL benefit for Gliadel in patients who died before 6 months. A treatment effect for Gliadel over Placebo was detected, but the result depended upon a statistical approach with a small sample size. Therefore interpretation of these results must be extremely cautious.

Masahiro Takeuchi Sc.D.
Mathematical Statistician

Concur: Dr. Gnecco, C Gnecco 7/3/96
Dr. Chi Chi 7/12/96

cc:
NDA#20,637
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HFD-150 / Dr. Alison Martin
HFD-150 / Paul Zimmerman, CSO
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HFD-710 / Dr. Gnecco
HFD-710 / Dr. Takeuchi
HFD-710 / Chron
HFD-150 / E Cutler
Takeuchi / 07-01-96 / WP3.1 - Gliadel_Review
This review consists of 25 pages of text, 7 figures, and 11 appendices.

Figure 1: Overall Kaplan-Meier Survival Curves for All Patients by Treatment Group (Study 8802)

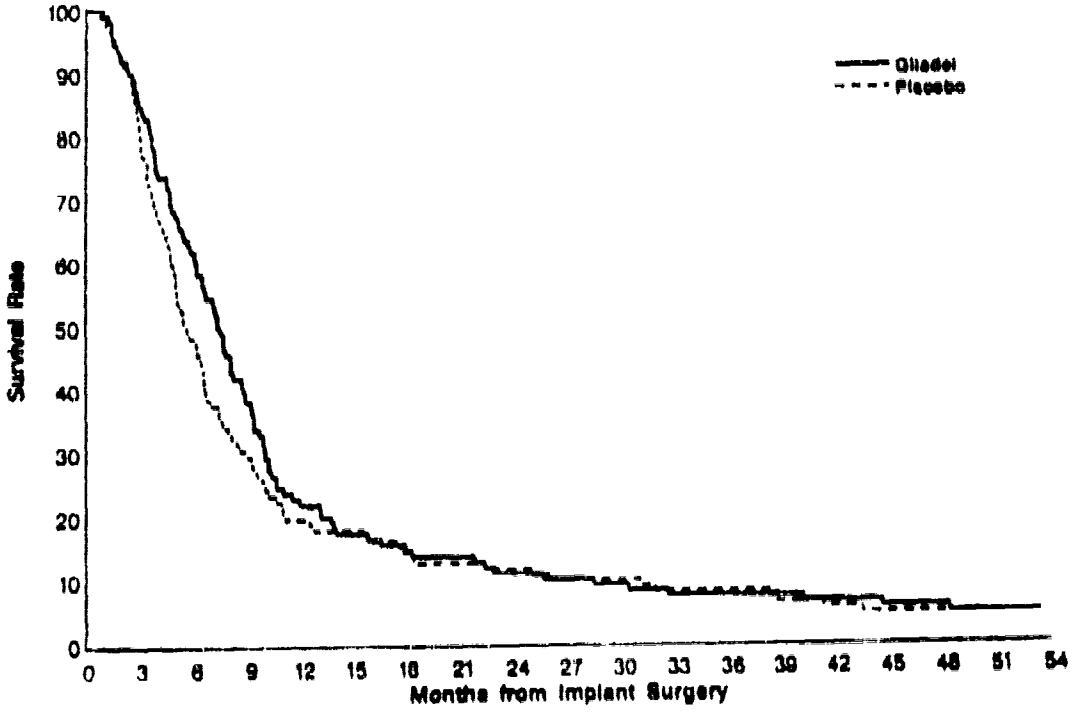


Figure 2: Overall Kaplan-Meier Survival Curves for All Patients by Treatment Group and Tumor Type (Study 8802)

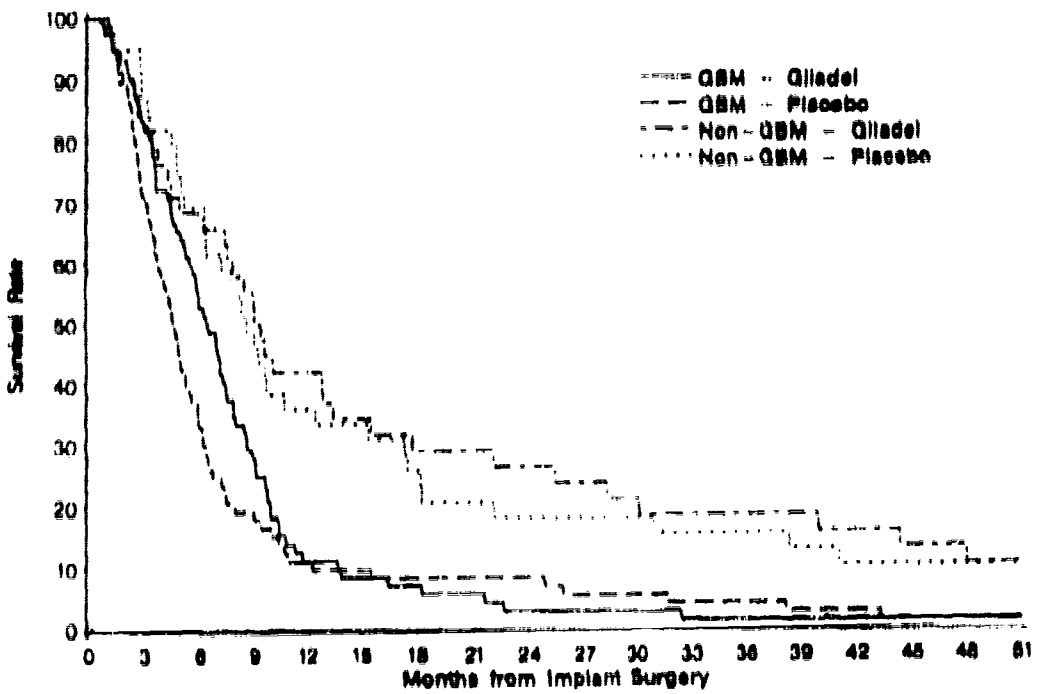


Figure 3:

Overview: A Longitudinal Approach

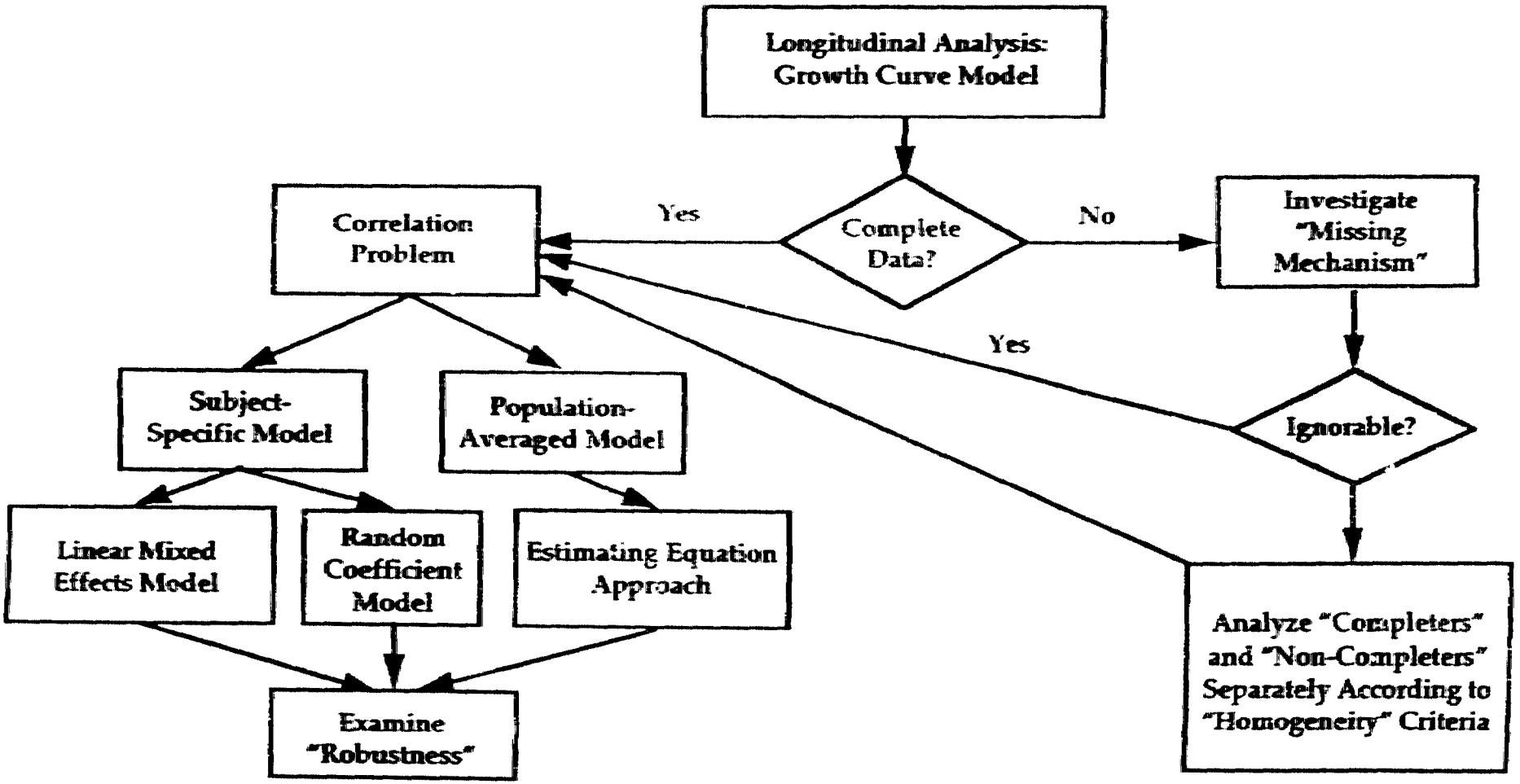


Figure 4: Overall Kaplan-Meier Survival Curves for All Patients by Treatment Group (Study CL-0190)

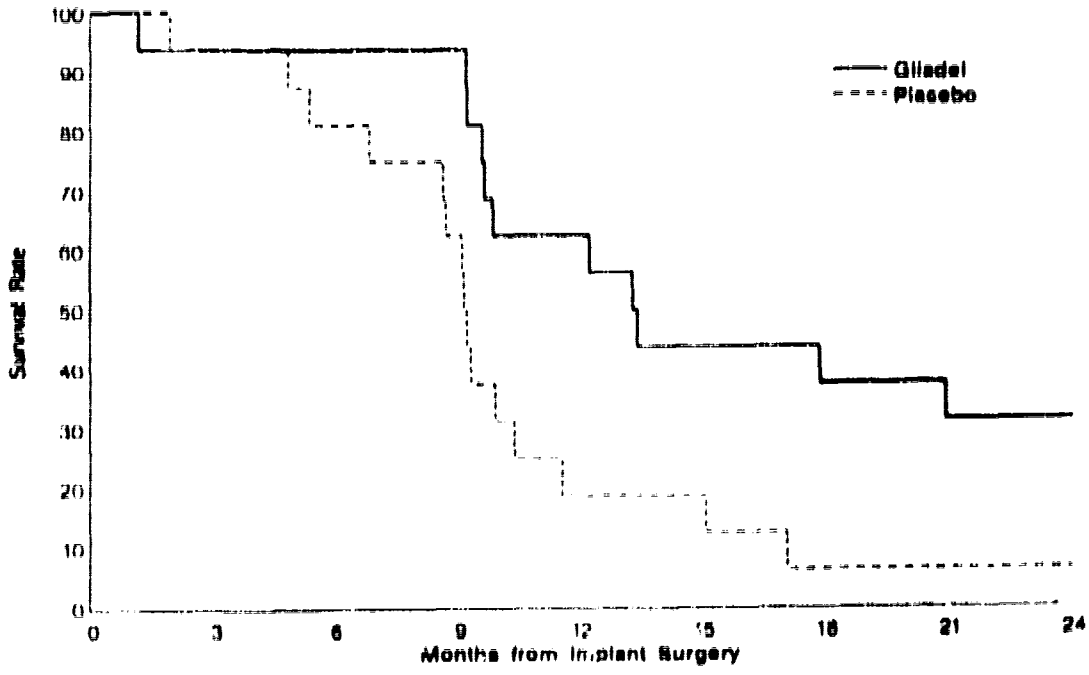


Figure 5: Overall Kaplan-Meier Survival Curves for GBM patinets by Treatment Group (Study CL-0190)

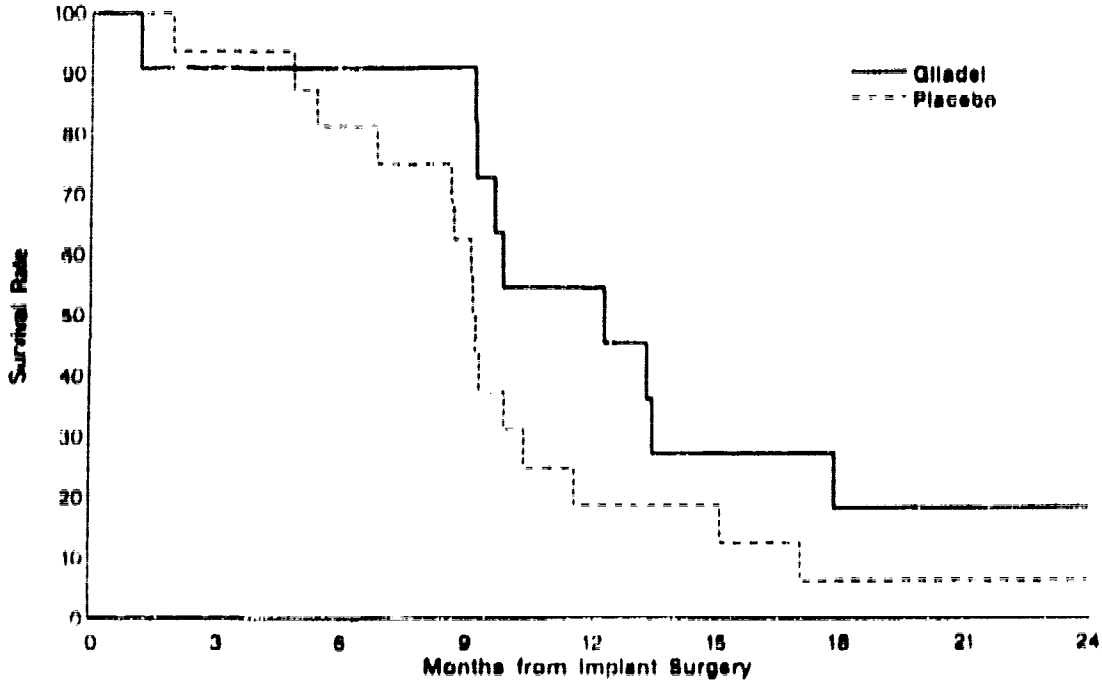


Figure 6:

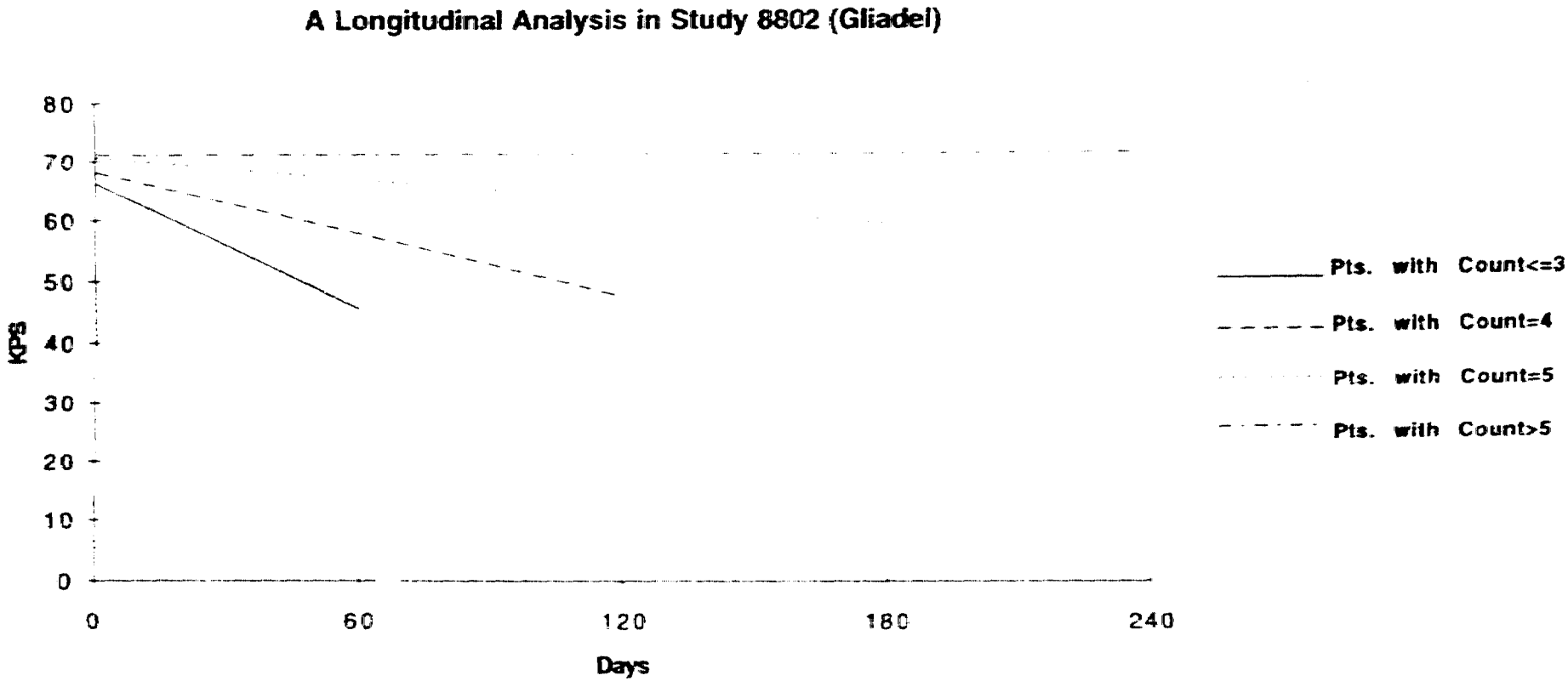
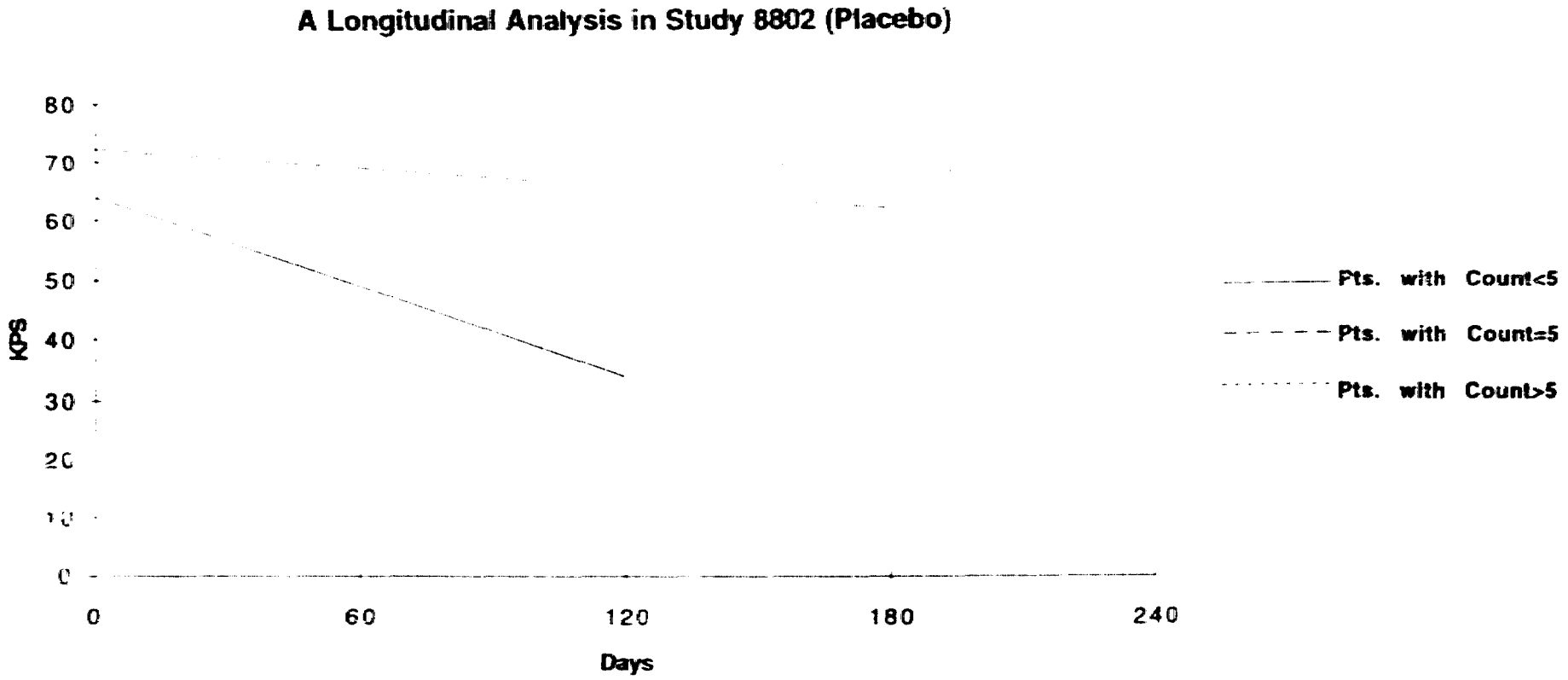

