CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21029

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW OF TEMODAL TRADEMARK

NDA 21-029

Drug: Temozolomide (TEMODAL)

SPONSOR: Schering Corp

M.O. Martin H. Cohen, M.D.

DATE: February 8, 1999

Points to be made for allowing Schering Corporation to use the Temodal brand name. Significant differences between Tramadol-HCl and TEMODAL.

1. Strength/Dosage form

   Tramadol is available as 50mg tablets. TEMODAL is available as 5mg, 20mg, 100mg and 250mg capsules.

2. Schedule of Administration

   Tramadol is administered every 4-6 hours. TEMODAL is administered once daily for 5 days.

3. Drug Dose

   Tramadol dose is 50mg to 100mg with a total daily dose not to exceed 400mg. TEMODAL is dosed on a mg/m2 basis. The total TEMODAL dose/day generally requires a combination of up to 4 differently colored capsules. There are only two possible TEMODAL doses where only one or two *identical* capsules are used, i.e. a dose of 200mg where two 100mg capsules are administered and a dose of 250mg where one 250mg capsule is given. All other potential doses require either three of the same capsule or more than one type of capsule.

4. Number of pills dispensed

   Because patients can take up to 8 Tramadol tablets/day it is likely that more than 60 tablets will be dispensed at a time. Because TEMODAL is administered as a 5-day course and because the largest number of capsules of a specific dose taken per day is 4 the maximum number of pills (250mg, 100mg, 20mg, or 5mg) dispensed for TEMODAL is 20.

5. Consequences of a Dispensing Error

It is unlikely that dispensing Tramadol instead of TEMODAL would result in life-threatening consequences. The maximum number of pills that a TEMODAL patient would take in one day is 6. Estimated Tramadol dosage to produce a fatality is 3-5g.

If TEMODAL were given instead of Tramadol the principal issue would be the number of TEMODAL capsules dispensed. One possible way to limit the number of TEMODAL capsules dispensed at one time would be in the way the capsules were packaged. For the TEMODAL 250 mg capsule no more than 5 capsules would be needed for a cycle of treatment. Corresponding numbers for TEMODAL 100mg are 15 capsules, TEMODAL 20 mg; 20 capsules and TEMODAL 5mg; 15 capsules. If Schering packaged the various TEMODAL dosage forms so that no more than the above number of capsules were contained in appropriately labeled containers or blister packs it should decrease the possibility that TEMODAL would be substituted for Tramadol.

RECOMMENDATION: Based on the above, and with the proposed packaging modifications, it seems reasonable to allow Schering to use the TEMODAL trademark.

/S/

Martin H. Cohen, M.D.
February 8, 1999

See my Review
dated 2-8-99

/S/

V 2-8-99

CLINICAL TEAM LEADER REVIEW OF TEMODAL TRADEMARK

NDA 21029

DRUG Temodal Capsules

The CDER Nomenclature Committee has recommended that the Temodal name not be permitted because of the risk that Temodal will be confused with tramadol. I have reviewed the arguments made by Schering to justify use of the Temodal Tradename in their FAX dated 2-4-99. I have also read Dr. Cohen's Medical Officer review of this issue.

The most favorable aspect is that Temodal is a capsule and tramadol is a tablet. Also they are different dosage strengths.

Even so, the risk of a mix-up exists. The worst case is a tramadol patient who gets Temodal by error. If the tramadol dose is 2 tablets up to four times a day (total of 8 Tablets) and by error the patient gets 8 Temodal capsules a day, this could be up to 2000 mg of Temodal a day (8 x 250 mg capsule) for an unlimited number of days. The Temodal dose is 150-200 mg/M2 daily for 5 days. This would be serious and possibly fatal. Dr. Cohen's recommendation that there be only 5 x 250 mg Temodal capsules in a blister pack would decrease the injury somewhat, but only if only one blister pack of Temodal (enough for one cycle) were dispensed at a time. The injury would less, but would still be unacceptable.

It is not possible to quantify the risk, but the risk of a mix-up with potentially serious consequences exists and there is no compensating benefit for patients if the Temodal name is used. It is not appropriate to weigh the risk to the patients against the benefit to the Pharmaceutical company.

Hopefully in the future these decisions will be made earlier in the process and we will be able to inform Pharmaceutical Companies earlier.

RECOMMENDATION

The Temodal Tradename name should not be used.

/S/
John R. Johnson, M.D.
February 8, 1999

CC NDA 21029
Div File
Martin Cohen
Patrick Guinn

MEDICAL OFFICER REVIEW OF:
NDA #21-050 (RELAPSED GLIOBLASTOMA MULTIFORME) AND
NDA #21-029 (RELAPSED ANAPLASTIC ASTROCYTOMA)

Drug Name: Temozolomide
Applicant: Schering-Plough Research Institute (SPRI)
Date Submitted: August 13, 1998
Date Received: August 18, 1998
Date of Review: January 29,1999

Review Team:

Martin H. Cohen, M.D.	Medical Reviewer
John R. Johnson, M.D.	Medical Team Leader
Safaa Ibrahim, Ph.D.	Pharmacology/Toxicology Reviewer
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Gary Gensinger	Operation Research Analyst
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Dottie Pease	Project Manager Team Leader

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1.1. Drug name and chemical characteristics

1.2. International non-proprietary name:

Temozolomide

1.3. United States approved name:

Temozolomide

1.4. British approved name:

Temozolomide

1.5. Generic name:

Temozolomide:

1.6. Chemical name:

1. Imidazo[5,1- d]-1,2,3,5-tetrazine-8-carboxamide,3,4-dihydro-3-methyl-4-oxo 2. 3,4-Dihydro-3-methyl-4-oxoimidazo [5,1 -d]- as-tetrazine-8-carboxamide 3. 8-Carbamoyl-3-methylimidazo [5,1- d], 1,2,3,5-tetrazin-4-(3H)-one

1.7. CAS registry number:

85622-93-1

1.8. Laboratory code names:

SCH 52365
M&B 39831

1.9. Other names:

Methazolastone

1.10. Physical form:

White to light pink/light tan powder.

1.11. International non-proprietary name:

Temozolomide

1.12. Structural formula:

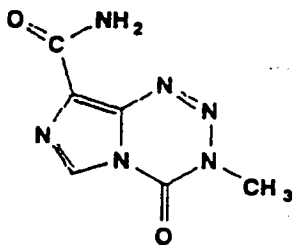

Figure 1 Chemical structure of Temazolamide

1.13. Molecular formula:

C 6 H 6 N 6 O 2

1.14. Formulation

Table 1 Temozolamide Formulation

Ingredient	mg/capsule			
Temozolomide (SCH 52365)	5.0	20.0	100.0	250.0
Lactose Anhydrous NF				
Sodium Starch Glycolate NF				
Colloidal Silicon Dioxide NF				
Tartaric Acid NF				
Stearic Acid NF				

1. Overview

2.1 Regulatory History

Schering-Plough Research Institute (SPRI) undertook the development of temozolomide therapy in June 1992 when worldwide rights were acquired from the Cancer Research Campaign in the UK. INDs were subsequently submitted on May 3, 1993 (NCI IND and December 17, 1993 (SPRI IND

An FDA-SPRI meeting, on November 17, 1994, discussed design features of the pivotal trial in GBM (C94-091, I96058). The FDA recommended a two-arm comparator study. The FDA also advised the sponsor that it would be important to establish a complete data base about disease free survival with/without treatment. The sponsor proposed to use the UCSF database to establish a 6 month progression rate. The FDA noted that the sponsor

has the burden of providing convincing data to FDA and to the Advisory Committee regarding the UCSF and other historical databases in terms of an accurate estimation of progression and progression free survival at 6 months. It was agreed that time to neurologic symptoms was not an appropriate endpoint. Use of the EORTC Quality of Life Scale a design of a population pharmacokinetic study were agreed upon. There is no record of discussion related to the primary efficacy endpoint of the glioblastoma multiforme study although the sponsor, in the NDA document, states that the FDA accepted progression-free survival at 6 months, based on MRI imaging, as the primary efficacy endpoint. The objective was to demonstrate that the lower bound of the 95% CI of the 6-month progression-free survival rate for temozolomide was above 10%.

The next meeting dealing with clinical issues was held on October 8, 1996. At that meeting, the FDA determined that the C94-091 interim data based on 60 patients (30 per group) having completed 6 months of treatment, discontinued due to progression or died were not sufficiently mature to allow conclusions regarding efficacy of temozolomide in the treatment of GBM. The study was continued until the target enrollment goal of 100 evaluable patients per group was reached. At that time, the FDA indicated that the open-label studies in GBM (I94-122) and anaplastic astrocytoma (C/I94-123) could support the randomized clinical trial. The FDA expressed concern related to potential investigator bias in a non-blinded trial determining time to event endpoints.