A Longitudinal Analysis in Study 8802 (Gliadel)
KPS
80
70
60
50
40
30
20
10
0
0
60
120
180
240
Days
Pts. with Count<=3
Pts. with Count=4
Pts. with Count=5
Pts. with Count>5

Figure 7:


A Longitudinal Analysis in Study 8802 (Placebo)
KPS
80
70
60
50
40
30
20
0
0
60
120
180
240
Days
Pts. with Count<5
Pts. with Count=5
Pts. with Count>5

APPENDIX 1: Baseline Covariates Employed in Cox Regression in Study 8802

Tumor Type			
	Non-GBM	GBM	
Placebo	39	73	112
Gliadel	38	72	110
Fisher's Exact p=1.0000			

Karnofsky Performance Score			
	<=70	> 70	
Placebo	56	56	112
Gliadel	49	61	110
Fisher's Exact p=0.4237			

Location of Prior Radiation Therapy			
	Whole Brain	Local/both	
Placebo	23	88	111
Gliadel	28	82	110
Fisher's Exact p=0.4283			

Tumor Resection ≥75% vs. <75%			
	< 75%	≥ 75%	
Placebo	30	82	112
Gliadel	28	82	110
Fisher's Exact p=0.8791			

Prior Chemotherapy			
	None	Yes	
Placebo	58	54	112
Gliadel	52	58	110
Fisher's Exact p=0.5059			

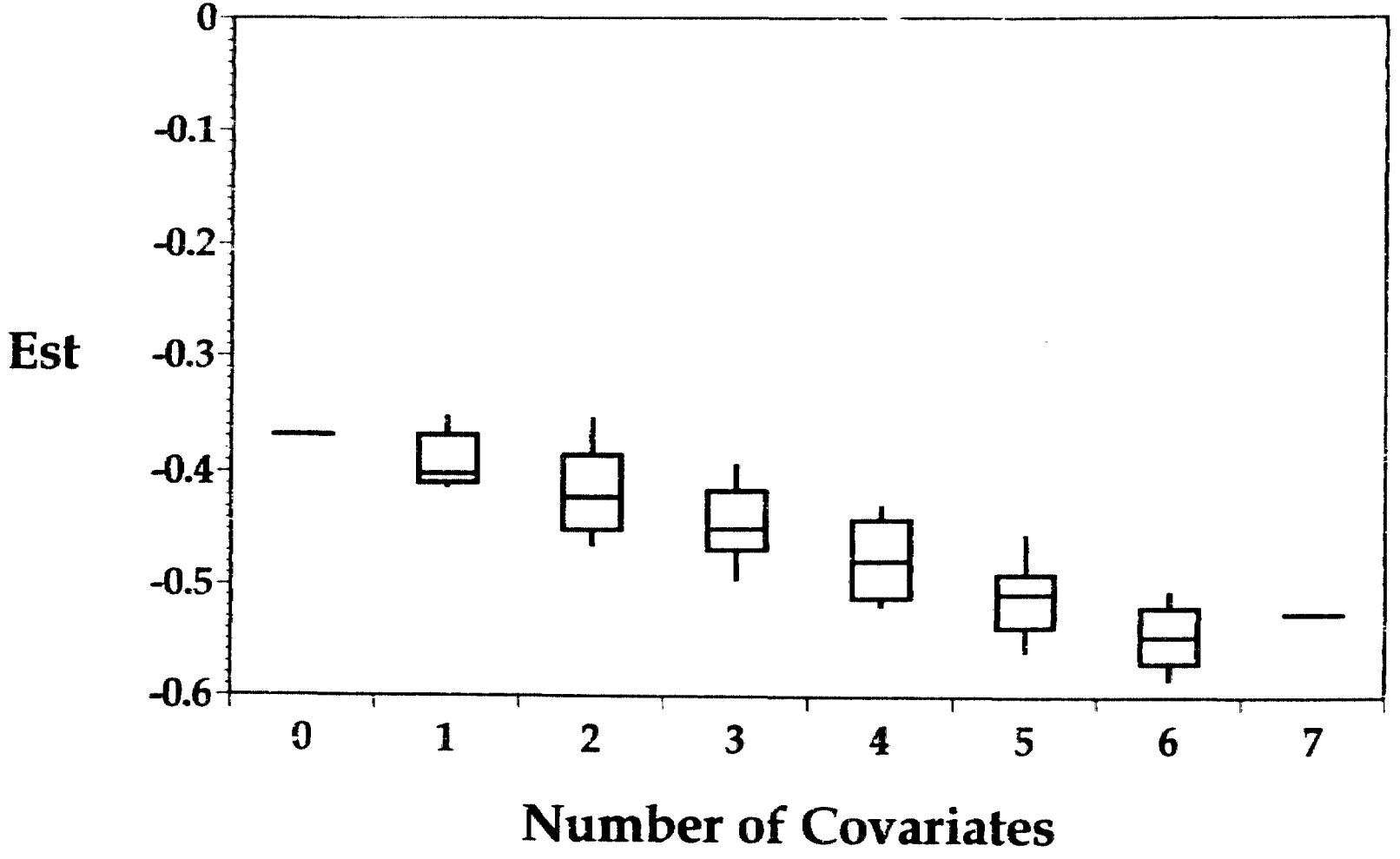
APPENDIX1: Baseline Covariates Employed in Cox Regression in Study 8802

Number of Wafers ≤6 vs. >6			
	> 6	≤ 6	
Placebo	101	11	112
Gliadel	104	6	110
Fisher's Exact p=0.3132			

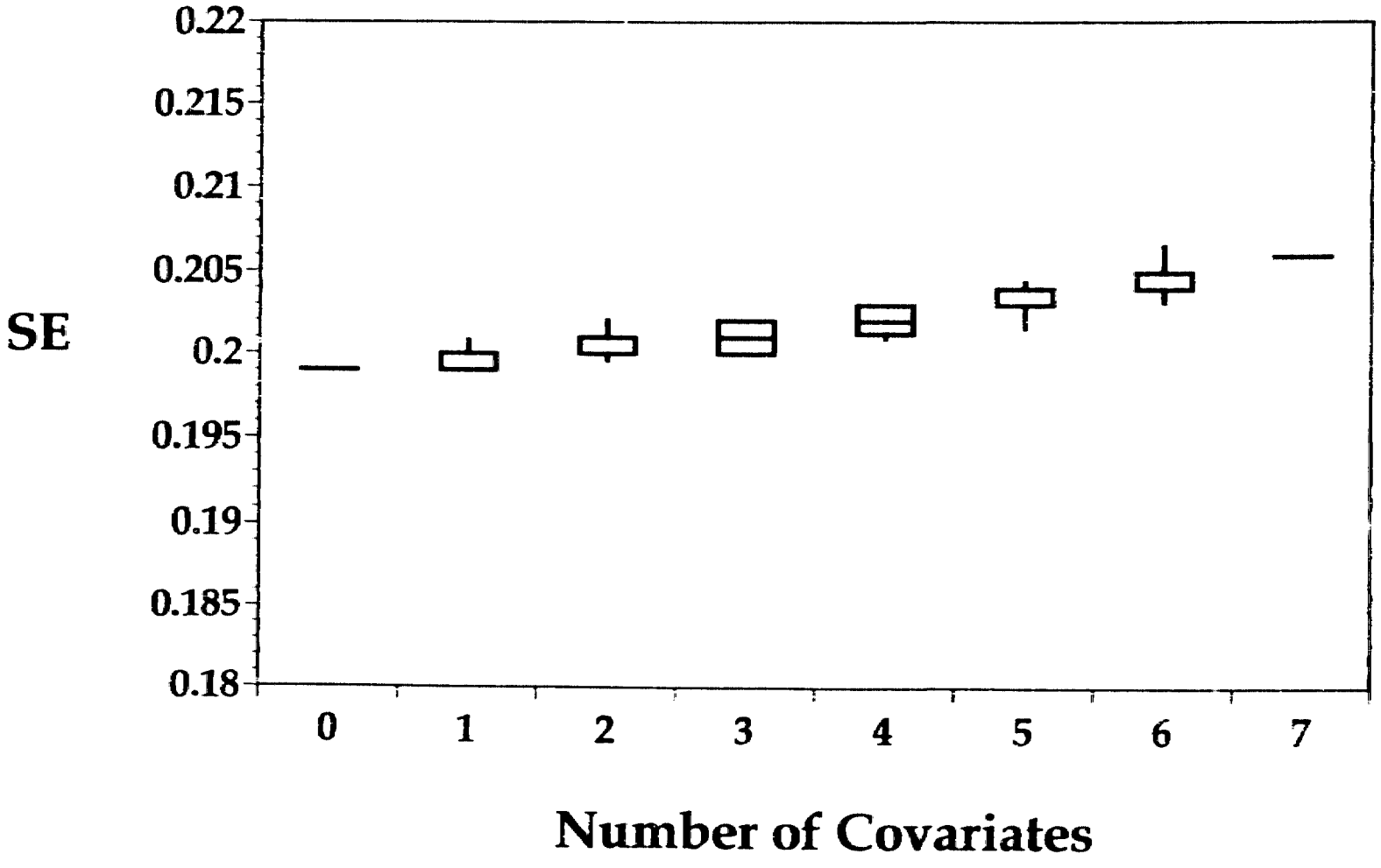
Age (Per Decade)		
	Placebo (N=112)	Gliadel (N=110)
Mean	4.806	4.862
SD	1.368	1.228
100%	8.073	7.915
75%	5.912	5.756
50%	4.813	4.906
25%	3.817	3.800
0%	1.961	2.772

Years From First Surgery to Index Surgery		
	Placebo (N=112)	Gliadel (N=110)
Mean	1.993	1.996
SD	2.732	2.433
100%	17.993	13.999
75%	2.029	1.878
50%	0.947	1.079
25%	0.604	0.715
0%	0.230	0.257

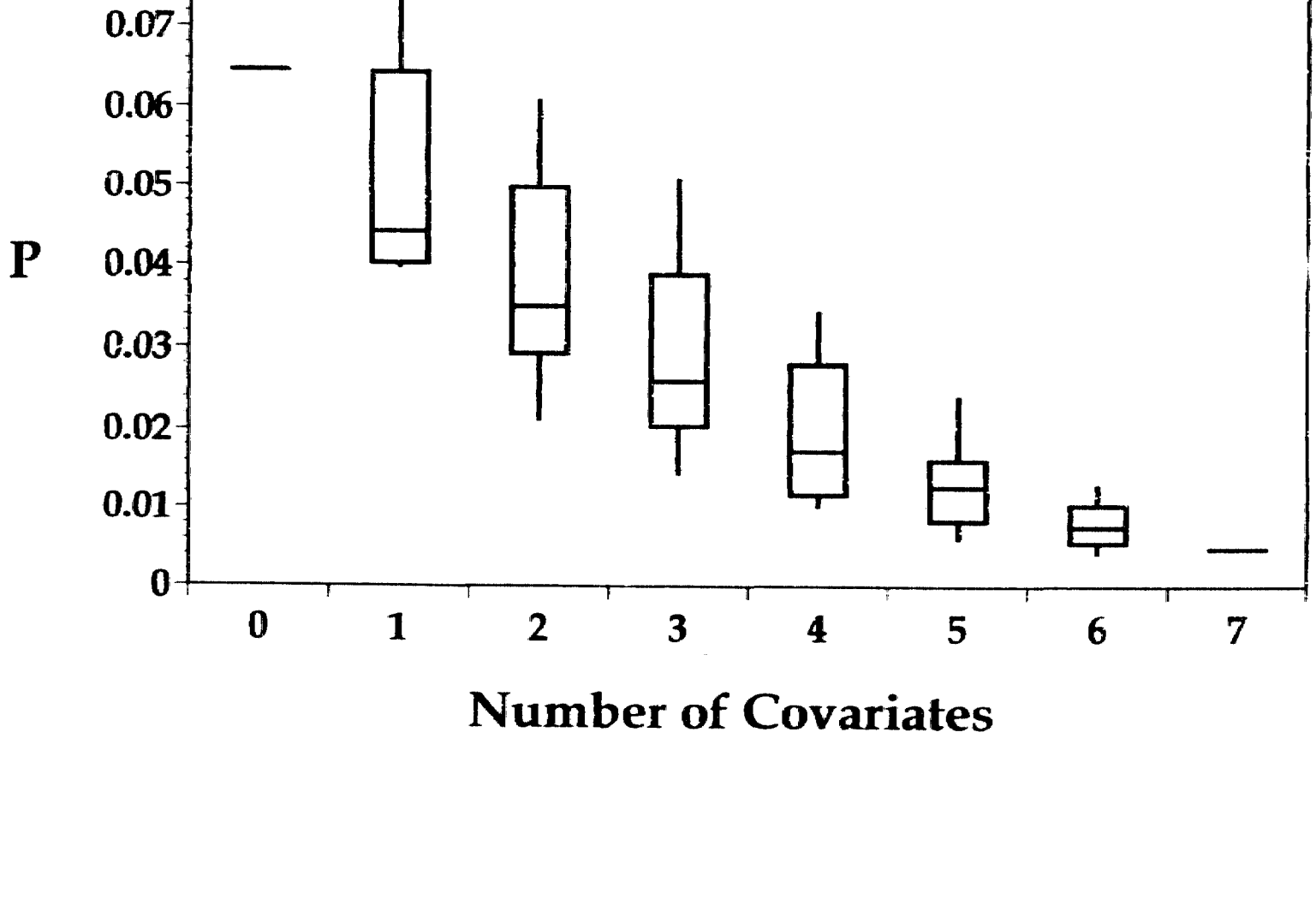
Appendix 2: Change of Treatment Effect Estimate Over A Number of Covariates in Six Month Survival (Study 8802)



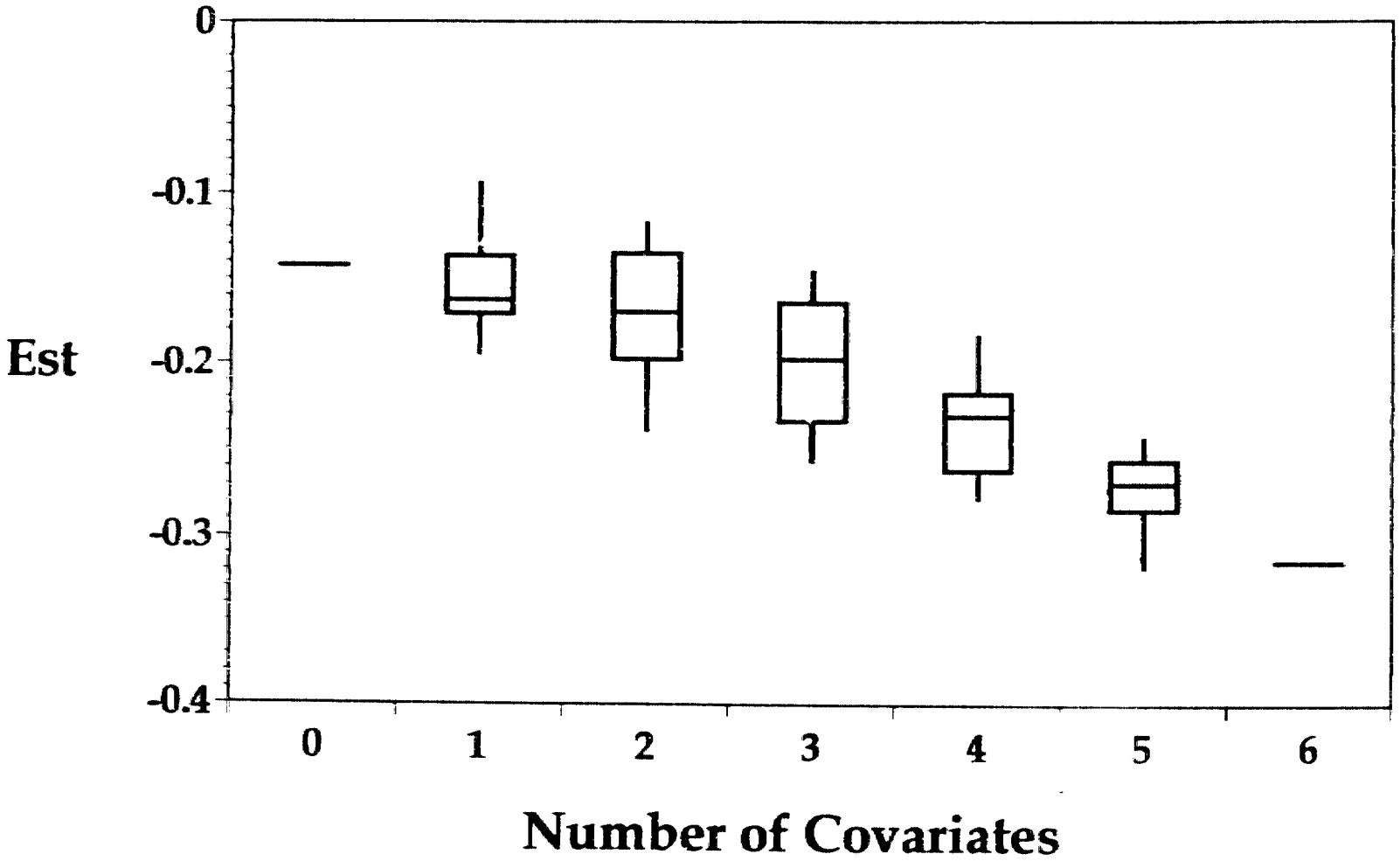
Appendix 3: Change of Standard Error Estimate Over A Number of Covariates in Six Month Survival (Study 8802)



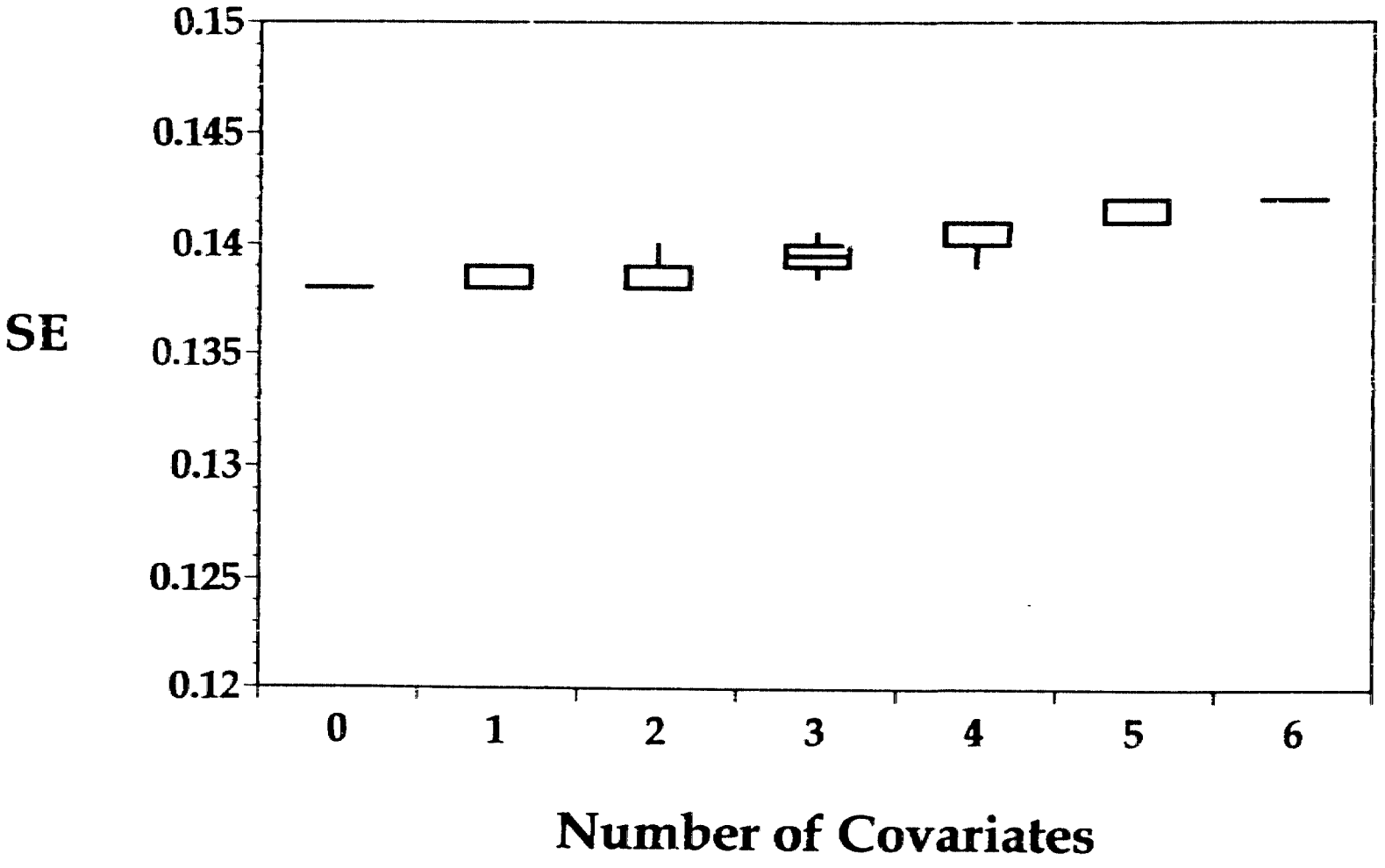
Appendix 4: Change of P-Value Over A Number of Covariates in Six Month Survival (Study 8802)