The sponsor's minutes of the October 8, 1996 Pre-NDA meeting states that at the November 17, 1994 meeting the endpoint of progression-free status at 6 months was accepted due to great difficulty in obtaining objective response data in this disease state. The Agency minutes of the November 17, 1994 meeting do not support this contention.

On August 7, 1997, results of the second interim analysis of C94-091 data based on 120 patients (60 per group) having completed 6 months of treatment, discontinued due to progression or died was submitted with a request for an opinion on the feasibility of the study to support registration. The FDA response, on October 7, 1997, was that the completed controlled trial (C94-091) supported with the open-label studies in GBM (I94-122) and anaplastic astrocytoma (C/I94-123) provided an adequate basis for filing an NDA.

On October 7, 1997, in response to an interim report of trial C94-091 the Agency stated that the basis for approval in GBM, primary or recurrent, is significant improvement in overall survival. Gliadel was approved for use in recurrent brain cancer based on significant overall survival improvement. Any new agent approved for the treatment of GBM would be expected to meet this standard. Three other pharmaceutical companies developing drugs for the treatment of GBM have been given this same advise and are proceeding with clinical trials on this basis.

At the pre-NDA meeting, on June 18, 1998, the final results of four SPRI-sponsored trials were presented: the completed randomized clinical trial in GBM (C94-091) supported by the multicenter open-label GBM trial (I94-122), the multicenter trial in anaplastic astrocytoma (C/I94-123), and the completed randomized clinical trial in advanced

metastatic melanoma (I95-018). Both the GBM and the melanoma multicenter randomized clinical trials had agents with demonstrated activity in the respective diseases as reference agents (procarbazine in C94-091 trial and dacarbazine in I95-018). The efficacy results of these trials were accompanied by extensive safety data in more than 1,000 temozolomide treated patients.

The FDA staff indicated that the Anaplastic Astrocytoma indication was not filable because there is only one Phase II study without a concurrent control. Further, as will be presented in greater detail later in this review, tumor size often can not be adequately assessed because of irregular dimensions, because tumor spread is not always associated with disruption of the blood-brain barrier and because isolated tumor cells may infiltrate for a considerable distance beyond the recognized tumor mass.

After some discussion of the above point, Dr. Temple, who had not participated in the previous FDA staff meeting, indicated that FDA would review the Anaplastic Astrocytoma indication under the accelerated (conditional) approval regulations providing that the sponsor committed to conducting a Phase IV RCT and submitted a satisfactory protocol for such a study.

The NDA's 21-029 (Relapsed Glioblastoma Multiforme) and 21-050 (Relapsed Anaplastic Astrocytoma) were submitted on August 13, 1998.

2.2 FDA Questions to Sponsor and Sponsor's Responses

On September 15 and 16, 1998 the FDA faxed a series of questions regarding data base evaluation to the sponsor. The questions, and the sponsor's replies, received September 18, 1998 are recorded below.

In the RCT in glioblastoma:

a. FDA: What is the difference between "perpendicular volume" in the table named Quantitative Tumor Measurement from Central Reviewer and "Total Volume" in the table named Tumor Volume from Central Reviewer? Which should be used for calculating tumor progression? Tumor response?

   SPRI: The protocol defined criteria (Section 6.2, 6.3, 6.4) for calculating tumor area were used for determining tumor progression or response. Tumor volume measurements were not used because the methodology has not been validated.

b. FDA: If there is a discrepancy between tumor area and tumor volume which is determinative for tumor progression? Tumor response ?

   SPRI: As noted above, tumor area was the only method used to determine tumor progression or tumor response for tumors which were quanmtifiable.

c. FDA: Is tumor volume used for calculating response?

SPRI: No

d.1 FDA: Can there be tumor progression based only on neurological worsening? Only an increase in steroids? Only a clinical worsening?

SPRI: As the protocol states in section 6.0 "a combination of the neurological exam and GD-MRI will be used to define overall response or progression...greater reliance is placed on neuroimaging to defrine respnse and progression". **Therefore, tumor progression can be based upon clinical and neurological worsening alone.**

Tumor progression could not be determined based on steroid use alone. Please see Section 6.0 of the protocol.

d.2 FDA: Can there be tumor response based only on neurological improvement? Only a decrease in steroids? Only a clinical improvement?