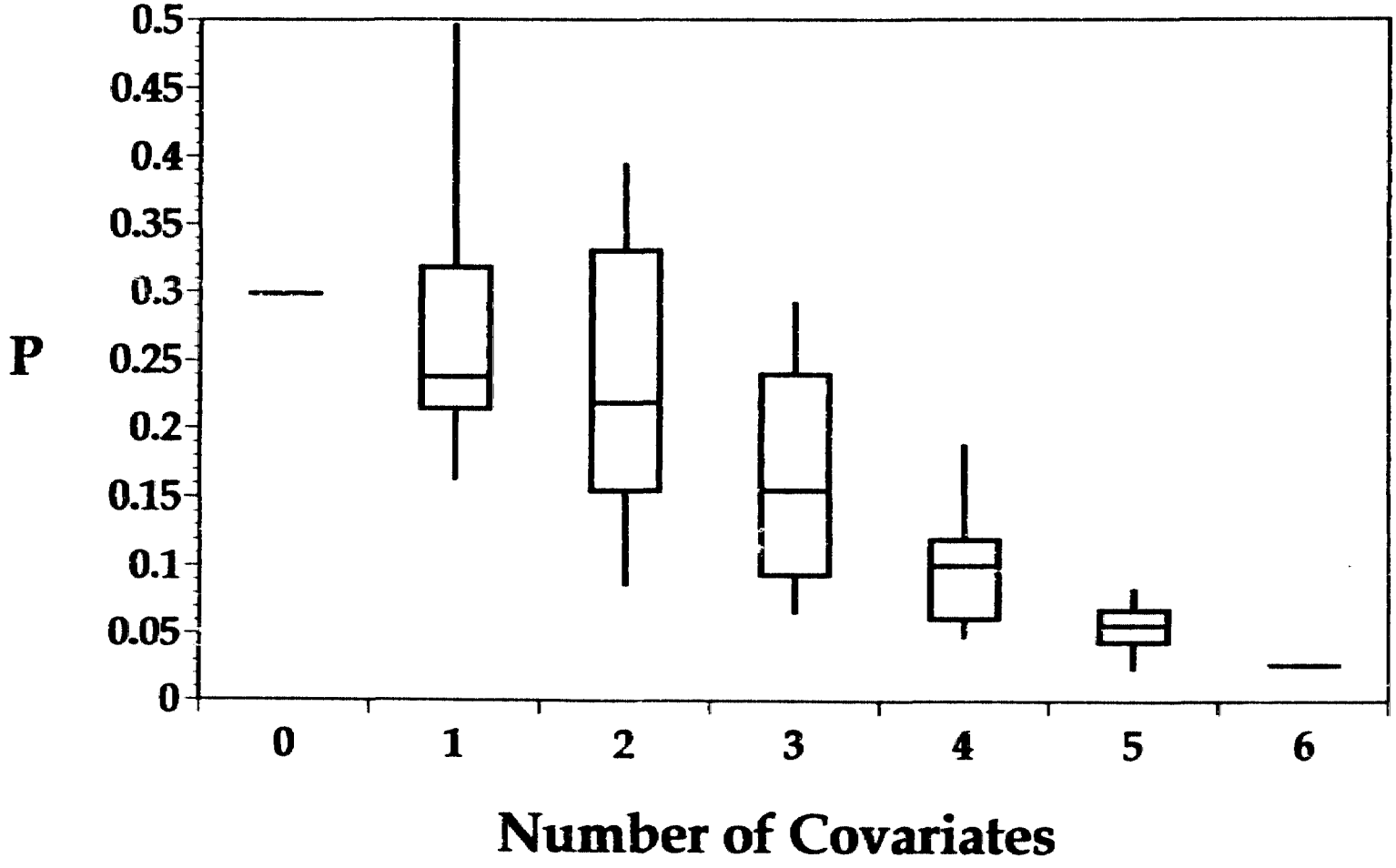
Appendix 5: Change of Treatment Effect Estimate Over A Number of Covariates in Overall Survival (Study 8802)



Appendix 6: Change of Standard Error Estimate Over A Number of Covariates in Overall Survival (Study 8802)



Appendix 7: Change of P-Value Over A Number of Covariates in Overall Survival (Study 8802)



APPENDIX 8: A Summary of Longitudinal Linear Models

We briefly outline longitudinal linear models, which can be applied under an ignorable missing assumption or within a homogeneity group under a nonignorable missing assumption.

In a general longitudinal analysis Zeger *et al* (1988) make a distinction between two types of longitudinal analyses: a "subject-specific (SS) model" (a type of mixed effects model) and a "population-averaged (PA) model". In the SS model, we are mainly concerned with individuals' response over time, and the heterogeneity of the data from each individual can be explicitly modeled. On the other hand, the PA model focuses on the average response and the heterogeneity of individuals is not considered in the model.

The SS model focuses on the between-subject variability in a data set. The variance can be modeled explicitly, and will contribute to the marginal covariance structure and/or the marginal mean functions in the SS models. This is the approach used in the linear mixed effects model. However, if the analysis is not focused on accounting for between subject variability, a PA model approach, with relaxed assumptions, can be applied. This is a Generalized Estimating Equations (GEE) approach. As noted by Zeger *et al* (1988), a marginal covariance structure, which is one of the challenges in a repeated measurement setting, can be explained by the two approaches in a different fashion. On the other hand, a marginal means, in our case, intercept and a slope, will not be affected by the two approaches.

1. Subject-Specific Linear Models

Linear mixed effects models have been investigated by a number of researchers (Harville, 1976 and 1977, and Rao, 1965, 1967, and 1975). As described above, by introducing distributional assumptions for each individual's random variability, a marginal covariance structures can be explained explicitly. Of particular interest in the regulatory context, Laird and Ware (1982) have described the application of these models to unbalanced (in general we have a balanced design in a clinical trial setting) and incomplete data based on the assumption that a missing mechanism is defined as "missing at random" (MAR), belonging to an ignorable missing mechanism. The model can be defined as

$$y_i = X_i\beta + Z_i b_i + \varepsilon_i$$

where Z_i is a known design matrix of random effects, b_i, and b_i and ε_i are N (0, Ω) and N (0, $\sigma^2 I_i$) respectively. Note that we assume that b_i and ε_i are independent of each other. To estimate the fixed effects parameters (population parameters), we need to know the marginal means and marginal covariance matrix. Applying the independence assumption of b_i and ε_i with the corresponding expectation equal to 0, we will obtain

$$E(y_i) = X_i\beta \text{ and } \operatorname{cov}(y_i) = Z_i\Omega Z_i^T + \sigma^2 I_i = V_i$$

Then the estimated fixed effects parameters can be obtained by

$$\hat{\beta} = \left(\sum_{i=1}^{K} X_i^T \hat{V}_i^{-1} X_i \right)^{-1} \left(\sum_{i=1}^{K} X_i^T \hat{V}_i^{-1} y_i \right) \text{ and } \operatorname{cov}(\hat{\beta}) = \left(\sum_{i=1}^{K} X_i^T \hat{V}_i^{-1} X_i \right)^{-1}$$

Note that (I) the random effects only contribute to the marginal covariance matrix, and not to the marginal means, i.e., V_i is the only function of random efects, and that the covariance structure will depend on a choice of random effects, Z_i, and that (II) the misspecification of the marginal covariance matrix due to a incorrect choice of the random effects, Z_i, may lead to an underestimate of the variance of the estimated parameters.

The second approach is called a "random coefficient models". This approach is similar to a linear mixed effects model. The model can be defined as

$$y_i = X_i \beta_i + \varepsilon_i$$

where β_i and ε_i are $N(\beta, \Sigma_{\beta\beta})$ and $N(0, \sigma^2 I_i)$ respectively, and we assume that β_i and ε_i are independent each other.

Then a simple unweighted estimator can be defined as

$$b_u = \frac{1}{K} \left(\sum_{i=1}^{K} \hat{\beta}_i \right), \quad \text{where } \hat{\beta}_i = (X_i^T X_i)^{-1} (X_i^T y_i) \text{ and } \operatorname{cov}(\hat{\beta}_i) = \Sigma_{\beta\beta} + \sigma^2 (X_i^T X_i)^{-1} = W_i$$

And a weighted estimator can be defined as

$$b_w = \frac{1}{\sum_{i=1}^{K} W_i} \left(\sum_{i=1}^{K} W_i \hat{\beta}_i \right)$$

Note that for a balanced and a complete design we have $b_u = b_w$.

The main difference between the two approaches is that (I) a weighted least squares (a generalized least squares) is applied to each subject in a linear mixed effects model, and a simple least squares is applied to each subject in a random coefficient model, and (II) the weighting scheme is different.

2. Population-Averaged Linear Models

In the PA approach to linear models we are interested in a model which is only a function of covariates without introducing subject to subject heterogeneity in the marginal covariance matrix. Therefore the model can be simply defined as

$$y_i = X_i \beta + \varepsilon_i$$

In the SS model, random effects variables are employed to describe the covariance structure.

This unknown correlation structure depends on the selection of Z_i matrix. Thus the selected covariance structure can be viewed as one of a number of possible alternatives. In applying the PA approach, Jennrich and Schluchter (1986) investigated a number of covariance structure (independent observations, compound symmetry, random-effects, first-order autoregressive structure, and so on). In a variety of situations (unbalanced and incomplete designs). They used a likelihood-based approach to the linear model. Therefore the only restriction required for the covariance matrix is a positive definite matrix. Note that the misspecification of the covariance matrix may lead to an underestimate of the variance of the estimated parameters.

Another approach to the linear model, not requiring distributional assumptions on the error term, is the application of an estimating equation. Invoking M-estimation theory (Huber 1967, White 1982, Liang and Zeger, 1986), the estimating equation can be defined as

$$U(\beta) = \sum_{i=1}^{K} X_i^T V_i^{-1} (y_i - X_i\beta) = 0$$

where V_i is known as a "working" covariance matrix. Note that the solution of the equation is consistent even if V_i is misspecified as long as the expected value of the estimating equation equal to 0. Liang and Zeger (1986) introduced the notion of a "working" correlation in the estimating equation --a parsimonious covariance structure. In addition, we can protect the underestimation of the variance of the estimators of the population parameters by introducing "sandwich" estimators of the variance, derived from M-estimation theory (Serfling, 1980). This is an important fact in a regulatory context in a sense that the variance estimator will be robust. The sandwich variance estimate of the parameters of interest can be given as

$$\hat{V}_\beta = (\sum_{i=1}^{K} X_i^T V_i^{-1} X_i)^{-1} (\sum_{i=1}^{K} X_i^T V_i^{-1} (y_i - X_i\hat{\beta})(y_i - X_i\hat{\beta})^T V_i^{-1} X_i) (\sum_{i=1}^{K} X_i^T V_i^{-1} X_i)^{-1}$$

Note that the asymptotic results will depend on having a large number of subjects, not on having a large number of data points per subject.

APPENDIX 9: SUMMARY RESULTS FROM A LONGITUDINAL ANALYSIS OF KPS MEASUREMENTS IN STUDY 8802

Gliadel						Placebo					
Count#	wcor*	ß	Est	N	R	Count#	wcor*	ß	Est	N	R
>5	comp	inter	71.15	3.48	2.53	>5	AR-1	inter	74.72	4.53	3.83
		slope	..	..	..			slope	-0.034	0.020	0.018
5	AR-1	inter	70.62	2.56	3.21	5	AR-1	inter	72.21	2.82	2.25
		slope*	-0.062	0.016	0.017			slope*	-0.057	0.018	0.019
4	AR-1	inter	68.08	3.61	3.27	4	AR-1	inter	65.12	3.39	3.27
		slope	-0.171	0.034	0.046			slope	-0.220	0.037	0.053
3	comp	inter	68.615	2.766	3.056	3	comp	inter	66.11	2.45	2.39
		slope	-0.366	0.075	0.090			slope	-0.307	0.046	0.066
2 or 3	comp	inter	66.242	2.853	2.992	2 or 3	comp	inter	64.02	2.356	2.324
		slope	-0.346	0.075	0.085			slope	-0.302	0.041	0.063
						<5	AR-1	inter	63.94	2.11	1.91
								slope	-0.251	0.027	0.044
Comments: (i) In count 5 a quadratic term was found to be statistically significant, but for a parsimonious model a linear model was selected. (ii) the estimated slope was statistically significantly different among each count category. This indicates that we have a nonignorable missing mechanism. (iii) for count# >5, LW model shows a similar time trend as GEE with a smaller standard error, indicating a significant time trend. (iv) a quadratic term was significant in count#=5						Comments: (i) In count 5 a quadratic term was found to be statistically significant, but for a parsimonious model a linear model was selected. (ii) In a category of count# 2, 3 , or 4 there was no different time trend found, i.e., among these categories we have an ignorable missing mechanism. (iii) There was a statistically significant difference in time trend among count# >5, 5, and <5, indicating that we have a nonignorable missing mechanism. (iv) a quadratic term was significant in count#=5.					
Possible Missing Mechanism						Possible Missing Mechanism					
Nonignorable						Nonignorable					

Note that wcor stands for a "working" correlation.

Note that N stands for a naive standard error calculated by the inverse of Fisher's information and R for a robust standard error calculated by a 'sandwich" estimator.

APPENDIX 10: Subgroup Analyses in CL-0190 Study

Subgroup Analyses for 12 Month Survival

Tumor Type				Age			
GBM (N_g=11, N_p=16)		Non-GBM (N_g=5, N_p=0)		< 65 (N_g=15, N_p=15)		≥ 65 (N_g=1, N_p=1)	
logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon
p=0.0587	p=0.0702	Not applicable	Not applicable	p=0.0097	p=0.0140	Not Applicable	Not Applicable

Gender				Race (Not Defined)			
Male (N_g=8, N_p=6)		Female (N_g=8, N_p=10)		White		Non-white	
logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon
p=0.788	p=0.691	P=0.0009	p=0.0016				

Subgroup Analyses for Overall Survival

Tumor Type				Age			
GBM (N_g=11, N_p=16)		Non-GBM (N_g=5, N_p=0)		< 65 (N_g=15, N_p=15)		≥ 65 (N_g=1, N_p=1)	
logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon
p=0.126	p=0.0931	Not applicable	Not applicable	p=0.0134	p=0.0144	Not Applicable	Not Applicable

Gender				Race (Not Defined)			
Male (N_g=8, N_p=6)		Female (N_g=8, N_p=10)		White		Non-white	
logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon	logrank	Wilcoxon
p=0.918	p=0.847	p=0.0003	p=0.0008				

APPENDIX 11: Baseline Covariates Employed in Cox regression in Study CL-0190

MMSE Score

	< Median	≥ Median
Placebo	8	8
Gliadel	8	8

AGE PER DECADE

	Placebo	Gliadel
Mean	5.3887	5.3521
SD	0.8026	0.9536
Range	6.0470 - 3.6038	6.7521 - 3.6789

APPENDIX 11: Baseline Covariates Employed in Cox regression in Study CL-0190

MMSE Score

	< Median	≥ Median
Placebo	8	8
Gliadel	8	8

AGE PER DECADE

	Placebo	Gliadel
Mean	5.3887	5.3521
SD	0.8026	0.9536
100%	6.0470	6.7521
75%	5.3918	6.0386
50%	5.3918	5.6155
25%	4.9175	4.4396
0%	3.6038	3.6789

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STATISTICAL REVIEW AND CONSULTATION, ADDENDUM #1

N.D.A.:	#20-637
SPONSOR:	Guilford Pharmaceuticals
PRODUCT:	Gliadel Wafer
TOPIC:	Stability testing statistical analysis
REVIEWING CHEMIST:	Paul E. Dietze, Ph.D.
LOT NUMBERS:	3U-017-012, 1V-017-013
DOCUMENTS REVIEWED:	CMC portion of NDA #20-637, update 1 dated 5/17/96

JUL 12 1996

After consultation with the Chemist, it was discovered that the only relevant studies for determining the expiry of Gliadel are S-9502, S-9503, S-9504, and S-9506. Since the expiry based on each of these studies exceeds 24 months, it is reasonable to grant the Sponsor's proposal of a 15-month expiry.

Vance Berger, Ph.D.
Mathematical Statistician

Concur: Dr. Gnecco
Dr. Chi
7/12/96

CC:

Archival NDA #20-637
HFD-150 / Division File
HFD-150 / Dr. Tolygesi
HFD-150 / Dr. Dietze
HFD-150 / Mr. Zimmerman, CSO
HFD-710 / Dr. Chi
HFD-710 / Dr. Gnecco
HFD-710 / Dr. Berger
HFD-710 / chron file

STATISTICAL REVIEW AND CONSULTATION

N.D.A.:	#20-637
SPONSOR:	Guilford Pharmaceuticals
PRODUCT:	Gliadel Wafer
TOPIC:	Stability testing statistical analysis
REVIEWING CHEMIST:	Paul E. Dietze, Ph.D.
LOT NUMBERS:	3U-017-012, 1V-017-013
DOCUMENTS REVIEWED:	CMC portion of NDA #20-637, update 1 dated 5/17/96

JUL

1. BACKGROUND

The objective was to determine the stability of Gliadel based on the time when an appropriate one-sided confidence interval for BCNU content crosses the specification limit for BCNU content or impurities. This was done for each of five studies (S-9501, S-9507, S-9513, S-9514, and S-9515). The lot numbers were 3U-017-012 for studies S-9501 and S-9507, and 1V-017-013 for the other three studies. The first intersection of a confidence interval and the specification limit for BCNU is the expiry. The impurities checked for were 2-chloroethylamine, 2-chloroethanol, acetaldehyde, unknowns, and total impurities (page 73). The storage conditions and duration appear in Sponsor's Table 7 (page 71). Twelve months of data is available for Study S-9501, nine months of data is available for Study S-9507, and three months of data is available for Studies S-9513, S-9514, and S-9515 (page 75).

2. SPONSOR'S RESULTS

Sponsor's Figure 4 presents data for Study S-9501. The expiry from this figure is 22.5 months based on BCNU content. The slope of the least squares line is positive, indicating that the BCNU content appears to be increasing on average as time elapses. Sponsor's Figure 5 presents data for Study S-9507. The expiry from this figure is 8.5 months based on BCNU content. Sponsor's Figure 6 presents data for Study S-9502 (which is not one of the ones previously listed). The expiry from this figure is 24 months based on BCNU content. The slope of the least squares line is positive, indicating that the BCNU content appears to be increasing on average as time elapses. Sponsor's Figure 7 presents data for Study S-9503 (which again is not one of the ones previously listed). The expiry from this figure exceeds 24 months based on BCNU content. The slope of the least squares line is positive, indicating that the BCNU content appears to be increasing on average as time elapses. Sponsor's Figure 8 presents data for Study S-9504 (which again is not one of the ones previously listed) The expiry from this figure exceeds 24 months based on BCNU content. The slope of the least squares line is positive, indicating that the BCNU content appears to be increasing on average as time elapses. Sponsor's Figure 9 presents data for Study S-9506 (which again is not one of the ones previously listed). The expiry from this figure exceeds 24 months based on BCNU content. The slope of the least squares line is positive, indicating that the BCNU content appears to be increasing as time elapses.

3. REVIEWER'S RESULTS

There appears to be little correspondence between the studies described in Sponsor's Table 7 and the studies in the figures. There appears to be only one batch tested per study. The slopes for BCNU content are generally increasing, yet one-sided lower confidence bands and specification limits were employed. Degradation products appeared not to be tested for. In a 6/7/96 conversation with the Supervisory Chemist I found these issues not to be of concern, as the Gliadel wafers are to be made up on an as-needed basis. What is referred to as a confidence interval is, presumably, a Working-Hotelling

confidence band. There was no statistical analysis of Studies S-9513, S-9514, or S-9515. This reviewer could not find a proposed expiry in this submission.

4. SUMMARY AND CONCLUSIONS

The data presented are quite incomplete. Nevertheless, this appears not to be a concern to the Supervisory Chemistry Reviewer. The study with the shortest expiry is S-9507, with an expiry of 8.5 months. Thus this reviewer recommends an overall expiry of 8.5 months for Gliadel.

Vance Berger, Ph.D.
Mathematical Statistician

Concur: Dr. Gnecco 6/25/96
Dr. Chi 6/27/96

CC:

Archival NDA #20-637
HFD-150 / Division File
HFD-150 / Dr. Tolygesi
HFD-150 / Dr. Dietze
HFD-150 / Mr. Zimmerman, CSO
HFD-710 / Dr. Chi
HFD-710 / Dr. Gnecco
HFD-710 / Dr. Berger
HFD-710 / chron file
HFD-150 / Division

VBERGER / 5-17-96 / WP6.1 - C:\GLIADEL\REVIEW.DOC
This review consists of three pages of text plus copies of Sponsor's tables and figures.

3.1.6 STABILITY

Introduction

There are five stability protocols for BCNU currently ongoing at Guilford. Two long term studies are being conducted on BCNU Lot 3U-017-012. This is the current lot of material being used in the manufacture of GLIADEL. Three additional studies are being conducted on a second lot of BCNU (Lot 1V-017-013). This material was received from late November, 1995. Information on the study numbers, lot numbers, storage temperatures and study durations is provided in TABLE 7.