SPRI: Improvement can only be based on MRI scan, per protocol (Section 6.3).

SPRI: **In summary, progression can be based upon clinical symptoms, neurologic worsening or by MRI scan. Response is based upon a positive MRI result only.**

e. FDA: If there is more than one lesion, is it correct that a >=25% increase in any single lesion is a tumor progression for that patient?

SPRI: This is correct. See protocol section 6.4.

f. FDA: The NDA indicates that if one of the lesions has "growth in the third dimension", this is tumor progression for the patient. Is "growth in the third dimension" different from tumor volume or perpendicular volume?

SPRI: Yes, they are different. Growth in the third dimension was a qualitative assessment made either by the investigator or the central reviewer and representeed extension of tumor into an adjacent anatomical structure which could be used as a basis for declaring progression.

g. FDA: Did patients have CAT scans or MRI's? The Central Reviewer table indicates CAT scans. The Tumor Measurement from Site Reviewer indicates MRI's.

SPRI: Patients received MRI's. The primary data are correct and the code file for central reviewer is correct. Unfortunately the label file for MRI and CT scan were transposed in the central reviewers table.

SPRI: In reviewing the data base we have discovered that one table was mislabelled. The table called Tumor Location from Site Reviewer should be called Tumor Location from Central Reviewer.

h. FDA: There are large discrepancies in all categorties of progression between the table labelled Final Response Calls SPRI and the table called Reason for Progressive Disease.

SPRI: You are correct in your observation that there are discrepancies between these tables. The table called Final Response Calls SPRI is based on site review of MRI scans while the table called Reason for Progressive Disease is based on central MRI review. The conclusions drawn nfrom these scans are concordant between the sites and the central reviewer, however, individual evaluations may vary. For example, patient no. 280 from C94-091-06 had progressive disease defined by the site as a 25% increase in tumor area, while the central reviewer also called this progressive disease but due to a qualitative evaluation of definitely worse (-2) non-measurable lesion. This is not surprising considering the number of investigational sites reading MRI scans.

i. FDA: In the glioblastoma studies and in the anaplastic astrocytoma studies there are large numbers of patients without any scan assessments of their tumors in some of the tables. For example in the anaplastic astrocytoma study the following tables have different numbers of patients.

Demographics 164
Quant. Tumor Measurement from central reviewer 118
Tumor area from central reviewer 152
Tumor measurement from site reviewer 162

Which of these tables did Schering use for determination of tumor progression and response and if more than one table was used what was the priority? If, for example the Quant. Tumor Measurement from central reviewer table was used, were other tables used for patients with missing data in this table? Also in the Conncomitant Steroid Medications table many dates are missing so that it is sometimes not possible to determine the start or end date for steroids. Please supply the missing dates, if possible. If not, did you deal with this in your analysis?

SPRI: All patients had MRI scans performed. Not all of these scans could be evaluated quantitatively. Those for which a tumor area could not be calculated were evaluated qualitatively as described in Section 6.3 of the protocol. Hence, the numbers of patients in each of these tables would not be expected to be the same.

We used the table called Final Response SPRI Calls for determining tumor progression. This table is based upon the site reviewers tables, Tumor measurement from site reviewer and Response from site reviewer. Tumor

response was based upon Central Reviewer's tables, Tumor area from Central Reviewer, Quantitative tumor measurement from Central Reviewer, and Qualitative tumor measurement from Central Reviewer. If a patient had no data for central review, response was not determined, even if the investigator had designated a response.

There are multiple columns of data describing steroid use, including type of steroid therapy, dose in units, reason for use, starting and stopping dates as well as a column to indicate if steroids were continued between cycles. Most patients were taking steroids prior to randomization and continued on steroids until progression. This data is summarized on a per cycle basis in Appendix 16.2.9.3 Listing of Previous and Concomitant steroids of the clinical study report for C94-091.

The FDA FAXed a second set of queries to SPRI on September 21, 1998.

FDA: The SPRI fax to FDA on 9/18/98 item 2f indicates that growth in the third
SPRI: The investigator validated (SPRI) calls assessments of progressive disease was based upon the evaluation of tumor area, clinical and neurological criteria.