Studies S-9501 and S-9513 are being conducted to evaluate the stability of BCNU at -35 ± 2°C. This is the storage temperature selected for long term storage of the material at Guilford. Study S-9507 is being conducted at 5 ± 2°C and Study S-9514 is being conducted at 8 ± 2°C in order to verify the vendor's label storage condition of 2 - 8°C. Study S-9515 is an accelerated study being conducted at 25 ± 2°C/60% RH.

TABLE 7: CURRENT STABILITY STUDIES FOR BCNU BULK DRUG

Study No.	Lot No. Evaluated	Storage Condition	Start Date	Duration
S-9501	3U-017-012	-35°C	3/95	24mos.
S-9507	3U-017-012	5°C	5/95	24 mos.
S-9513	1V-017-013	-35°C	12/95	24 mos.
S-9514	1V-017-013	8°C	12/95	24 mos.
S-9515	1V-017-013	25°C 60% RH	12/95	6 mos.

Summary of Studies

- Lots Evaluated

Two production lots of BCNU are being evaluated in these studies. Manufacturing information for the lots is provided below.

FIGURE 4 Study No. S-9501 - BCNU, Lot No. 3U-017-12 @ -35 ±2°C

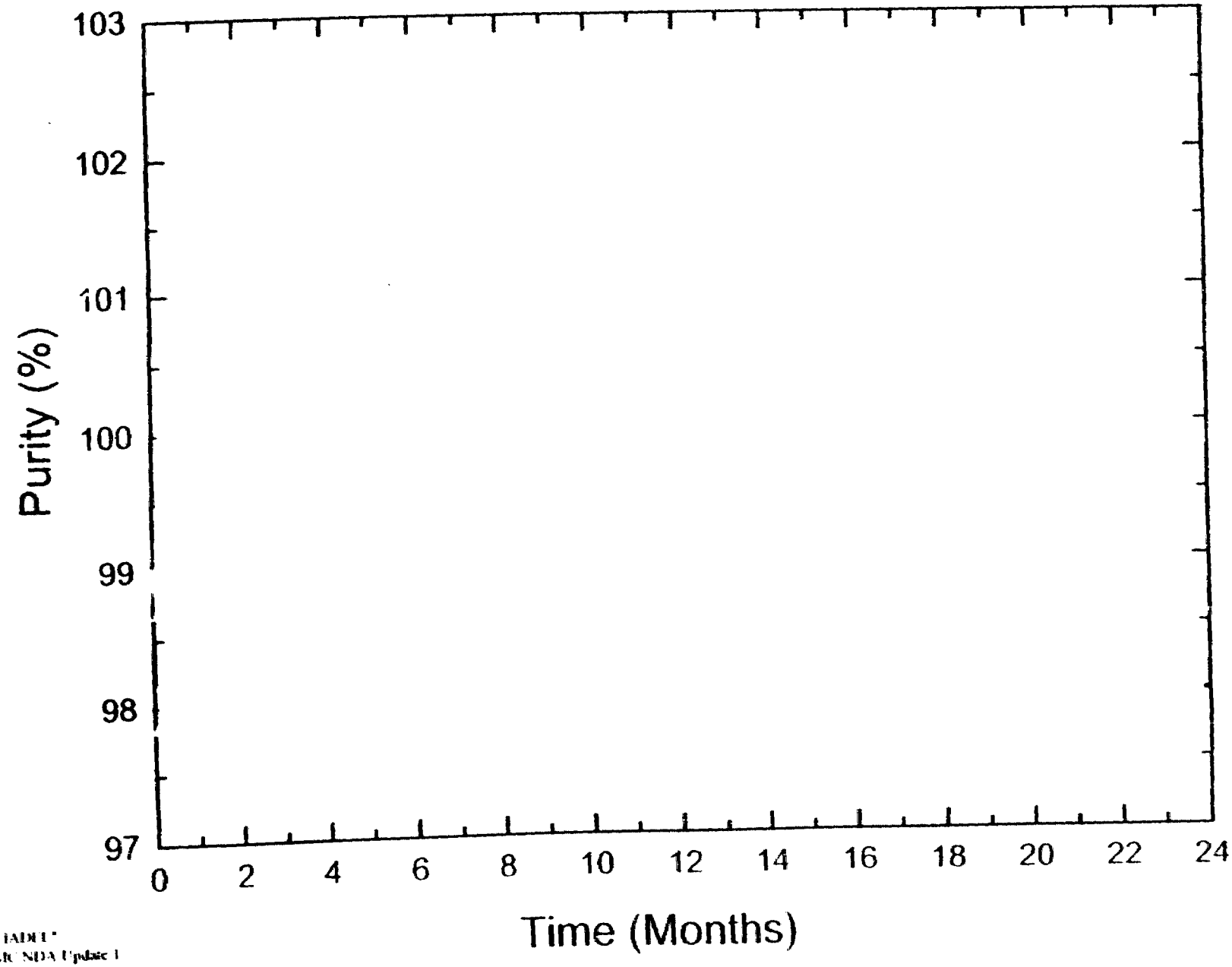


FIGURE 5 Study No. S-9507 - BCNU, Lot No. 3U-017-12 @ 5 ± 2°C

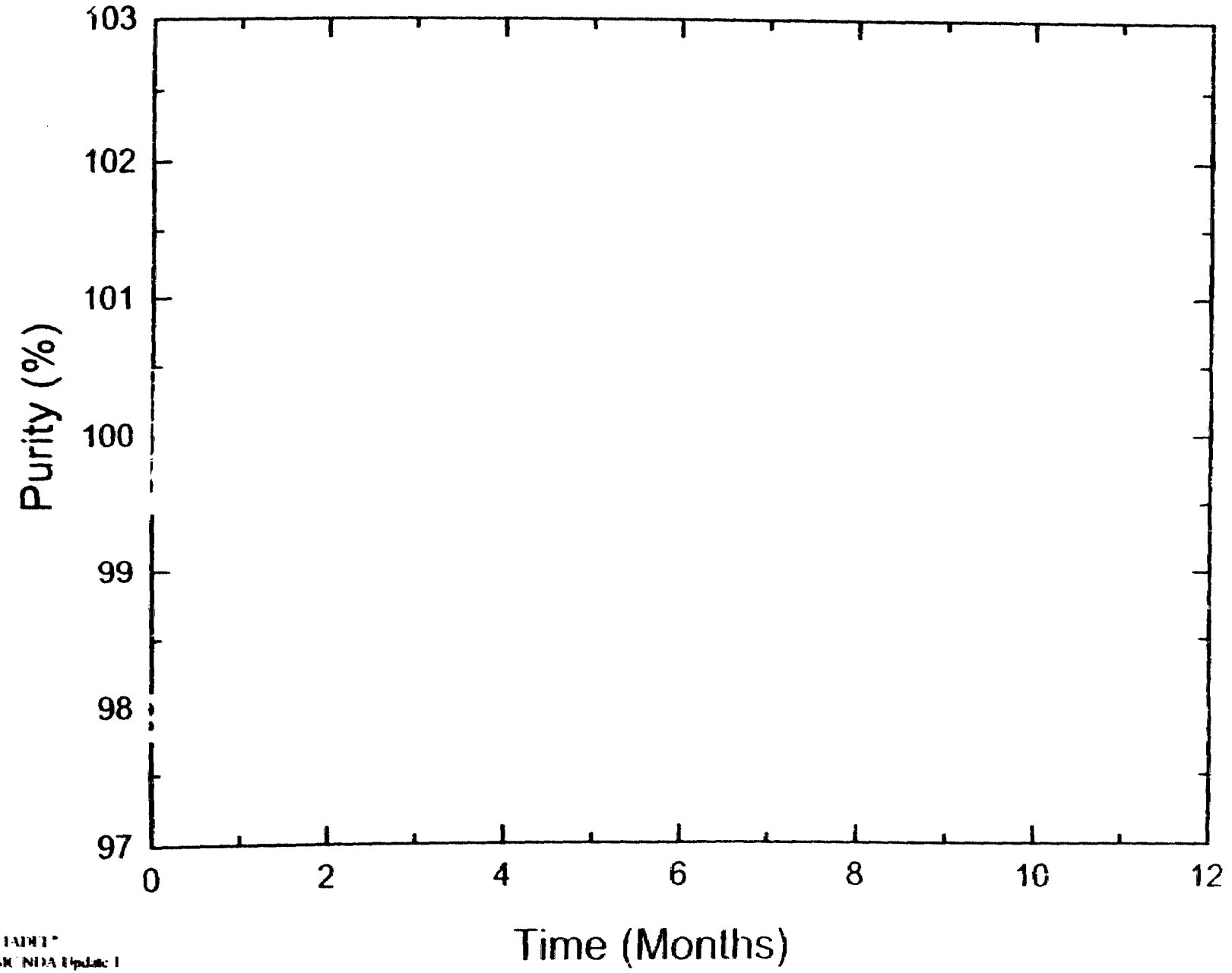


FIGURE 6 Study No. S-9502 - GLIADEL, Lot No. 5C002 @ -20° C

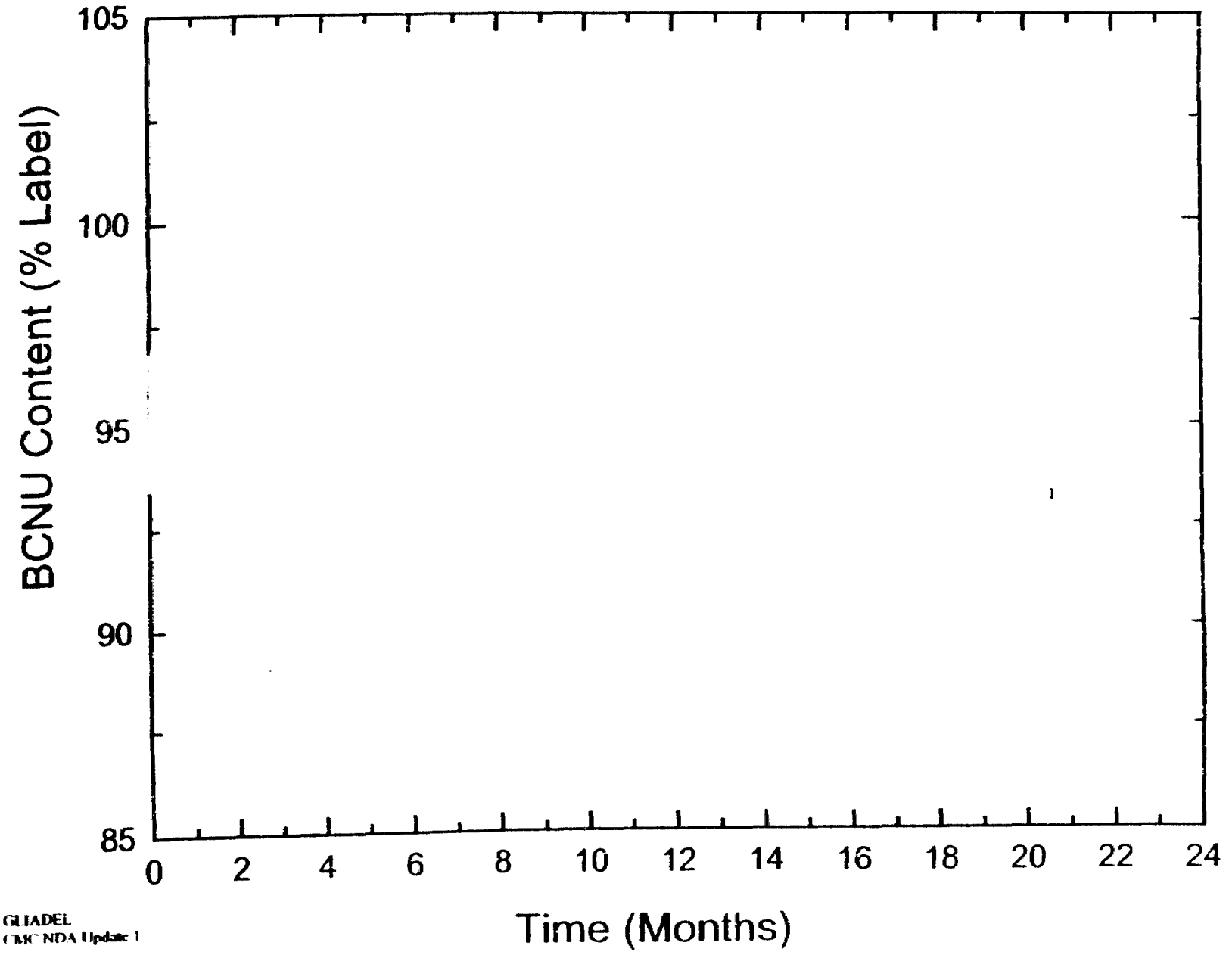


FIGURE 7 Study No. S-9503 - GLIADEL, Lot No. 5C003 @ -20°C

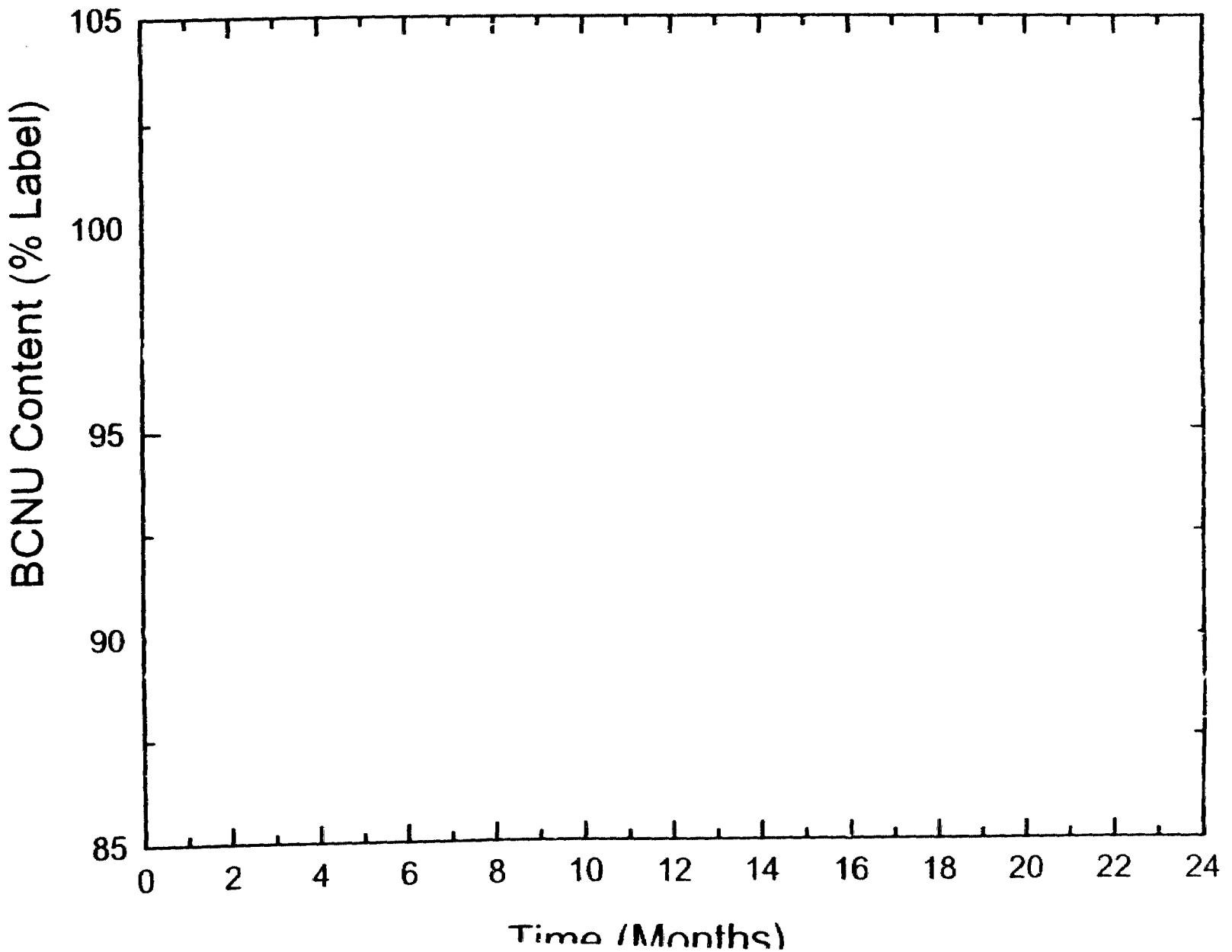


FIGURE 8 Study No. S-9504 - GLIADEL, Lot No. 5D004 @ -20°C

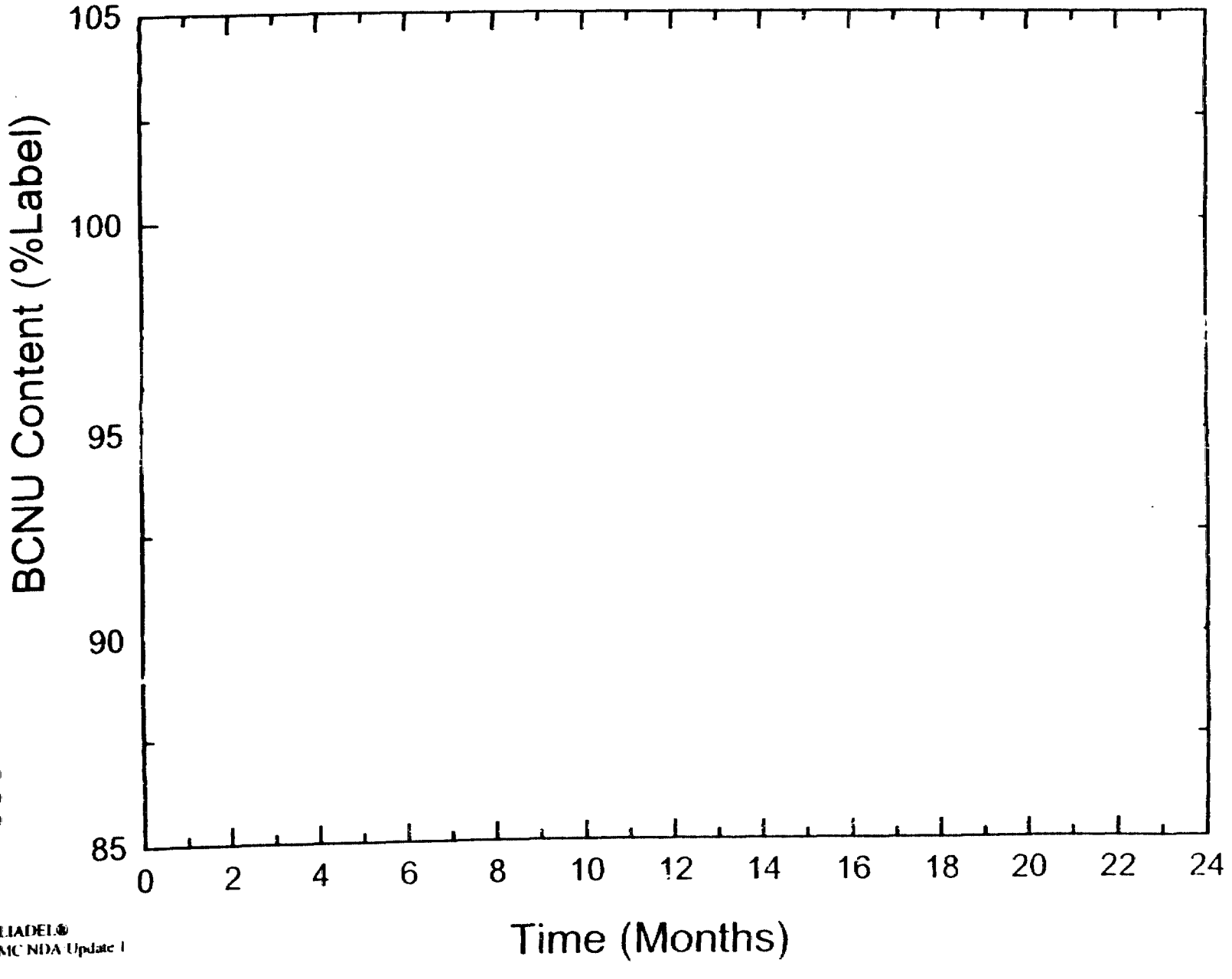
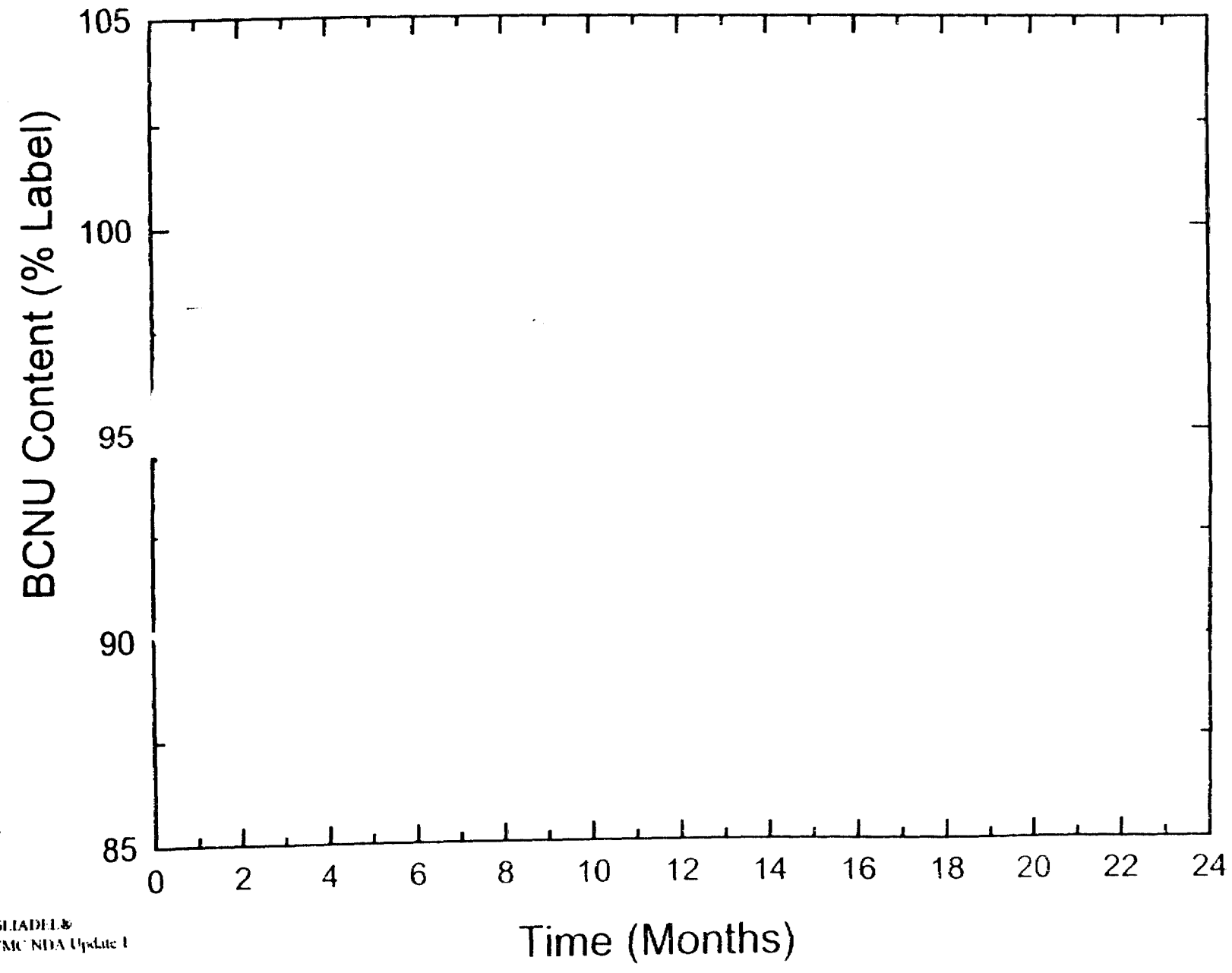


FIGURE 9 Study No. S-9506 - GLIADEL, Lot No. 5E005 @ -20°C



Chemist Review

CHEMISTRY CONSULT

NDA 20-637 **Submission Date:** August 6, 1996
August 9, 1996

Drug Name, Dose and Formulation: Polifeprosan 20 with Carmustine, 7.7mg/m^2, Carmustine/ wafer

Brand Name: Gliadel® Wafer

Sponsor: Guilford Pharmaceuticals, Baltimore, Maryland 21224

Reviewer: N.A.M. Atiqur Rahman

Type of Submission: New Drug Application/ Chemistry Consult/ Phase IV Commitment

The original amendment submitted on August 6 includes additional *in-vitro* release test data from 11 production lots of Gliadel for evaluation. Submission dated August 9 presents Phase IV commitment for *in vitro* release testing of Gliadel according to a revised interim *in vitro* release test specification as proposed by the sponsor.

COMMENTS

1. The revised interim *in vitro* release test specification as proposed by the sponsor is not acceptable. The revised interim *in vitro* release test specification should be as follows:

Methodology:	Flow-Through System	
	Guilford Method No. AC-2029	
Units:	6 individual units	
Percent Carmustine Released:	Time (h)	% Release (Range)

/s

RECOMMENDATION

The sponsor should provide *in-vitro* release test data according to the revised interim *in vitro* release test specifications as mentioned in comment 1 of at least three commercial lots as a Phase IV commitment.

Please provide the comments of this review to the respective Chemistry reviewer.

N.A.M. Atiqur Rahman, Ph. D. 08/20/96
Division of Pharmaceutical Evaluation I

Mehul U. Mehta, Ph.D. 8/20/96
Division of Pharmaceutical Evaluation I

cc: NDA 20-637 (original)
HFD-150/ Division File
HFD-150/PZimmerman, PDietze, ETolgyesi
HFD-150/AMartin
HFD-850/LLesko
HFD-860/ HMalinowski, MMehta, ARahman
HFD-870/ Drug File (Clarence Bott, PKLN RM. 13B-31)
HFD-870/Chron File (Clarence Bott, PKLN RM. 13B-31)
HFD-870/Reviewer's File (Clarence Bott, PKLN RM. 13B-31)

additional
Biopharm response to

AUG 13 1996

CHEMISTRY CONSULT of 2/14/96

NDA 20-637 **Submission Date:** February 06, 1996

Drug Name, Dose and Formulation: Polifeprosan 20 with Carmustine, 7.7mg/m^2 Carmustine/ wafer

Brand Name: Gliadel® Wafer

Sponsor: Guilford Pharmaceuticals, Baltimore, Maryland 21224

Reviewer: N.A.M. Atiqur Rahman

Type of Submission: New Drug Application/ Chemistry Consult

BACKGROUND

The submission has been forwarded by the Chemistry Reviewer, Dr. Paul Dietze, to provide comments on:

1. In vitro-release test of Gliadel

2. the study comparing the *in vitro* erosion of Gliadel wafer versus wafer erosion and release of BCNU in rat (appendix 16)

3. tissue biocompatibility study report (appendix 28)

COMMENTS

The comments provided below relate to the study investigating the effect of Gliadel wafer molecular weight on its performance, i.e., erosion of the polymer and release of BCNU from the wafer.

1. In the *in vitro* study, the sponsor demonstrated that the wafer mass loss was independent of its initial molecular weight. The study also demonstrated that despite the differences in the initial wafer molecular weight, the molecular weight decreases

in vitro were similar. The molecular weight of the wafers used in the *in vitro* study were 48, 72, and 110 KDa. In the *in vivo* study, the sponsor demonstrated, using wafers of molecular weight 20.5, 28.9, 46.6, and 55.5 KDa, that molecular weight profiles as a function of implantation time were similar up to hours and the release profiles of BCNU in rat brains were similar up to hours. The ranges in the wafer molecular weights were different for wafers used in the *in vivo* and *in vitro* studies. In addition, the sponsor did not provide any information on the ***in vitro*** release profiles of BCNU from wafers with molecular weight ranging from in the submission. Therefore, the initial wafer molecular weight specification of is not completely supported by the data provided in the submission.

2. The sponsor should demonstrate that the **in vitro** release rates of BCNU from Gliadelwafers of molecular weight ranging from are similar before setting an initial wafer molecular weight specification at for the drug product.

RECOMMENDATION

The tissue biocompatibility study review by the Biopharmaceutics reviewer appeared to provide no meaningful information regarding setting of any specifications based on tissue biocompatibility. The study may be consulted with the Pharmacologists.

Please provide the comments of this review to the respective Chemistry reviewer.

N.A.M. Atiqur Rahman 08/13/96

N.A.M. Atiqur Rahman, Ph. D.
Division of Pharmaceutical Evaluation I

Mehul 8/13/96

Mehul U. Mehta, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA 20-637 (original)
HFD-150/ Division File
HFD-150/PZimmerman, PDietze, ETolgyesi
HFD-150/AMartin
HFD-850/LLesko
HFD-860/ HMalinowski, MMehta, ARahman
HFD-870/ Drug File (Clarence Bott, PKLN RM. 13B-31)
HFD-870/Chron File (Clarence Bott, PKLN RM. 13B-31)
HFD-870/Reviewer's File (Clarence Bott, PKLN RM. 13B-31)

Division of Oncology Drug Products
Chemist's Memo

To: Paul Zimmerman, HFD-150

From: Paul E. Dietze, HFD-150
through Eva Tolgyesi, HFD-150

Concerning: Proposed interim specifications for In Vitro Release Rate for Gliadel Wafer.
NDA 20-637

Date: September 5, 1996

In a facsimile from Guilford Pharmaceuticals (attached) dated September 4, 1996 the company agreed to the interim specifications for In Vitro Release Rate that we proposed in CMC review #9 (and communicated to Guilford by Agency facsimile on September 3, 1996).

The applicant also agreed to be responsive to our request to make the test more discriminating.

Finally, the applicant has provided, as we requested, the release rate for the three hour time point. Examination of the three hour time point data suggests the three hour time point, if included in the specifications, would make the test more discriminating. A specification for release rate at the three hour time point would be useful. See comments in CMC review 9 concerning this issue. The data provided by Guilford suggest a reasonable specification for release rate at the three hour time point would be 10 - 35%.

The applicant will provide, as we requested, the three our time point (as well as other time points) for the first eight batches of drug product that are manufactured. A final specification will then be adopted after examination of all the data. However, the initial data suggests that including the three hour time point in the specifications will lead to a more discriminating test.

The proposed interim specifications for in vitro release rate, provided below, are what was agreed on.

Time (h)	% Released (range)

NDA # 20-637 for Gliadel Wafers is approved with respect to chemistry manufacturing and controls issues.

Paul E. Dietze, Ph.D.
Review Chemist, HFD-150

3/5/96

Eva Tolgyesi, Ph.D.
Chemistry Team Leader, HFD-150

cc: NDA 20637
Orig File
HFD-150/PDietze
HFD-150/ETolgyesi
HFD-150/PZimmerman
HFD 150/ARahman

File: c:\ndas\n20637m3.000

DIVISION OF ONCOLOGY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-637 **CHEM.REVIEW #:** 9 **REVIEW DATE:** 9-3-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment BC	8-27-96	8-28-96	9-3-96
Facsimile	8-29-96		

NAME & ADDRESS OF APPLICANT: Guilford Pharmaceuticals Inc.
6611 Tributary Street
Baltimore, MD 21224

DRUG PRODUCT NAME

Proprietary:	Gliadel® Wafer
Nonproprietary/USAN:	Polifeprosan 20 with Carmustine
Code Name/#:	GPI-100
Chem.Type/Ther.Class:	3P

ANDA Suitability Petition/DESI/Patent Status: USP 5,179,186 (exp. date 9/9/2011)
USP 4,789,724 (exp. date 10/17/2006)

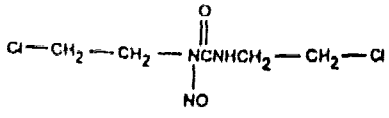
PHARMACOL.CATEGORY/INDICATION: antineoplastic/malignant glioma

DOSAGE FORM: Implant, Biodegradable wafer
STRENGTHS: 3.85% carmustine, 7.7 mg carmustine/wafer
ROUTE OF ADMINISTRATION: Surgical implant
DISPENSED: __X__ Rx _____ OTC

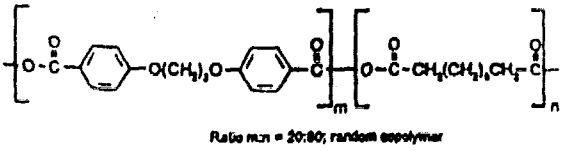
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Poly[bis(p-carboxyphenoxy) propane:sebacic acid 20:80] with 1,3-bis(2-chloroethyl)-1-nitrosourea

1,3-bis(2-chloroethyl)-1-nitrosourea:
M.W. = 214.06, Chemical Formula = $C_5H_9Cl_2N_3O_2$



Polifeprosan:



Ratio m:n = 20:80; random copolymer

SUPPORTING DOCUMENTS:

IND Guilford Pharmaceuticals Inc. Gliadel Wafer

DMF

		Sterilization	reviewed by HFD-160 as part of the microbiology review
DMF			Reviewed by D. Klein and found adequate for a DMF
DMF		Packaging	Reviewed on 10-13-93 by HFD-632 and found acceptable

RELATED DOCUMENTS (if applicable): NDA 17-422 BiCNU (sterile carmustine) Bristol-Myers Squibb

CONSULTS:

EA	Approved	EA and FONSI was submitted to HFD-102 for review, found to be acceptable and was approved on 5-7-96.
Microbiology	Approved	Submitted to HFD-160 to evaluate the sterilization process for manufacture of the submitted on 2-14-96. Approved on 5-3-96
Biometrics	Approved	Analysis of stability data was requested on 5-23-96. Biometrics initial review was completed on 7-11-96 and updated on 7-12-96. The requested 15 month expiry date was found to be acceptable.
Biopharm.	Approved	Submitted to HFD-860 to evaluate the in vitro release test and tissue compatibility studies. Submitted on 2-14-96. Consult review received on 7-22-96. However, additional information was requested. The additional, information was provided on 8-12-96.
Pharm./Tox.	Approved	Submitted to evaluate the proposed

		specification for CHCl . Found to be acceptable on 3-28-96

OTHER REQUESTS:

Trademark Review	Approved	Submitted on 2-14-96. Approved on 4-4-96.
EER	Approved	Submitted on 2-14-96. All manufacturing sites found acceptable on 7-26-96.
Methods Validation	Pending	Will be initiated after all methods deficiencies have been addressed.

REMARKS/COMMENTS:

This submission provides updated information concerning the in vitro release test. The amendment responds to comments indicated in review #8.

CONCLUSIONS & RECOMMENDATIONS:

The proposed interim release specifications are acceptable as interim specifications. However, The CSO should forward the following comments to the applicant:

The proposed interim specifications for in vitro release rate, provided below, are acceptable. However, we would like to see, as was requested, the data for percent released, for each lot, at the 3 hour time point.

Time (h)	% Released (range)

We also remind you that we are interested in developing a discriminatory test for in vitro release rate. We do not feel that the current test is sufficiently discriminating. As was mentioned in our teleconference on August 28 we are concerned that the acceptable value for each of the last three time points is essentially the same. As you pointed out, this is due to the fact that the value for percent released has leveled off for the last three data points. One way to make the test method more informative would be to have earlier time points. We anticipate that a more discriminating test will be developed, we do not envision that the interim specifications will be acceptable as final release specifications (due to the method being non-discriminating). Therefore, we would like to see the data for the 3 hour time point for each lot of drug product for which you have provided us with data. In addition, please provide the 3 hour time point, along with the other time points, for the first eight lots of drug product you manufacture. We would

also be interested in other suggestions you might have to develop a more discriminating and rigorous test method.

All of the other deficiencies cited in review #8 have been addressed. If the above stipulations are acceptable to the applicant the NDA is approved with respect to chemistry manufacturing and controls.

cc:
Orig. NDA 20-367
HFD-150/Division File
HFD-150/PDietze
HFD-150/DKlein
HFD-151/PZimmerman
HFD-150/ETolgyesi
HFD-860/ARahman

9/3/96

Paul E Dietze, Ph.D
Chemist

9/3/96

Eva Tolgyesi, Ph.D.
Chemistry Team Leader

AUG 29 1996

Division of Oncology Drug Products
Chemist's Memo

To: Paul Zimmerman, HFD-150

From: Paul E. Dietze, HFD-150
through Eva Tolgyesi, HFD-150

Concerning: Labelling for Gliadel Wafer, NDA 20-637

Date: August 27, 1996

I have examined the revised labelling for Gliadel wafer. The revised labelling was submitted, by the applicant, by facsimile on 8-26-96. With regards to CMC issues the labelling is satisfactory. The applicant has made the requested change in the Description section of the package insert. The package insert is acceptable from a CMC perspective.

8/27/96

Paul E. Dietze, Ph.D.
Review Chemist, HFD-150

8/27/96

cc: HFD-150/PDietze
HFD-150/ETolgyesi
HFD-150PZimmerman

File: c:\ndas\n20637m2.000

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-637 **CHEM.REVIEW #:** 8 **REVIEW DATE:** 8-13-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment BC	8-9-96	8-12-96	8-9-96

NAME & ADDRESS OF APPLICANT: Guilford Pharmaceuticals Inc.
6611 Tributary Street
Baltimore, MD 21224

DRUG PRODUCT NAME

Proprietary:	Gliadel® Wafer
Nonproprietary/USAN:	Polifeprosan 20 with Carmustine
Code Name/#:	GPI-100
Chem.Type/Ther.Class:	3P

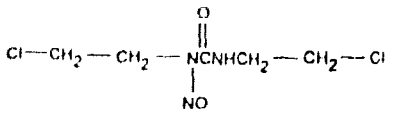
ANDA Suitability Petition/DESI/Patent Status: USP 5,179,186 (exp. date 9/9/2011)
USP 4,789,724 (exp. date 10/17/2006)

PHARMACOL.CATEGORY/INDICATION: antineoplastic/malignant glioma

DOSAGE FORM: Implant, Biodegradable wafer
STRENGTHS: 3.85% carmustine, 7.7 mg carmustine/wafer
ROUTE OF ADMINISTRATION: Surgical implant
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Poly[bis(p-carboxyphenoxy) propane:sebacic acid 20:80] with 1,3-bis(2-chloroethyl)-1-nitrosourea

1,3-bis(2-chloroethyl)-1-nitrosourea:
M.W. = 214.06, Chemical Formula = $C_5H_9Cl_2N_3O_2$



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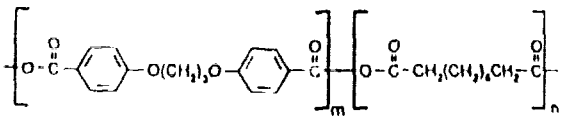


Ratio m:n = 20:80; random copolymer

SUPPORTING DOCUMENTS:

IND	Guilford Pharmaceuticals Inc.	Gliadel Wafer	
DMF 1		Terminal Sterilization	Being reviewed by HFD-160 as part of the microbiology review
DMF		Manufacturer of	Reviewed by D. Klein and found

			adequate for a DMF
DMF		Packaging	Reviewed on 10-13-93 by HFD-632 and found acceptable

RELATED DOCUMENTS (if applicable): NDA 17-422 BiCNU (sterile carmustine) Bristol-Myers Squibb

CONSULTS:

EA	Approved	EA and FONSI was submitted to HFD-102 for review, found to be acceptable and was approved on 5-7-96.
Microbiology	Approved	Submitted to HFD-160 to evaluate the sterilization process for manufacture of the DP. Submitted on 2-14-96. Approved on 5-3-96
Biometrics	Approved	Analysis of stability data was requested on 3-23-96. Biometrics initial review was completed on 7-11-96 and updated on 7-12-96. The requested 15 month expiry date was found to be acceptable.
Biopharm.	Pending	Submitted to HFD-860 to evaluate the in vitro release test and tissue compatibility studies. Submitted on 2-14-96. Consult review received on 7-22-96. However, additional information was requested. The additional, information was provided on 8-12-96.
Pharm./Tox.	Approved	Submitted to evaluate the proposed specification for $CHCl_3$. Found to be acceptable on 3-28-96

OTHER REQUESTS:

Trademark Review	Approved	Submitted on 2-14-96. Approved on 4-4-96.
EER	Approved	Submitted on 2-14-96. All manufacturing sites found acceptable on 7-26-96.
Methods Validation	Pending	Will be initiated after all methods deficiencies have been addressed.

REMARKS/COMMENTS:

This submission provides updated information concerning the in vitro release test.

CONCLUSIONS & RECOMMENDATIONS:

The CSO should communicate the deficiencies, listed below, to the applicant. If the applicant commits to provide the information, listed below, the NDA can be approved with regards to chemistry manufacturing and controls.

i. The proposal to conduct in vitro-release testing of the first eight production lots, in order to establish a final specification is acceptable. However the original specifications proposed by the applicant are unacceptable. The following interim specifications, provided below, would be acceptable to the Agency. The applicant should commit to adopting the following interim specifications and to submit the data to the Agency in order to set proper in-vitro release specifications.