As indicated in 9/18/98 FAX, tumor response and progression was not based on volumetric measurements. Growth in the third dimension, indicating tumor infiltration in an adjacent anatomical structure was expressed not as a quantitative but as a qualitative determination and was one possible criterion qualifying for tumor progression.

The determination of tumor response was based upon tumor area only (section 6.3 of protocol). If an objective response was assigned, the patient could not have had growth in the third dimension.

2. FDA: The SPRI FAX on 9/18/98 states that Site Reviewer measurements are used to determine progression while Central Reviewer measurements are used to determine tumor response. Please explain the reason for this disparity.

SPRI: The answer given in the 9/18/98 fax is correct. The determination of tumor progression was based on the SPRI validated "calls" (investigational site) for tumor progression. Objective tumor response was determined by the Central Reviewer. Determination of progressive disease was based on three criteria; two-dimensional area, clinical and neurological findings as reported by the treating physician (site reviewer) and all contributed to the determination of progressive disease. Tumor response, CR/PR, was based solely on MRI documented tumor shrinkage of at least 50%. This is described in section 6.4 of the protocol. Since progression involved clinical and neurological assessments as well as MRI, the site physician was considered the most appropriate person for this call. The Central Reviewer only confirmed the MRI reading for progression.

3. FDA: In the Table "Response calls from central and site reviewer with SPRI comments many of the field names are ambiguous. For example best overall response, overall response, central reviewer response, best central reviewer response, etc. Please provide definitions so that one field can be distinguished from the others.

   SPRI: Definitions are provided.

4. FDA: Which field in which table represents the official tumor response and the official progression determination?

   SPRI: The official table for tumor response determination is the table called Response calls from central and site reviewer with SPRI comments and is based on the field called "Best central Reviewer response". The official tumor progression determination is in the table called "Final response SPRI calls" in the field called "Event Category" and uses the term Progressive Disease.

2.3 Agency Submission of Progression and Response Analysis to Sponsor for Comments

The FDA's summary of progression dates and objectiveresponses for patients enrolled onto the controlled trial in GBM (C94-091), the open-label GBM trial (I94-122), and the trial in anaplastic astrocytoma (C/I94-123) was sent to the sponsor on October 21,1998 and October 29, 1998 for their comments. A teleconference, with the sponsor, regarding this information was held on October 26, 1998. The sponsor's response was received October 30, 1998. All cases in which FDA and sponsor dates of progression differed were reviewed again and a final date of progression and tumor response status were assigned.

3.0 Manufacturing Controls

3.1 Reference

See CMC review by Dr. Liang

4.0 Pharmacology

4.1 Overview

Temozolomide is a cytotoxic agent of the imidazotetrazine class and is chemically related to the approved chemotherapeutic agent dacarbazine. Temozolomide undergoes spontaneous hydrolysis at physiologic pH to MTIC which then decomposes to a reactive methyl-diazonium ion and to AIC. The cytotoxicity of MTIC is thought to be due to alkylation of the O-6 position of guanine with

additional alkylation at the N-7 position. MTIC is thought to be the active metabolite of dacarbazine, however, unlike temozolomide, dacarbazine must be metabolically converted in the liver to MTIC (Figure 2). The final degradation product of both temozolomide and dacarbazine is AIC, an intermediate in purine and nucleic acid biosynthesis.

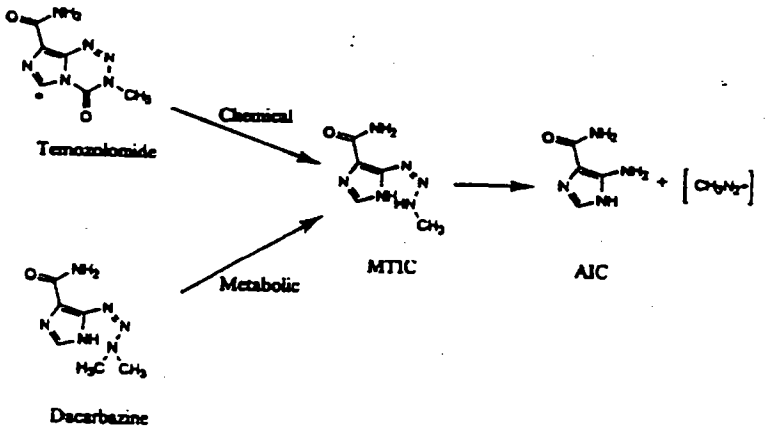

Figure 2 Conversion of Temozolomide (SCH 52365) and Dacarbazine to AIC.