In-vitro Release Test Specifications (Interim):

Methodology: Flow-Through System
Guilford Method No. AC-2029

Units: 6 individual units

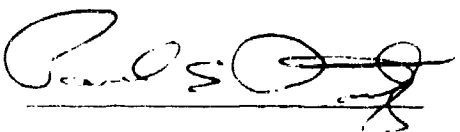
Percent BCNU released: Time(h) % Released (Range)

ii. Provide information on the pharmacokinetics of carmustine after intravenous administration in the package insert.

iii. The applicant stated CFR code for waiver, 21 CFR 314.50(d)(3), is incorrect. This section of the code describes the content and format of an application. The waiver request should follow the procedure in 21 CFR 320.22

iv. Before a final specification for molecular weight can be established it needs to be demonstrated, using the in vitro release method, that BCNU release rates from wafers having molecular weights ranging from 20 KDa to 100 KDa are similar. A comparison of release rates, using the in vitro test method, for polymers having a molecular weight of 20 KDa and 100 KDa needs to be provided to demonstrate release rates are the same. The specification for molecular weight of 20 KDa to 100 KDa is acceptable as an interim specification and will be finalized after the results of the suggested study are completed.

cc:
Orig. NDA 20-367
HFD-150/Division File
HFD-150/PDietze
HFD-150/DKlein
HFD-151/PZimmerman
HFD-150/ETolgyesi
HFD-860/ARahman



8/13/96

Paul E Dietze, Ph.D
Chemist

Eva Tolgyesi 8/17/96

Eva Tolgyesi, Ph.D.
Chemistry Team Leader

1996

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-637 **CHEM.REVIEW #:** 7 **REVIEW DATE:** 8-7-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment BL	7-30-96	7-31-96	8-2-96
Amendment BC	7-19-96	7-22-96	7-24-96
Amendment BC	7-19-96	7-22-96	7-24-96
Amendment BC	7-19-96	7-22-96	7-24-96
Amendment BC	7-17-96	7-18-96	7-22-96
Amendment BC	7-11-96	7-12-96	7-15-96
Amendment AC	6-27-96	6-28-96	7-1-96
Amendment AC	5-17-96	5-20-96	5-21-96
ORIGINAL	2-6-96	2-7-96	2-12-96

NAME & ADDRESS OF APPLICANT: Guilford Pharmaceuticals Inc.
6611 Tributary Street
Baltimore, MD 21224

DRUG PRODUCT NAME

Proprietary:	Gliadel® Wafer
Nonproprietary/USAN:	Polifeprosan 20 with Carmustine
Code Name/#:	GPI-100
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ROUTE OF ADMINISTRATION: Surgical implant
DISPENSED: __X__ Rx _____ OTC

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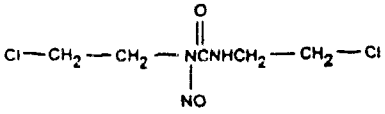
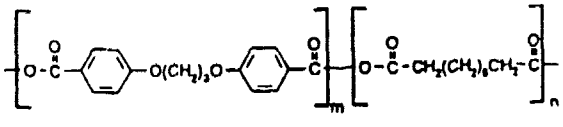
M.W. = 214.06, Chemical Formula = $C_5H_9Cl_2N_3O_2$



Polifeprosan:



Ratio m:n = 20:80; random copolymer

SUPPORTING DOCUMENTS:

IND	Guilford Pharmaceuticals Inc.	Gliadel Wafer	
DMF		Terminal Sterilization	Being reviewed by HFD-160 as part of the microbiology

review

DMF	Manufacturer	Reviewed by D. Klein and found adequate for a DMF
DMF	Packaging	Reviewed on 10-13-93 by HFD-632 and found acceptable

RELATED DOCUMENTS (if applicable): NDA 17-422 BiCNU (sterile carmustine) Bristol-Myers Squibb

CONSULTS:

EA	Approved	EA and FONSI was submitted to HFD-102 for review, found to be acceptable and was approved on 5-7-96.
Microbiology	Approved	Submitted to HFD-160 to evaluate the sterilization process for manufacture of the DP. Submitted on 2-14-96. Approved on 5-3-96
Biometrics	Approved	Analysis of stability data was requested on 5-23-96. Biometrics initial review was completed on 7-11-96 and updated on 7-12-96. The requested 15 month expiry date was found to be acceptable.
Biopharm.	Pending	Submitted to HFD-860 to evaluate the in vitro release test and tissue compatibility studies. Submitted on 2-14-96. Consult review received on 7-22-96. However, additional information was requested.
Pharm./Tox.	Approved	Submitted to evaluate the proposed specification for $CHCl_3$. Found to be acceptable on 3-28-96

OTHER REQUESTS:

Trademark Review	Approved	Submitted on 2-14-96. Approved on 4-4-96.
EER	Approved	Submitted on 2-14-96. All manufacturing sites found acceptable on 7-26-96.
Methods Validation	Pending	Will be initiated after all methods deficiencies have been addressed.

REMARKS/COMMENTS:

This submission provides revised pouch and carton labelling for Gliadel.

CONCLUSIONS & RECOMMENDATIONS:

With respect to CMC issues the revised pouch and carton labelling for Gliadel is acceptable. All of our comments, made in earlier reviews, have been incorporated into the labelling. The revised labelling includes the fact that Gliadel Wafers are now manufactured by Guilford for

The NDA can be approved, with respect to chemistry manufacturing and controls issues, after the applicant addresses the concerns raised by the biopharmacist and discussed in review 6.

cc:
Orig. NDA 20-367
HFD-150/Division File
HFD-150/PDietze
HFD-150/DKlein
[redacted]
HFD-150/ETolgyesi
HFD-860/ARahman

8/7/96

Paul E Dietze, Ph.D
Chemist

8/8/96

Eva Tolgyesi, Ph.D.
Chemistry Team Leader

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

JUL 25 1996

NDA #: 20-637 **CHEM.REVIEW #:** 5 **REVIEW DATE:** 7-25-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment BC	7-19-96	7-22-96	7-24-96
Amendment BC	7-19-96	7-22-96	7-24-96
Amendment BC	7-19-96	7-22-96	7-24-96
Amendment BC	7-17-96	7-18-96	7-22-96
Amendment BC	7-11-96	7-12-96	7-15-96
Amendment AC	6-27-96	6-28-96	7-1-96
Amendment AC	5-17-96	5-20-96	5-21-96
ORIGINAL	2-6-96	2-7-96	2-12-96

NAME & ADDRESS OF APPLICANT: Guilford Pharmaceuticals Inc.
6611 Tributary Street
Baltimore, MD 21224

DRUG PRODUCT NAME
Proprietary: Gliadel ® Wafer
Nonproprietary/USAN: Polifeprosan 20 with Carmustine
Code Name/#: GPI-100
Chem.Type/Ther.Class: 3P

ANDA Suitability Petition/DESI/Patent Status: USP 5,179,186 (exp. date 9/9/2011)
USP 4,789,724 (exp. date 10/17/2006)

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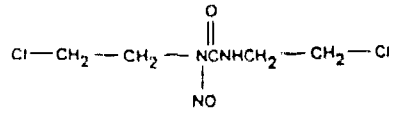
1,3-bis(2-chloroethyl)-1-nitrosourea:
M.W. = 214.06, Chemical Formula = $C_5H_9Cl_2N_3O_2$



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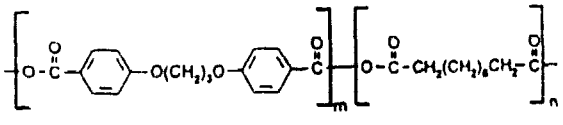

Ratio m:n = 20:80; random copolymer

SUPPORTING DOCUMENTS:

IND	Guilford Pharmaceuticals Inc.	Gliadel Wafer	
DMF		Terminal Sterilization	Being reviewed by HFD-160 as part of the microbiology review

DMF	Manufacturer	Reviewed by D. Klein and found adequate for a DMF
DMF	Packaging	Reviewed on 10-13-93 by HFD-632 and found acceptable

RELATED DOCUMENTS (if applicable): NDA 17-422 BiCNU (sterile carmustine) Bristol-Myers Squibb

CONSULTS:

EA	Approved	EA and FONSI was submitted to HFD-102 for review, found to be acceptable and was approved on 5-7-96.
Microbiology	Approved	Submitted to HFD-160 to evaluate the sterilization process for manufacture of the DP. Submitted on 2-14-96. Approved on 5-3-96
Biometrics	Approved	Analysis of stability data was requested on 5-23-96. Biometrics initial review was completed on 7-11-96 and updated on 7-12-96. The requested 15 month expiry date was found to be acceptable.
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OTHER REQUESTS:

Trademark Review	Approved	Submitted on 2-14-96. Approved on 4-4-96.
EER	Pending	Submitted on 2-14-96.
Methods Validation	Pending	Will be initiated after all methods deficiencies have been addressed.

REMARKS/COMMENTS:
Drug Substance: Updated stability data and minor editorial changes to the specifications and methods for the drug substance is provided. Additionally, test data is provided for the bulk drug substance lot 1V-017-013.

Drug Product: The amendment to NDA 20-637 dated 7-17-96 provides updated stability data for the drug product. The amendment dated 7-19-96 withdraws the applicants earlier request to add as a second contract facility for LAL and sterility testing of the drug product.

The Biopharm. consult and EER are still pending.

See attached review notes.

CONCLUSIONS & RECOMMENDATIONS:
Drug Substance: Satisfactory information provided for the drug substance.

Drug Product: Updated stability data is provided. The updated stability data is satisfactory and does not appear to show any unusual trends.

With respect to CMC issues the NDA can be approved if the pending Biopharm. consult and EER are found to be acceptable.

cc:
Orig. NDA 20-367
HFD-150/Division File
HFD-150/PDietze
HFD-150/DKlein
HFD-151/PZimmerman
HFD-150/ETolgyesi

7/25/96

Paul E Dietze, Ph.D
Chemist

The statistical review of the stability data support the 15 month expiration dating period requested by the Applicant.

7/25/96

Donald Klein, Ph.D
Chemist

7/25/96

Eva Tolgyesi, Ph.D.
Chemistry Team Leader

7/25/96

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-637 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 7-16-96 JUL 17 1996

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment BC	7-11-96	7-12-96	7-15-96
Amendment AC	6-27-96	6-28-96	7-1-96
Amendment AC	5-17-96	5-20-96	5-21-96
ORIGINAL	2-6-96	2-7-96	2-12-96

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DISPENSED: ___X___ Rx _____ OTC

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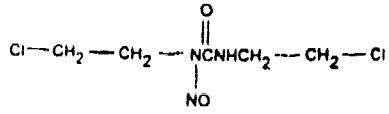
1,3-bis(2-chloroethyl)-1-nitrosourea:
M.W. = 214.06, Chemical Formula = $C_5H_9Cl_2N_3O_2$



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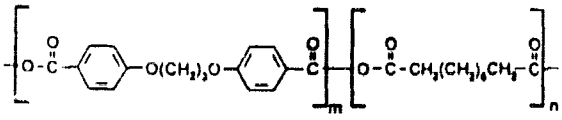

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SUPPORTING DOCUMENTS:

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DMF	Manufacturer	Reviewed by D. Klein and found adequate for a DMF
DMF	Packaging	Reviewed on 10-13-93 by HFD-632 and found acceptable

RELATED DOCUMENTS (if applicable): NDA 17-422 BiCNU (sterile carmustine) Bristol-Myers Squibb

CONSULTS:

EA	Approved	EA and FONSI was submitted to HFD-102 for review, found to be acceptable and was approved.
Microbiology	Approved	To HFD-160 to evaluate the sterilization process for manufacture of the DP. Submitted on 2-14-96. Approved on 5/3/96
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OTHER REQUESTS:

Trademark Review	Approved	Submitted on 2-14-96. Approved on 4/4/96.
EER	Pending	Submitted on 2-14-96.
Methods Validation	Pending	Will be initiated after all methods deficiencies have been addressed.

REMARKS/COMMENTS: This amendment to NDA 20-637 provides for minor changes in the May 17, 1996 submission. All of the changes are acceptable. The changes correct minor errors in the NDA and the May 17, 1996 amendment. Most of the changes correct typographical errors or minor omissions. The only change that is of concern is that the applicant provides for a new testing laboratory. This could delay NDA approval since a EER will be required.

The Biometrics consult, Biopharm. consult and EER are still pending.

See attached review notes.

CONCLUSIONS & RECOMMENDATIONS:
All of the changes are minor and are acceptable.

The only change that is of concern is that the applicant provides for a new testing laboratory. This could delay NDA approval since an EER will be required. I have requested that the CSO discuss this with the applicant. If the applicant decides to maintain their request for addition of a new testing facility an EER will have to be requested to evaluate the new testing facility. Alternatively, the applicant could withdraw their request for approval of the second testing facility, and thus preclude any delay that might occur due to EER approval. After approval of the NDA the applicant could then request approval of the new testing facility in a supplemental application.

With respect to CMC issues the NDA can be approved if the pending Biometrics consult, Biopharm. consult and EER are found to be acceptable.

cc:
Orig. NDA 20-367
HFD-150/Division File
HFD-150/PDietze
HFD-150/DKlein
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HFD-150/ETolgyesi

7/16/96

Paul E Dietze, Ph.D

7/16/96

Eva Tolgyesi, Ph.D
Chemistry Team Leader

JUL 11 1996

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-637 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 7-2-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment AC	6-27-96	6-28-96	7-1-96
Amendment AC	5-17-96	5-20-96	5-21-96
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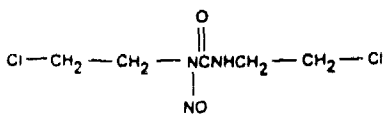

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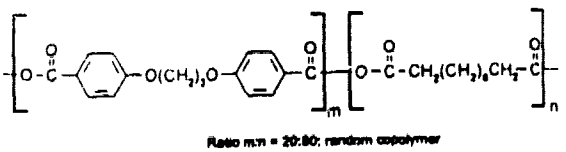

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Pharm./Tox.	Approved	To evaluate the proposed specification for $CHCl_3$. Found to be acceptable on 3-28-96

OTHER REQUESTS:

Trademark Review	Approved	Submitted on 2-14-96. Approved on 4/4/96. However, see comments to deficiency 26 in review.
EER	Pending	Submitted on 2-14-96.
Methods Validation	Pending	Will be initiated after all methods deficiencies have been addressed.

REMARKS/COMMENTS: This amendment to NDA 20-637 is a response to deficiencies regarding our review of the 5-17-96 amendment. The deficiencies were communicated to the applicant by facsimile on June 6, 1996.

The Biometrics consult, Biopharm. consult and EER are still pending.

CONCLUSIONS & RECOMMENDATIONS:
Drug Substance: The sponsor has adequately addressed all drug substance deficiencies.

Drug Product: With regards to the drug product the applicant has adequately addressed all of the deficiencies.

The applicant has addressed all deficiencies in a satisfactory way and has made all requested changes. With respect to CMC issues the NDA can be approved if the pending Biometrics consult, Biopharm. consult and EER are found to be acceptable.

cc:
Orig. NDA 20-367
HFD-150/Division File
HFD-150/PDietze
HFD-150/DKlein
HFD-151/PZimmerman
HFD-150/ETolgyesi

7/2/96

Paul E Dietze, Ph.D
Drug Product Section

Donald M. Klein 7/2/96

Donald Klein, Ph.D.
Drug Substance Section

7/11/96

Eva Tolgyesi, Ph.D.
Chemistry Team Leader

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-637 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 5-21-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	5-17-96	5-20-96	5-21-96
ORIGINAL	2-6-96	2-7-96	2-12-96

NAME & ADDRESS OF APPLICANT: Guilford Pharmaceuticals Inc.
6611 Tributary Street
Baltimore, MD 21224

DRUG PRODUCT NAME

Proprietary:	Gliadel ® Wafer
Nonproprietary/USAN:	Polifeprosan 20 with Carmustine
Code Name/#:	GPI-100
Chem.Type/Ther.Class:	3P

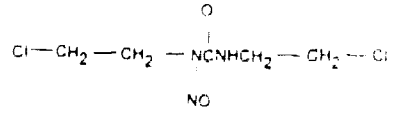
ANDA Suitability Petition/DESI/Patent Status: USP 5,179,186 (exp. date 9/9/2011)
USP 4,789,724 (exp. date 10/17/2006)

PHARMACOL.CATEGORY/INDICATION: antineoplastic/malignant glioma

DOSAGE FORM: Implant, Biodegradable wafer
STRENGTHS: 3.85% carmustine, 7.7 mg carmustine/wafer
ROUTE OF ADMINISTRATION: Surgical implant
DISPENSED: _X_ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Poly[bis(p-carboxyphenoxy) propane:sebacic acid 20:80] with 1,3-bis(2-chloroethyl)-1-nitrosourea

1,3-bis(2-chloroethyl)-1-nitrosourea:
M.W. = 214.06, Chemical Formula = $C_5H_9Cl_2N_3O_2$



Polifeprosan:

Ratio m:n = 20:80 random copolymer

SUPPORTING DOCUMENTS:

IND	Guilford Pharmaceuticals Inc.	Gliadel Wafer	
DMF		Terminal Sterilization	Being reviewed by HFD-160 as part of the microbiology review
DMF		Manufacturer	Reviewed by D. Klein and found

			adequate for a DMF
DMF		Packaging	Reviewed on 10-13-93 by HFD-632 and found acceptable

RELATED DOCUMENTS (if applicable): NDA 17-422 BiCNU (sterile carmustine) Bristol-Myers Squibb

CONSULTS:

EA	Approved	EA and FONSI was submitted to HFD-102 for review, found to be acceptable and was approved.
Microbiology	Approved	To HFD-160 to evaluate the sterilization process for manufacture of the DP. Submitted on 2-14-96. Approved on 5/3/96
Biometrics	Pending	Analysis of stability data was requested on 5-23-96.
Biopharm.	Pending	Submitted to HFD-860 to evaluate the in vitro release test and tissue compatibility studies. Submitted on 2-14-96.
Pharm./Tox.	Approved	To evaluate the proposed specification for $CHCl_3$. Found to be acceptable on 3-28-96

OTHER REQUESTS:

Trademark Review	Approved	Submitted on 2-14-96. Approved on 4/4/96. However, see comments to deficiency 26 in review.
EER	Pending	Submitted on 2-14-96.
Methods Validation	Pending	Will be initiated after all methods deficiencies have been addressed.

REMARKS/COMMENTS: This amendment to NDA 20-637 is a response to deficiencies regarding our review of the original submission. The deficiencies were communicated to the applicant by facsimile on April 22, 1996.

The Biometrics consult, Biopharm. consult and EER are still pending.

The EA is acceptable. A FONSI has been prepared and was approved.

CONCLUSIONS & RECOMMENDATIONS:
Drug Substance: The sponsor has adequately addressed all drug substance deficiencies except for one deficiency. The sponsor should provide both the physical and chemical characteristics of carmustine that have been requested by the Agency.

Drug Product: With regards to the drug product the applicant has addressed almost all of the deficiencies cited in our original review of the NDA. However, there are still some minor deficiencies that need to be addressed. These deficiencies, concerning the DP, are minor and should be easy for the applicant to address.

Once these minor deficiencies are addressed and the Biometrics consult, Biopharm. consult and EER are received the NDA can be approved.

See draft deficiency letter.

cc:
Orig. NDA 20-367
HFD-150/Division File
HFD-150/PDietze
HFD-150/DKlein
HFD-151/PZimmerman
HFD-150/ETolgyesi

Paul E Dietze, Ph.D
Drug Product Section

Donald M. Klein 6/6/96

Donald Klein, Ph.D.
Drug Substance Section

6/6/96

Eva Tolgyesi, Ph.D.
Chemistry Team Leader

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

APR 18 1996

NDA #: 20-637 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 4-17-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	2-6-96	2-7-96	2-12-96

NAME & ADDRESS OF APPLICANT: Guilford Pharmaceutical Inc.
6611 Tributary Street
Baltimore, MD 21224

DRUG PRODUCT NAME

Proprietary:	Gliadel ® Wafer
Nonproprietary/USAN:	Polifeprosan 20 with Carmustine
Code Name/#:	GPI-100
Chem.Type/Ther.Class:	3P

ANDA Suitability Petition/DESI/Patent Status: USP 5,179,186 (exp. date 9/9/2011)
USP 4,789,724 (exp. date 10/17/2006)

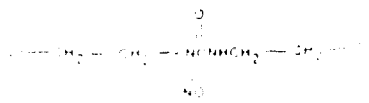
PHARMACOL.CATEGORY/INDICATION: antineoplastic/malignant glioma

DOSAGE FORM: Biodegradable wafer
STRENGTHS: 3.85% carmustine, 7.7 mg carmustine/wafer
ROUTE OF ADMINISTRATION: Surgical implant
DISPENSED: ___X___ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Poly[bis(p-carboxyphenoxy) propane:sebacic acid 20:80] with 1,3-bis(2-chloroethyl)-1-nitrosourea

1,3-bis(2-chloroethyl)-1-nitrosourea:
M.W. = 214.06, Chemical Formula = $C_5H_9Cl_2N_3O_2$



Polifeprosan:

SUPPORTING DOCUMENTS:

IND	Guilford Pharmaceuticals Inc.	Gliadel Wafer	
DMF		Terminal Sterilization	Being reviewed by HFD-160 as part of the microbiology review
DMF		Manufacturer	Reviewed by D. Klein and found adequate for a DMF

DMF	Packaging	Reviewed on 10-13-93 by HFD-630 and found acceptable

RELATED DOCUMENTS (if applicable):

NDA 17-422 BiCNU (sterile carmustine) Bristol-Myers Squibb

CONSULTS:

EA	Pending	Will be submitted to HFD-102 for review after initial deficiencies have been addressed by the sponsor.
Microbiology	Pending	To HFD-160 to evaluate the sterilization process for manufacture of the DP. Submitted on 2-14-96.
Biometrics	Hold	Analysis of stability data will be requested when updated stability data is provided.
Biopharm. Pharm/Tox.	Pending	To HFD-860 to evaluate the in vitro release test and tissue compatibility studies. Submitted on 2-14-96.

OTHER REQUESTS:

Trademark Review	Approved	Submitted on 2-14-96. Approved on 4/4/96
EER	Pending	Submitted on 2-14-96.
Methods Validation	Pending	Will be initiated after all methods deficiencies have been addressed.

REMARKS/COMMENTS:

Drug Substance: The applicant will need to address the deficiencies before the NDA can be approved. For the drug substance, the two categories that contain the major deficiencies are quality control and stability study data.

Drug Product: The applicant will need to address several deficiencies before the NDA can be approved. Most important is to provide analysis of representative lots of drug product to insure that the drug product can be made reproducibly, more detailed specifications need to be established for the drug product and the stability data is limited (additional stability data will be required and the stability protocol needs to include additional tests).