Temozolomide (SCH 52365) has a relatively well-tolerated safety profile in Phase I and II trials in patients with various advanced cancers, including malignant gliomas and malignant melanoma. The antitumor activity of temozolomide is schedule dependent with higher activity demonstrated using a daily schedule for 5 consecutive days and repeated every 28 days. Temozolomide is rapidly and completely absorbed following oral administration and has a well-defined and predictable pharmacokinetic profile.

As indicated by the sponsor, Temozolomide was developed as a potential alternative to dacarbazine in view of its demonstrated antitumor activity and better toxicity profile in preclinical testing. Temozolomide is rapidly and completely absorbed when administered orally at therapeutic doses to humans. Preclinical studies in rats and dogs have demonstrated that temozolomide penetrates well into the central nervous system. The Cmax and AUC increased in a dose-proportional manner, and no accumulation occurs on multiple dosing. The volume of distribution, clearance, and half-life are dose-independent, have very low coefficients of variation, and are predictable and reproducible. The major pathways for elimination of temozolomide from plasma are non-enzymatic hydrolysis to MTIC and renal excretion of parent drug. Temozolomide carboxylic acid (TMA) is the only metabolite of significance and accounts for less than 3% of the SCH 52365 dose excreted in urine.13 Cytochrome P450 (CYP450)-mediated metabolism as assessed by measuring TMA levels does not contribute significantly to the plasma clearance of temozolomide.

The clearance of temozolomide has not been affected by interactions of concurrent medications with specific isozymes of CYP450 and administration of temozolomide does not alter, by competitive inhibition, the metabolism of other drugs. Analysis of data from

Phase II studies confirmed that the clearance of temozolomide was unaffected by commonly administered medications, such as dexamethasone, phenobarbital, phenytoin, carbamazepine, valproic acid, ondansetron, prochlorperazine, and H 2 -receptor antagonists. Patient age, renal function, hepatic function and use of tobacco do not alter the clearance of temozolomide. Administration of temozolomide with food delayed absorption of temozolomide and resulted in a clinically insignificant 9% decrease in exposure.

MTIC degrades to 5-aminoimidazole-4-carboxamide (AIC) at a rate approximately 40 times greater than its rate of formation from temozolomide. Therefore following oral dosing with temozolomide, the plasma t ½ for MTIC is the same as that for temozolomide (1.8 hours). Since the volume of distribution for temozolomide and MTIC are approximately the same, the AUC for MTIC can be predicted. The AUC for MTIC is approximately 2-4% of that of the parent drug.

Phase I and II studies with temozolomide support a starting dose of temozolomide of 1000 mg/m2 for patients who have not received prior chemotherapy and 750 mg/m2 for patients who have received prior chemotherapy. In either case, the total dose is administered in equally divided doses over 5 days. In the absence of CTC Grade 3 or 4 myelosuppression, patients who receive 750 mg/m2 can have the dose increased to 1000 mg/m2 per cycle at subsequent cycles. Subsequent cycles can be administered every 28 days after the first dose of the previous cycle in the absence of dose-limiting toxicity or disease progression. In these studies, myelosuppression was usually predictable, occurring in the first several cycles, with platelet and neutrophil nadir counts late in the cycle (i.e., around Days 21 to 28), with rapid recovery (i.e., usually within 1-2 weeks), and no evidence of cumulative myelosuppression. If CTC Grade 3 or 4 hematologic toxicity did occur at the 1000 mg/m2 dose level, it usually did not recur when the dose was reduced to 750 mg/m2 in subsequent cycles.

4.2 Summary of Pharmacology per Sponsor

Temozolomide was rapidly and completely absorbed when administered orally at therapeutic doses to humans. Cmax and AUC increased in a dose-proportional manner. No accumulation occurred on multiple dosing.

The volume of distribution, clearance, and half-life were dose-independent, had very low coefficient of variation, and were predictable and reproducible.

The major pathways for elimination of temozolomide from plasma were non-enzymatic hydrolysis to MTIC and renal excretion of parent drug. Temozolomide acid (TMA) was the only metabolite of significance and accounted for <3% of the dose excreted in urine.

Cytochrome P450 (CYP450)-mediated metabolism as assessed by measuring TMA levels did not contribute significantly to the plasma clearance of temozolomide. Consequently, clearance of temozolomide should not be affected to a clinically meaningful degree by interaction of concurrent medications with specific isozymes of CYP450 nor would

administration of temozolomide alter by competitive inhibition the metabolism of other drugs.