In addition, the microbiology consult and EER are still pending.

CONCLUSIONS & RECOMMENDATIONS:

With regards to chemistry manufacturing and controls NDA #20-637 is not approvable. There are several deficiencies. The applicant must address the deficiencies before the NDA can be approved.

cc:
Orig. NDA 20-367
HFD-150/Division File
HFD-150/PDietze
HFD-150/DKlein
HFD-151/PZimmerman
HFD-150/ETolgyesi

Donald N. Klein, Ph.D.
Drug Substance Section

4/11/96

Paul E Dietze, Ph.D
Drug Product Section

4/18/96

Eva Tolgyesi, Ph.D.
Chemistry Team Leader

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee 530 CDRP
Attention: ~~Mary Jane Mills~~, Chair, (HFD-~~600~~) ~~MPN II~~
Daniel Goring

FROM: Division of [illegible] HFD-[illegible]
Attention: [illegible] Phone [illegible]

DATE: 2/14/96

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: [illegible] NDA/ANDA# [illegible]

Company Name: [illegible]

Established name, including dosage form: [illegible]

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy): [illegible]

Initial comments from the submitter: (concerns, observations, etc.)
None

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 93

cc: [illegible] HFD-150 /D Klein
HFD-150/Division File HFD-150 /L Tengesdal
HFD-[illegible] /D Dierke HFD-[illegible] /Primary

Consult #553 (HFD-150)

GLIADEL WAFER polifeprosan 20 with carmustine

The Committe has no reason to find the proposed proprietary name unacceptable however, the Committee suggests that the USP dosage form of "implant" should be used in conjunction with the USAN name as the established name.

N Boring 4/4/96, Chair

CDER Labeling and Nomenclature Committee

EA And
Fonsi

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

GLIADEL WAFER®
[POLIFEPROSAN 20 WITH CARMUSTINE]

NDA 20-637

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-150

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-637

GLIADEL WAFER

[Polifeprosan 20 with Carmustine]

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action wi" ot have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application, for Gliadel Wafer®, Guilford Pharmaceutica Inc. has prepared an environmental assessment in accordance with 21 CFR 25.3la(b)(3) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Gliadel Wafer is a biodegradable copolymer of polycarboxyphenoxypropane (PCPP) and sebacic acid (SA) with 7.7 mg carmustine. The wafer is implanted into surgical cavaties created by the removal of tumors in patients' brains. Gliadel Wafer is used as an adjunct to surgery to prolong survival in patients with malignant glioma. Bulk drug substance will be manufactured by Formulation, final container packaging, labeling, and release for commercial distribution will be conducted by Guilford Pharmaceutica Inc. at the facility located in Baltimore, MD. The finished drug product will be used in hospitals.

Waste products generated at the production facilities in California will be disposed of in accordance with applicable national,state and local environmental regulations. has provided a Certificate of Environmental Compliance.

Waste products generated at the Baltimore facility result from the manufacturing process.At least 97% of the volatile organic chemicals used in the processes are recovered for hazardous waste disposal and sent to a permitted disposal facility. To reduce emissions where possible engineering and administrative controls have been implemented. These include standard operating procedures for handling of materials and management of hazardous waste and the use of high efficiency air particulate filtration system for the exhausts from entire clean room operations. Other engineering controls for emission reduction includes dry ice traps and water aspirator baths, which are used to capture volatile organic chemicals in the production of the copolymer. The applicant certifies that they comply with all applicable applicable environmental and occupational safety regulations specified by local, state and federal permitted governments. Air emissions include traces of the organic solvent dichloromethane. This emission was reported this emission to the Maryland Department of the Environment's Air and Radiation Management Administration as part of an application for a permit to construct.

Guilford's hazardous wastes are shipped, for incineration, to a licensed facility in the mainland USA. After the hazardous waste undergoes thermal destruction in high temperature incinerators and is destroyed, a Certificate of Treatment is sent to Guilford.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product,

and user disposal of empty or partly used product and packaging. Returned or out of specification drug substance and rejected or returned drug product will be shipped to a licensed incineration facility in the U.S. Waste at hospitals and clinics will be disposed with biological or medical waste according to hospital/clinic regulations.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposure and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects.

DATE

PREPARED BY:
Paul E. Dietze, Ph.D.
Review Chemist
Center for Drug Evaluation and Research

5/6/96
DATE

DIVISION CONCURRENCE
Eva Tolgyesi, Ph.D.
Supervisory Chemist
Center for Drug Evaluation and Research

5/7/96
DATE

CONCURRED
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

cc. Original NDA 20-637
HFD-357/EA File NDA 20-637
HFD-357/ Docket File
HFD-205/ FOI Copy

3.3 ABBREVIATED ENVIRONMENTAL ASSESSMENT

3.3.1 DATE: February 2, 1996

3.3.2 NAME OF APPLICANT/PETITIONER

Guilford Pharmaceuticals Inc.

3.3.3 ADDRESS

6611 Tributary Street
Baltimore, Maryland 21224
(410) 631-6300

3.3.4 DESCRIPTION OF PROPOSED ACTION

A. Requested Approval

Guilford Pharmaceuticals Inc. has filed a New Drug Application (NDA), NDA No. 20-637, pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for GLIADEL® Wafer (polifeprosan 20 with carmustine).

Each GLIADEL® wafer consists of a copolymer of polycarboxyphenoxy-propane (PCPP) and sebacic acid (SA), with 7.7 mg (3.85% by weight) BCNU (carmustine).

An Abbreviated Environmental Assessment (AEA) is being submitted pursuant to 21 CFR Part 25.31a(b)(3).

B. Need for Action

GLIADEL® is an FDA designated orphan drug product (Application No. 89-370) under Section 526 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. Part 360bb and is intended as a treatment for malignant glioma, a condition affecting about 17,500 patients in the U.S. each year.

Items 7-11 and 15 have been omitted from this Abbreviated Environmental Assessment.

C. Production Locations

Drug Substance

The drug substance BCNU (carmustine) is supplied to Guilford Pharmaceuticals by a bulk drug manufacturer.

has authorized the FDA to refer to their Drug Master File (DMF) A copy of this letter may be found in ATTACHMENT 1. Please refer to this DMF for additional information regarding manufacturing facilities.

Additionally, has provided a Certificate of Environmental Compliance. A copy of this certificate is provided in ATTACHMENT 2.

Drug Product

The drug product and any intermediates are manufactured at 6611 Tributary Street, Baltimore, MD 21224. Packaging, labeling and shipping activities are conducted at the same facility. The 83,027 square foot facility is located on a 7.487 acre parcel of land owned by
This is a former site of a U.S. Army military installation known as Fort Holabird. The U.S. Government owned the property from 1918 to October 20, 1977.

The facility is bordered by an unnamed tributary to the south that flows into Colgate Creek, which is about 40 meters west of the facility. The sight is relatively level with a slight slope toward Colgate Creek. Storm water drainage is controlled by municipal storm drains.

To the east of the facility are warehouses. The nearest residential area is Cummins Apartments about a 100 meters southeast of the facilities. The facility is zoned for industrial and commercial use. A copy of a site location map is provided in ATTACHMENT 3.

D. Locations of Use

The product will be used in hospitals and implanted into surgical cavities created by the removal of brain tumors in patients' brains

E. Disposal Sites

Rejected, expired, returned and/or waste drug substances are collected for disposal at the Tributary Street facility and sent to Environmental

Enterprises, Inc. located at 4650 Spring Grove Avenue, Cincinnati, Ohio 45232. Their EPA identification number is OHD 083377010 and the Ohio facility permit number is 05-31-0466. According to their Ohio Hazardous Waste Facility Installation and Operation Permit Renewal, Environmental Enterprises, Inc. permit was approved on June 16, 1995 and does not expire until June 16, 2000.

Guilford's hazardous wastes are sent from Environmental Enterprises, Inc. to
. has the EPA identification number ARD069748192, and was issued a RCRA Part B Permit, number 10-HR-1 from the State of Arkansas' Department of Pollution Control and Ecology. This permit is in effect until June 26, 1998.

When receives Guilford's hazardous waste, it undergoes thermal destruction in high temperature incinerators with an operating capacity of 18.2 tons per hour. Once the material is destroyed, a Certificate of Treatment is sent to Guilford from Environmental Enterprises' Director of Quality Assurance.

Wastes at the clinics and hospitals have been requested by Guilford to be disposed with the biological or medical waste. Packages and products not used or damaged in shipment are to be returned to Guilford for disposal with the other hazardous wastes sent for incineration. Empty packages are discarded into the municipal wastes.

3.3.5 IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

A. Drug Substance

Nomenclature

- USAN Name: carmustine
- Chemical Name: 1,3-bis(2-chloroethyl)-1-nitrosourea
  N,N'-bis(2-chloroethyl-1-nitrosourea)

Chemical Abstracts Services (CAS) Registration Number

Exempt (CAS154-93-8)

(Please see ATTACHMENT 4 for additional information on bischloroethyl nitrosourea reported in the Seventh Annual Report on Carcinogens, 1995.)

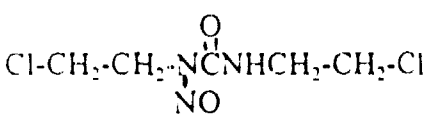
Molecular Formula

$C_5H_9Cl_2N_3O_2$

Molecular Weight

214.06

Structural Formula



Physical Description

BCNU is a light yellow powder. It is highly soluble in alcohol and lipids. It is poorly soluble in water. Its melting point is 29.5-32.0°C.

Impurities

In the Aerojet synthetic process for the manufacture of BCNU, potential process related impurities include 1,3-bis(2-chloroethyl) urea (BCU), the key intermediate, and sodium nitrite. Montgomery, et al.

has shown that BCNU degrades to BCU, 2-chloroethanol, N_2 and CO_2 under aqueous condition at 50°C. Acetaldehyde and 2-chloroethylamine hydrochloride were found to be other degradants of BCNU in aqueous solution at room temperature by Montgomery. Other investigators have also found that the predominant degradants of BCNU are BCU, acetaldehyde, 2-chloroethanol, and 2-chloroethylamine.

Based on studies reported in the literature and discussions with the Aerojet technical staff, the major impurities and/or degradants of BCNU have been identified as BCU, acetaldehyde, 2-chloroethanol, 2-chloroethylamine, and sodium nitrite.

B Drug Product

Nomenclature

- USAN Name: polifeprosan 20
- Chemical Name: Poly[bis(p-carboxyphenoxy)propane: sebacic acid 20:80] with 1,3-bis (2-chloroethyl)-1-nitrosourea
- Generic Name: polifeprosan 20 with carmustine

Chemical Abstracts Services (CAS) Registration Number

Exempt (CAS-90409-78-2)

Molecular Formula

(polifeprosan 20)
$(C_{17}H_{16}O_6)_m.(C_{10}H_{18}O_4)_n$

(Carmustine)
$C_5H_9Cl_2N_3O_2$

Molecular Weight

Per Wafer
Weight Average Molecular Weight
20,100 - 100,000

Structural Formula

Please refer to the structural formula of polifeprosan 20 as provided in the USAN and the USP Dictionary of Drug Names in ATTACHMENT 5.

Physical Description

GLIADEL is a sterile, off-white to pale yellow wafer approximately 1.45 cm in diameter and 1 mm thick. It is insoluble in water. It is soluble in methylene chloride. Its melting point is 60-70°C.

Impurities

The drug product is not monitored for impurities..

3.3.6 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

A. Substances Expected to be Emitted

Drug Substance
As stated in section 3.3.4-C the manufacturer of the drug substance BCNU, has provided Guilford with a Certificate of Environmental Compliance.

Drug Product
The production of Gliadel wafers produces minimal emissions into the environment. Accompanying this AEA in ATTACHMENT 6 is a mass balance report that identifies the constituents and quantities used in the production process. The report simplifies the process into three stages; Production of Copolymer, Copolymer/BCNU Blend, and Pressing and Packaging of Gliadel Wafers.

At least 97% of the volatile organic chemicals used in the processes are recovered for hazardous waste disposal and sent to the permitted facilities described in section 3.3.4-E of this AEA. The only exception is the dichloromethane that is used during the Copolymer/BCNU Blend. During

these processes, spray drying of the blended material causes an emission of dichloromethane at a rate of .78 kg hour and a total of 624 kg year. This emission has been reported to the Maryland Department of the Environment's Air and Radiation Management Administration as part of an application for a permit to construct.

B. Controls Exercised

Engineering and administrative controls have been implemented to reduce emissions where possible. The administrative controls include specific standard operating procedures for handling of materials and management of hazardous waste. One major engineering control is the high efficiency air particulate filtration system for the exhausts from entire clean room operations. This system is continuously monitored and an alarm is activated when there is a drop in the volume of exhausting air or there is a malfunction in the system. Other engineering controls for emission reduction includes dry ice traps and water aspirator baths, which are used to capture volatile organic chemicals in the production of the copolymer.

Exposures to employees from volatile organic chemicals have been monitored and are considerably less than the permissible exposure limits or any action levels. Fume hoods are use to reduce the exposures to solvents. The fume hoods are tested semi-annually to ensure proper exhaust flow and they are designed to activate an alarm if there is a malfunction. Solvents and hazardous wastes are stored in flammable storage cabinets or in the appropriately ventillated storage rooms. Floor drains do not exist in the facility to prevent any potential for contaminating the waste water discharges

Eye washes, emergency showers, fire blankets and first aid kits are readily available to all employees in the production area. The entire area is monitored for fire protection with the use of smoke detectors and sprinklers. These devices are monitored by an outside agency 24 hours a day.

Emergency response procedures are in place for containing spills and the necessary equipment and training has been made available to the employees. A 24 hour emergency response service is also available in the event the chemical spill is beyond Guilford's capabilities.

C. Citation of and Statement of Compliance with Applicable Emission Requirements

Guilford complies with all environmental and occupational safety regulation

specified by the federal, state and local governments. Guilford abides by the state's "Air Quality" regulations (Code of Maryland Regulations, Title 26, Subtitle 11) and the regulations for "Disposal of Controlled Hazardous Substances" (Code of Maryland Regulations, Title 26, Subtitle 13). Also, Guilford complies with the local regulations for the controlling waste water discharges, which are specified in Article 25 of the Baltimore City Code. Federal requirements for environmental compliance are dictated in Title 40 of the Code of Federal Regulations and Guilford also conforms to these regulations. The Maryland Department of the Environment has been authorized to enforce regulations as strict or stricter than those in the federal regulations, which Guilford also obeys.

Guilford follows occupational safety requirements specified in Title 29 of the Code of Federal Regulations and state adopted safety regulations in Title 9 of the Code of Maryland Regulations, which enforced by the state's Maryland and Occupational Safety and Health Division. Other safety requirements that are followed pertain to building design, such as the BOCA National Building Codes of 1993, the National Fire Protection Association Codes and the standards from the American National Standards Institute.

The material safety data sheets for each chemical used in the production process are located in Attachment 7.

Below is a list of the emission permits and licenses for the facility:

- EPA ID# for generation of hazardous waste is MD0000993980 with no expiration date specified
- City of Baltimore's Waste Water Discharged permit # 4-09848; expiration date 9-30-96
- City of Baltimore's Fire Prevention Permit # 31658; expiration date 7-12-96

- The Maryland Department of the Environment (Code of Maryland Regulations 26.11.13) requires a Permit to Construct for processing equipment that generates air pollutants. By utilizing the Maryland Department of the Environment's Risk Based Screening levels and the screening analysis that may be used to demonstrate compliance (Code of Maryland Regulation 26.11.15.06), Guilford is exempt from installing emission control devices on the spray dryer. An application has been submitted for the spray drying process that generates the methylene chloride emissions. The Maryland Department of the Environment has reviewed and approved the process. Guilford received a billing notice on December 27, 1995 and the payment has

been forwarded but at the time of this submission, Guilford is awaiting receipt of the permit.

D. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

Current production plans are for 6000 Gliadel wafers per month which exceed current and expected demands for the product. If an increase in production is necessary, it will require changes to the current equipment due to the limited capacities. At that point, emission controls could be necessary. Processes may not be conducted with new or altered equipment until an application for modifications is submitted and granted by the Maryland Department of the Environment.

E. Expected Introduction Concentrations (EIC)

Expected Introduction Concentration from Use

The expected introduction of drug substance into the environment is estimated below without consideration of metabolism or depletion mechanisms:

EIC-Aquatic (ppm)= 3.5 E-07
where A= 14.4 kg/year of production
B= 1/ liter per day entering POTW's
C= year/365
D= 10E6 mg/kg (conversion factor)

The EIC into the Terrestrial and atmosphereic environment from the metabolism/excretion of patients in whom GLIADEL wafers have been implanted is a factor of the individual metabolism of the patient.

No drug product should enter the air as an emission since HEPA filtration is used in the production process. In the unlikely event that all the drug substance (BCNU) used in production were to enter the HEPA exhaust system, only 3.57E-07 kg/hour would enter an air volume of 15.97E03 cubic meters. This would create a maximum concentration of 2.24E-11 kg/cubic meter.

Expected Introduction Concentration from Disposal

The EIC from disposal does not need to be calculated since this material is completely destroyed by incineration.

NOTE: SECTIONS 3.37 THROUGH 3.3.11 AND 3.3.15 OF THIS ABBREVIATED ENVIRONMENTAL ASSESSMENT ARE NOT REQUIRED.

3.3.12 LIST OF PREPARERS

Frederick A. Miller Social Security No. 211-56-9068
Safety & Environmental Health Officer

Qualifications of Preparer
Mr. Miller has worked in the pharmaceutical industry as a safety and environmental professional for more than 11 years. He has an Associates of Applied Science degree in Occupational Safety and Health Technology. He attended several courses in environmental law, radiation safety and OSHA compliance. He is responsible for acquiring Guilford's environmental permits which include waste water discharge, hazardous waste, air quality and radioactive materials. He has assisted in the preparation of a previous AEA for Nova Pharmaceuticals. Also, he is responsible for administering and maintaining Guilford's Safety and Environmental Health programs.

3.3.13 CERTIFICATION

The undersigned Guilford Pharmaceuticals Inc. official certifies that the information presented in this AEA is true accurate and complete to the knowledge of the company. The AEA contains non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR §1506.6.

3.3.14 REFERENCES

N/A

3.3.15 APPENDICES

N/A.

Ross S. Laderman
Vice President, Regulatory Affairs

2/2/96
Date

CERTIFICATE OF ENVIRONMENTAL COMPLIANCE

CERTIFICATE OF ENVIRONMENTAL COMPLIANCE

The offeror currently ☒ IS ☐ IS NOT in compliance with applicable national, state, and local environmental laws and regulations. *(If not in compliance, attach details and evidence of approved mitigation measures.)*

The offeror has examined the activities encompassed within the proposed action entitled "Supplying BCNU to Guilford Pharmaceuticals, Inc. (David Woodman, Manager, Fine Chemicals and Pharmaceuticals)" *(enter title and/or Solicitation number and Principal Investigator's name)*, for compliance with environmental laws and regulations. The offeror states that the conduct of the proposed action ☐ WILL ☒ WILL NOT violate any applicable national, state, or local environmental law or regulation. *(If a violation will result, attach details describing the nature of the violation and evidence of approved mitigation measures.)*

The offeror agrees that if the work required under the proposed action at any time results in a violation of any applicable environmental law or regulatioin, the offeror will immediately take appropriate action, to include notifying the Contracting Officer, and coordinating with the appropriate regulatory agencies.

for
Karen J. Gunderson
(Name of Official Responsible for Environmental Compliance)

E G. David
Signature
Manager, Waste Management

Manager, Environmental Management
(Title)

1/24/96
Date

Aerojet-General Corporation
(Name of Organization)

L0689

BISCHLOROETHYL NITROSOUREA
CAS No. 154-93-8

CARCINOGENICITY

There is sufficient evidence for the carcinogenicity of bischloroethyl nitrosourea in experimental animals (IARC V.26, 1981; IARC S.4, 1982; IARC S.7, 1987). When administered intraperitoneally or intravenously, bischloroethyl nitrosourea induced lung tumors including adenocarcinomas, and neurogenic tumors in rats. When administered by intraperitoneal injection, the compound induced malignant tumors in the peritoneal cavity. Other studies of bischloroethyl nitrosourea in rats and mice were determined to provide insufficient data for evaluation by an IARC Working Group.

An IARC Working Group reported that there is limited evidence for the carcinogenicity of bischloroethyl nitrosourea in humans (IARC S.4, 1982; IARC V.26, 1981; IARC S.7, 1987). No epidemiological study on the effect of bischloroethyl nitrosourea alone in humans is available, but bischloroethyl nitrosourea is associated with acute nonlymphocytic leukemia following its use with other anticancer therapies in the treatment of previously existing cancer.

PROPERTIES

Bischloroethyl nitrosourea is a light yellow powder that is slightly soluble in water and 50% ethanol, soluble in ethanol, and highly soluble in lipids. This compound is sensitive to oxidation and hydrolysis, subsequently forming alkylating and carbamoylating intermediates. When heated to decomposition, it emits toxic fumes of hydrochloric acid and other chlorinated compounds as well as nitrogen oxides (NO_x).

USE

Bischloroethyl nitrosourea has been used since 1971 as an antineoplastic agent in the treatment of Hodgkin's lymphoma, multiple myeloma, and primary or metastatic brain tumors. It has also been reported to have antiviral, antibacterial, and antifungal activity, but no evidence was found that it is currently used in these ways (IARC V.26, 1981).

PRODUCTION

The USITC does not list any current production volume for bischloroethyl nitrosourea (USITC, 1987). In 1981, bischloroethyl nitrosourea was believed to be produced by only one U.S. company in an undisclosed amount, and was available in the United States in vials containing 100 mg (IARC V.26, 1981).

EXPOSURE

The primary routes of potential human exposure to bischloroethyl nitrosourea are injection, inhalation, and dermal contact. It is administered to patients in doses of 100-250 mg/m^2 body surface by intravenous injection daily, for courses of 2 or 3 days (IARC V.26, 1981). The National Occupational Exposure Survey (1981-1983) estimated that 5,596 total workers, including 2,809 women, potentially were exposed to bischloroethyl nitrosourea in the work place (NIOSH, 1984). Potential exposure of health professionals who handle this drug (e.g., pharmacists, nurses, and physicians) may occur during drug preparation, administration, or cleanup; however, the risks can be avoided through use of containment equipment and proper work practices (Zimmerman et al., 1981). Potential occupational exposure to bischloroethyl nitrosourea may also occur for workers involved in the formulation and packaging of the pharmaceuticals. Bischloroethyl nitrosourea is not known to be a naturally occurring compound (IARC V.26, 1981).

REGULATIONS

Bischloroethyl nitrosourea is used as a pharmaceutical and in low quantities relative to other chemicals; therefore, it is of little regulatory concern to EPA. However, there may be a small pollution problem relative to hospital wastes. FDA regulates bischloroethyl nitrosourea under the Food, Drug, and Cosmetic Act (FD&CA) as a prescription drug, approved for human use. FDA requires warning labels on bischloroethyl nitrosourea regarding its potential carcinogenicity, mutagenicity, teratogenicity, and/or fertility impairment. OSHA regulates bischloroethyl nitrosourea under the Hazard Communication Standard and as a chemical hazard in laboratories.

REGULATIONS

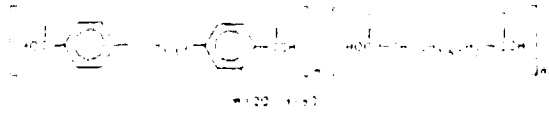
	Regulatory Action	Effect of Regulation/Other Comments
F D A	21 CFR 314. Promulgated 3/29/74. FD&CA 505: Prescription drug approved for human use.	Approved for use as an antineoplastic agent.
	21 CFR 201.57. Promulgated 6/26/79. FD&CA: Drug labeling requirements for human prescription drugs.	Includes provisional requirements for warning labels regarding potential carcinogenicity, mutagenicity, teratogenicity, and/or impairment of fertility.

(Continued)

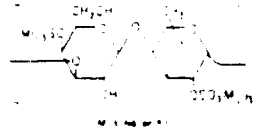
REGULATIONS

	Regulatory Action	Effect of Regulation/Other Commen
OSHA	29 CFR 1910.1200. Promulgated 11/25/83. OSH Act: Hazard Communication.	Requires chemical manufacturers a importers and all employers to assess chemical hazards and to pr vide information to employees. Hazard Communication Program to include labels, material safety data sheets, and worker training. Labels may be subject to FD&CA requirements.
	29 CFR 1910.1450. Promulgated 1/31/90. OSH Act: Final rule for occupational exposure to hazardous chemicals in laboratories.	As a select carcinogen (IARC Grou 2A), bischloroethyl nitrosourea i included as a chemical hazard in laboratories. Employers required to provide employee information a training and to provide Chemical Hygiene Plan.

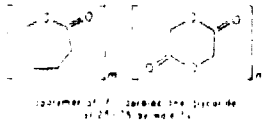
Polifeprosan 20 *[1991]* (pol ee fep' roe san) $(C_{11}H_{10}O_4)_m$-$(C_{20}H_{14}O_4)_n$ 20,000–200,000. [Polifeprosan is INN.] The numerical value 20 represents the weight percent of the 4,4'-(trimethylenedioxy)dibenzoic acid monomer (monomer *m*) present in the polymer. (1) Benzoic acid, 4,4'-[1,3-propanediylbis(oxy)]bis-, polymer with decanedioic acid; (2) 4,4'-(Trimethylenedioxy)dibenzoic acid, polymer with sebacic acid. *CAS-90409-78-2. Pharmaceutic aid.* Biodel (Scios Nova)



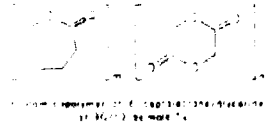
Poligeenan *[1969]* (pol i gee' nan). $[C_{12}H_{16}M_2O_{15}S_2]n$ (Nominal, the value of *n* is 30 to 60). Polysaccharide derived from extensive hydrolysis of carrageenan from red algae. (1) Poligeenan; (2) 3,6-Anhydro-4-*O*-β-D-galactopyranosyl-α-D-galactopyranose 2,4'-bis(potassium/sodium sulfate)-(1→3)-polysaccharide. *CAS-53973-98-1.* INN. *Pharmaceutic aid (dispersing agent).*



Poliglecaprone 25 *[1991]* (pol ee glek' a prone). $(C_6H_{10}O_2)_m(C_4H_4O_4)_n$. 70,000 (wt. avg.). [Poliglecaprone is BAN.] (1) 2-Oxepanone, polymer with 1,4-dioxane-2,5-dione; (2) 2-Oxepanone polymer with *p*-dioxane-2,5-dione. *CAS-41706-81-4.* INN. *Surgical aid (surgical suture material, absorbable).* (Ethicon)



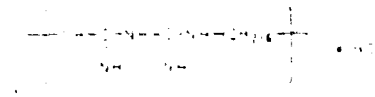
Poliglecaprone 90 *[1991]* $(C_6H_{10}O_2)_m(C_4H_4O_4)_n$. 5,000–15,000 (wt. avg.). (1) 2-Oxepanone, polymer with 1,4-dioxane-2,5-dione; (2) 2-Oxepanone polymer with *p*-dioxane-2,5-dione. *CAS-41706-81-4.* INN. *Surgical aid (surgical suture coating, absorbable).* (Ethicon)



Poliglusam *[1991]* (pol ee gloo' sam). Linear homopolymer of partially acetylated glucosamine. (1) Chitosan. (2) Chitosan. *CAS-9012-76-4.* INN. *Antihemorrhagic.* (Hoechst-Roussel)

Polignate Sodium *[1970]* (pol ig' nate). The sulfonated form of a polymer similar to the sub-unit of coniferyl alcohol polymer derived from coniferous wood. (The individual polymer units are considered to be three-dimensional structures with molecular weights in the range of several thousand.) (1) Lignosulfonic acid, sodium salt; (2) Sodium lignosulfonate. *CAS-8061-51-6. CAS-7061-51-6* [sodium lignosulfonate]. *Enzyme inhibitor (pepsin).* ◇ *4HR-2438B*

Polihexanide $(C_8H_{17}N_5 \cdot HCl)_n$. [Polyhexanide is BAN.] Polyiminoimidocarbonyliminoimidocarbonyliminohexamethylene monohydrochloride. *CAS-28757-48-4.* INN

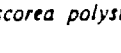


Poliomyelitis Vaccine (previously used name) — *See* Poliovirus Vaccine Inactivated.

Poliovirus Vaccine Inactivated (poe lee oh vye' russ). USP. *Immunizing agent (active). [Name previously used: Poliomyelitis Vaccine.]*

Poliovirus Vaccine Live Oral. USP. *Immunizing agent (active).* Orimune (Lederle)

Polipropene 25 *[1974]* (pol i proe' peen). $(C_3H_6)_n$. (1) 1-Propene homopolymer; (2) Polypropene. *CAS-9003-07-0. Pharmaceutic aid (tablet excipient).*



Polisaponin. Mixture of all the steroid saponins isolated from the rhizome of *Dioscorea polystachya. CAS-8063-80-7.* INN.

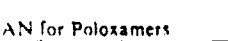
Politef (INN) — *See* Polytef.

Polmiror. Polichimica Sap, Italy, brand of Nifuratel.

Polocaine. Astra brand of Mepivacaine Hydrochloride.

Poloxalene *[1965]* (pol ox' a leen). Liquid nonionic surfactant polymer of the polyethylene-polypropylene glycol type, having a molecular weight of approximately 3000. (In the graphic formula, average values are: $a = 12$; $b = 34$; $c = 12$.) (1) Oxirane, methyl-, polymer with oxirane; (2) Polyethylene-polypropylene glycol. *CAS-9003-11-6.* INN; BAN. *Pharmaceutic aid (surfactant).* Bloat Guard (SmithKline Beecham Animal Health); Therabloat (SmithKline Beecham Animal Health) ◇*SK&F 18,667*

Poloxamer *[1971]* (pol ox' a mer). NF. $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$. [Poloxamer-188 is JAN.] (1) Oxirane, methyl-, polymer with oxirane; (2) α-Hydro-ω-hydroxypoly(oxyethylene)$_a$-poly(oxopropylene)$_b$-poly(oxyethylene)$_a$ block copolymer. [*Note—Poloxamer (used in conjunction with a numeric suffix for individual unique identification) is the nonproprietary name that applies to products for which a food, drug, or cosmetic use is likely. These copolymers may function as surfactants, emulsifiers, solubilizers, or stabilizers. See accompanying table for poloxamer names.*] *CAS-106392-12-5* [block copolymer]. INN; BAN. *Pharmaceutic aid (ointment base); pharmaceutic aid (suppository base); pharmaceutic aid (surfactant); pharmaceutic aid (tablet binder and emulsifying agent); pharmaceutic aid (tablet coating agent).* (BASF)



USAN for Poloxamers

	Physical Form	Average Molecular Weight	Average Values		BASF Corp Brand Name
			a	*b*	
Poloxamer					Pluronic
124	Liquid	2090 to 2360	12	20	L 44
188	Solid	7680 to 9510	80	27	F 68
237	Solid	6840 to 8830	64	37	F 87
338	Solid	12700 to 17400	141	44	F 108
407	Solid	9840 to 14600	101	56	F 127

DIVISION OF ONCOLOGY DRUG PRODUCTS

REVIEW OF ENVIRONMENTAL ASSESSMENT

EQR

NDA 20-637 GLIADEL® Wafer (Polifeprosan 20 with Carmustine)

1. **DATE OF DOCUMENT**: 02-April-1996

2. **NAME OF APPLICANT**: Guilford Pharmaceuticals Inc.

3. **ADDRESS**: 6611 Tributary Street
Baltimore, MD 21224

4. **DESCRIPTION OF PROPOSED ACTION**:

A. Describe the requested approval. Guilford Pharmaceuticals Inc. is requesting approval of NDA 20-637 for the use of GLIADEL® Wafers (Polifeprosan 20 with Carmustine), for use as an adjunct to surgery to prolong survival in patients with malignant glioma. Each GLIADEL® Wafer consists of a copolymer of polycorboxyphenoxypropane (PCPP) and sebacic acid (SA), with 7.7 mg of carmustine per wafer (3.85% carmustine per wafer).

GLIADEL is an FDA designated orphan drug product (Application No. 8--370).

The applicant has not included a description of the packaging for the drug product. However, the drug product packaging consists of two foil laminate pouches. The inner pouch is a laminate and considered the product closure system. The inner pouch maintains product sterility and protection from moisture. The outer pouch is a peelable overwrap. Each pouch contains an individual wafer. Eight pouches are then placed in a carton.

B. Describe the need for action. The drug is indicated as an adjunct to surgery to prolong survival in patients with malignant glioma. The treatment may be used in conjunction with external beam radiation therapy. The condition affects about 17,500 people per year.

C. Describe the locations where the products are to be:

1. **Produced**: The drug substance carmustine is supplied to Guilford Pharmaceuticals by a bulk drug manufacturer.

The drug product and any intermediates are manufactured at 6611 Tributary Street, Baltimore, MD 21224. Packaging, labeling and shipping activities are conducted at the same facility. The 83,027 square foot facility is located on a 7.487 acre parcel of land owned by

This is a former site of a U.S. Army military installation known as Fort Holabird. The U.S. Government owned the property from 1918 to October 20, 1977. In Attachment 3 is a copy of the site location map.

The applicant has not included a description of the environment adjacent to the drug substance manufacturing facility needs to be included. However, Nancy Sager, HFD-102, has indicated that this is not necessary since the company has been manufacturing the drug substance for many years. See attached E-mail.

2. **Used**: GLIADEL® Wafer will be used in hospitals and implanted into surgical cavities created by the removal of brain tumors in patients' brains

3. **Disposal**:

a. Drug Substance: Rejected expired, returned and/or waste drug substances are collected for disposal at the Tributary Street facility and sent to

Their EPA identification number is OHD 083377010 and the Ohio facility permit number is 05-31-0466. According to their Ohio Hazardous Waste Facility Installation and Operation Permit Renewal, Environmental Enterprises. Inc. permit was approved on June 16, 1995 and does not expire until June 16, 2000.

Guilford's hazardous wastes are sent from

has the EPA identification number

ARD069748192, and was issued a RCRA Part B Permit, number I0-HR- I from the State of Arkansas' Department of Pollution Control and Ecology. This permit is in effect until June 26, 1998.

When receives Guilford's hazardous waste, it undergoes thermal destruction in high temperature incinerators with an operating capacity of 18.2 tons per hour. Once the material is destroyed, a Certificate of Treatment is sent to Guilford from Environmental Enterprises' Director of Quality Assurance.

b. Drug Product: Wastes at the clinics and hospitals have been requested by Guilford to be disposed of with the biological or medical waste. Packages and products not used or damaged in shipment are to be returned to Guilford for disposal with the other hazardous wastes sent for incineration.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THE PROPOSED ACTION: A complete description of the drug substance is provided on page 4. Also included is a list of process related impurities and degradants from carmustine . The sponsor includes in Attachment 4 additional information on the drug substance can be reported in the Seventh Annual Report on Carcinogens. Similarly, a complete description of the drug product is provided on page 5. The applicant provides (Attachment 7) Material Safety Data Sheets (MSDS) for the drug substance, materials used in the manufacture of the drug substance and for the drug product.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

A. Drug Substance Production Sites: The drug substance is manufactured at The sponsor indicates in section 3.3.4-C that the manufacturer of the drug substance, carmustine , has provided Guilford with a Certificate of Environmental Compliance.

No information is provided pertaining to the manufacturing site for the drug substance, listing the substances to be emitted, the controls exercised, compliance with applicable emission requirements at the production site, type and quantities of substances to enter the environment. However, in discussion with Nancy Sager, HFD-102, she indicated that this is not necessary since the company has been manufacturing the drug substance for many years. See attached E-mail.

B. Drug Product Manufacturing Sites:

Substances Expected to be Emitted: The sponsor indicates the production of GLIADEL wafers produces minimal emissions into the environment. In ATTACHMENT 6 is provided a mass balance report identifying the constituents and quantities used in the production process, CAS registry numbers for these compounds and maximum expected emission levels. The report simplifies the process into three stages; Production of Copolymer, Copolymer/carmustine Blend, and Pressing and Packaging of GLIADEL Wafers.

The sponsor indicates at least 97% of the volatile organic chemicals used in the processes are recovered for hazardous waste disposal and sent to the permitted disposal facilities described earlier. The only exception is the dichloromethane that is used during the Copolymer/carmustine Blend. During this processes, spray drying of the blended material causes an emission of dichloromethane at a rate of 0.78kg/hour and a total of 624kg/year. It is indicated that the sponsor has reported this emission to the Maryland Department of the Environment's Air and Radiation Management Administration as part of an application for a permit to construct.

Controls Exercised: The following controls are exercised to reduce emissions where possible. Engineering and administrative controls have been implemented to reduce emissions. The administrative controls include specific standard operating procedures for handling of materials and management of hazardous waste. One major engineering control is the high efficiency air particulate filtration system for the exhausts from entire clean room operations. This system is continuously monitored and an alarm is activated when there is a drop in the volume of exhausting air or there is a malfunction in the system. Other engineering controls for emission reduction includes dry ice traps and

water aspirator baths, which are used to capture volatile organic chemicals in the production of the copolymer.

Exposures to employees from volatile organic chemicals have been monitored and are considerably less than the permissible exposure limits or any action levels. Fume hoods are use to reduce the exposures to solvents. The fume hoods are tested semi-annually to ensure proper exhaust flow and they are designed to activate an alarm if there is a malfunction. Solvents and hazardous wastes are stored in flammable storage cabinets or in the appropriately ventilated storage rooms. Floor drains do not exist in the facility to prevent any potential for contaminating the waste water discharges.

Eye washes, emergency showers, fire blankets and first aid kits are readily available to all employees in the production area. The entire area is monitored for fire protection with the use of smoke detectors and sprinklers. These devices are monitored by an outside agency 24 hours a day.

Emergency response procedures are in place for containing spills and the necessary equipment and training has been made available to the employees. A 24 hour emergency response service is also available in the event the chemical spill is beyond Guilford's capabilities.

Citation and Statement of Compliance with Applicable Emission Requirements: The applicant certifies that they comply with all applicable environmental and occupational safety regulations specified by federal, state and local governments. A list of emission permits and licenses for the manufacturing facility is provided.

MSDS are provided in Attachment 7 for compounds used in the drug product manufacturing process.

Discussion of the Effect of Approval on Compliance with Current Emission Requirements: Current production plans are for 6000 GLIADEL wafers per month which exceed current and expected demands for the product. If an increase in production is necessary, it will require changes to the current equipment due to limited capacities. At that point, emission controls could be necessary. Processes will not be conducted with new or altered equipment until an application for modifications is submitted and granted by the Maryland Department of the Environment.

Expected Introduction Concentrations (EIC): Calculations concerning the expected introduction of drug substance into the environment from use was calculated without consideration of metabolism or depletion mechanisms. The EIC-Aquatic (ppm) = 3.5 E-07.

An EIC from disposal was not calculated since the material is destroyed by incineration.

12. **LIST OF PREPARERS:** A list of persons who prepared the Environmental Assessment document and their qualifications is provided.

13. **CERTIFICATION:** Certification (signed by the Vice President, Regulatory Affairs) is provided that the information presented in the Environmental Assessment document is "true, accurate and complete to the knowledge of the company".

14. **REFERENCES:** No references are listed.

15. **APPENDICES:** Appendices are attached. These include: A LOA to examine the DMF of the drug substance manufacturer, A Certificate of Compliance for drug substance manufacturer, Information on carmustine contained in their Seventh Annual Report on Carcinogens (1995), the structure of Polifeprosan (from USAN), a mass balance report for GLIADEL manufacturing process and material data safety sheets.

Prepared by:

Paul E. Dietze, Ph.D. Date
Chemist
HFD-150

Division Concurrence:

5/6/96

Eva Tolgyesi, Ph.D. Date
Chemist
HFD-150

Concurred:

5/7/96

Nancy Sager Date
Environmental Scientist
Center for Drug Evaluation and Research

cc:
HFD-150 Div. File for NDA # 20-637
HFD-150/PDietze
HFD-150/ETolgyesi
HFD-151/PZimmerman
File: n20637e2.001

DEBARMENT CERTIFICATION FOR NDA

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

_____ _____

Date

FIRM:RHONE POULENC RORER

TRADE NAME:GLIADEL

GENERIC NAME:POLIFEPROSAN 20 WITH CARMUSTINE

Microbiologist Review

MAY 3 1996

[redacted]

REVIEW TO HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF NDA
May 3, 1996

A. 1. **NDA 20-637** **APPLICANT:** Guilford Pharmaceuticals Inc
6611 Tributary Street
Baltimore, Maryland 21224

2. **PRODUCT NAMES:** GLIADEL® Wafer
Polifeprosan 20 with Carmustine

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:**
Each Gliadel® wafer consists of 7.7 mg BCNU/wafer and 192.3 mg of a biodegradable polyanhydride copolymer. Up to eight Gliadel® wafers (cumulative dose of 61.6 mg carmustine) may be implanted into the surgical cavity

4. **METHODS OF STERILIZATION:**
Terminal Sterilization by Gamma Irradiation

5. **PHARMACOLOGICAL CATEGORY:**
Anti-neoplastic

B. 1. **DATE OF INITIAL SUBMISSION:** February 6, 1996
2. **ASSIGNED FOR REVIEW:** February 29, 1996

C. **REMARKS:** Gliadel® is a biodegradable polyanhydride polymer containing BCNU. It is surgically implanted in the brain of patients with a malignant glioma. Up to eight wafers are implanted at the tumor site to provide sustained release over a three week period. Each wafer is packaged in a double foil pouch system. The outer pouch is not sterile. The inner pouch and the Gliadel® wafer inside are sterile. Gliadel® wafer is the subject of an approved orphan drug designation.

D. **CONCLUSIONS:** The NDA 20-637 for Gliadel® wafers is recommended for approval from the standpoint of microbiology. Specific comments are provided in Section E "Review Notes".

5/3/96
Patricia F. Hughes, Ph.D.
Review Microbiologist

5/3/96

cc: Original NDA 20-637
HFD-160/Consult File
HFD-160/P.F. Hughes
HFD-150/Division File
HFD-150/P. Dantus/D. Kleuvel Tolgyesi/P. Zimmerman
Drafted by P.F. Hughes, 05/01/96
R/D initialed by P. Cooney, 05/01/96

END

BT

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011