Analysis of data from Phase II studies confirmed that clearance of temozolomide was unaffected by 7 medications commonly used by this patient population (i.e., phenytoin, phenobarbital, carbamazepine, dexamethasone, H2-receptor antagonists, prochlorperazine, and ondansetron).

Valproic acid was associated with a statistically significant (p=0.019) but clinically insignificant 4.7% decrease in the clearance of temozolomide.

Data from the population pharmacokinetic analyses demonstrated that age, renal function and use of tobacco did not alter clearance of temozolomide.

The half-life of temozolomide did not change with increasing degree of hepatic insufficiency.

Females had a lower clearance of temozolomide than did male patients, however this difference was not considered to be clinically significant.

Administration of temozolomide with food delayed absorption of temozolomide and resulted in a clinically insignificant 9% decrease in exposure.

MTIC degrades to AIC at a much faster rate than its rate of formation from temozolomide. Following oral dosing with temozolomide, the plasma t1/2 for MTIC was the same as that for temozolomide (1.8 hours). Since the volume of distribution for temozolomide and MTIC are approximately the same, the AUC for MTIC could be predicted. The AUC for MTIC was approximately 2-4% of that of temozolomide.

Exposure to MTIC based upon plasma AUC was greater after administration of 200 mg/m2 of temozolomide than after intravenous administration of 250 mg/m2 of DTIC.

CSF temozolomide concentrations measured in one patient are approximately 1/3 of those observed in plasma.

4.3 Toxicology

See pharm/tox review by Dr. Ibrahim.

4.4 Human Pharmacokinetics/Bioavailability

Single- and multiple dose pharmacokinetics of SCH 52365 were evaluated in Study I93-114, an open-label, parallel-group, rising dose Phase I Study in adult patients with advanced cancer.

Fifteen adult patients between the ages of 25 to 71 were enrolled. Cohorts of patients were treated with a 5-day treatment regimen per 28 day at four dose levels. Blood and urine samples were collected at specified times on Days 1 and 5. Plasma and urine SCH 52365 concentrations were determined using validated assays with limits of quantitation (LOQ) of 0.1 µg/mL and 1 µg/mL, respectively.

Mean plasma pharmacokinetic parameters on Days 1 and 5 are summarized in Table 2.

Table 2 Pharmacokinetics

Parameter	Unit	Group 1: 100 mg/m²/day		Group 2: 150 mg/m²/day		Group 3: 200 mg/m²/day		Group 4: 250 mg/m²/day	
		Mean[a]	%CV	Mean[a]	%CV	Mean[b]	%CV	Mean[a]	%CV
Day 1									
Cmax	µg/mL	7.00	21	5.84	56	13.9	46	13.7	17
Tmax	hr	0.50	0	0.94	62	0.94	87	1.00	0
AUC(0-24 hr)	µg·hr/mL	15.5	8	17.0	35	33.2	15	43.0	7
AUC(I)	µg·hr/mL	15.5	8	17.0	35	33.2	15	43.0	7
t1/2	hr	1.72	4	1.75	4	1.79	6	1.91	8
CL/F	mL/min	208	8	310	32	197	22	180	18
CL/F (kg)	mL/min·kg	2.48	10	4.12	45	2.54	17	2.43	5
Vdarea/F	L	31.0	11	47.2	36	30.6	26	30.0	25
Vdarea/F (/kg)	L/kg	0.37	9	0.63	49	0.39	13	0.40	4
Day 5									
Cmax	µg/mL	6.92	30	5.71	27	13.0	39	12.2	15
Tmax	hr	0.39	25	1.17	25	1.25	55	1.33	78
AUC(0-24 hr)	µg·hr/mL	16.7	9	16.8	13	34.5	15	42.6	3
t1/2	hr	1.81	4	1.72	15	1.79	9	1.85	5
CL/F	mL/min	207	9	293	10	189	20	181	14
CL/F (kg)	mL/min·kg	2.48	13	3.84	23	2.45	18	2.45	9
Vdarea/F	L	32.6	13	43.2	5	29.6	27	29.0	17
Vdarea/F (/kg)	L/kg	0.39	15	0.56	20	0.38	16	0.39	9
R	–	1.00	4	1.04	22	1.04	8	0.99	4

a: n=3
b: n=6

4.5 Pharmacokinetic/Bioavailability Studies Summary

SCH 52365 was absorbed rapidly following oral administration. Maximum plasma concentrations were achieved within 0.33 to 2.5 hours post-dose.
SCH 52365 was eliminated rapidly with mean t1/2 values ranging from 1.7 to 1.9 hours.

Overall, the pharmacokinetic parameters were similar on Days 1 and 5. The minimum observed plasma concentrations were zero on Days 2 through 6 indicating that SCH 52365 did not accumulate in plasma following multiple-dose administration.

There were dose-related increases in Cmax and AUC. In general, the inter-patient variability was small.

Total body clearance (CL/F) and volume of distribution (Vdarea/F) were similar on Days 1 and 5 and were independent of dose. The mean Vdarea/F values ranged from 0.37 to 0.63 L/kg, approximating the volume of total body water.

Urinary recovery of SCH 52365 ranged from 4.8 to 9.6% of the dose over the 24-hours collection interval. The amount (mg) of SCH 52365 excreted in the urine was dose-related, with the largest portion excreted within 0-4 hours. The CLr values ranged from 0.12 to 0.26 mL/min kg. In general, CLr was similar on Days 1 and 5 and was independent of dose. Since SCH 52365 undergoes rapid and extensive chemical degradation in the body at physiological pH, the CLr was small compared to total body clearance.

5.0 Clinical Studies

5.1 Overview

Gliomas, which account for 60% of primary brain tumors in adults, are among the most serious and devastating of malignant diseases, being associated with significant morbidity and mortality despite aggressive treatment. The majority of patients have suboptimal response to any treatment, including surgery, radiotherapy, and often, chemotherapy, such that survival of these patients has not changed significantly over the past 20 years. Gliomas are rapidly growing tumors associated with a high rate of recurrence following primary therapy. Median survival is only 1-2 years from initial diagnosis. Gliomas are also associated with significant morbidity, including severe disabilities such as motor dysfunction, seizures, vision abnormalities, and communication deficits. Although, historically, malignant high-grade gliomas have been separated into two grades (anaplastic astrocytoma, AA and glioblastoma multiforme, GBM) based on histologic criteria, the neuro-oncology community generally does not always separate these histologies when reporting treatment results in recurrent disease studies.

The standard of care for primary disease has been surgery and radiation therapy; the use of adjuvant chemotherapy is still controversial. The most commonly used chemotherapeutic agents for newly diagnosed gliomas are the nitrosoureas, BCNU (carmustine) and CCNU (lomustine), although AA patients are more likely to receive the nitrosourea-based combination of PVC (procarbazine, vincristine, CCNU). Nitrosourea therapy, at the time of recurrence, is limited because of expected tumor cell resistance to these agents as well as by chronic toxicities such as delayed and cumulative myelosuppression and by pulmonary toxicity.

In recurrent disease, no standard of care for either relapsed or AA histology exists. Review of the literature, including a recent meta-analysis of treatment of recurrent high-grade glioma failed to identify a consensus on an appropriate standard of care in recurrent AA. The meta-analysis reported by Huncharek et al identified the nitrosoureas as the only agents with any efficacy in recurrent high-grade gliomas AA). However, as detailed in the clinical report of C/I94-123 and discussed in this and other sections, the majority of AA patients will have received adjuvant chemotherapy with the combination

regimen PCV for initial disease. At the time of recurrence there are no standard therapeutic options The sponsor states that C/I94-123 was designed as a single-arm trial because of the lack of therapeutic options for recurrent AA patients. While this may or may not be true it is evident that there is an urgent need for new and effective therapies in recurrent glioma.

The search for effective chemotherapy for individuals with recurrent high-grade malignant glioma is one of the priorities in oncology. It is important to find an agent that is not only effective, but has an acceptable safety profile, does not adversely impact patients' quality of life, and is easy to administer.

As indicated by the sponsor, Temozolomide is an alkylating agent that has demonstrated antitumor activity and a well-tolerated safety profile in Phase I and II trials in adult and pediatric patients with various advanced cancers, including recurrent malignant glioma. It is rapidly and completely absorbed following oral administration and undergoes spontaneous hydrolysis at physiologic pH to an active metabolite, MTIC. The cytotoxicity of MTIC is thought to be due to alkylation at the O-6 position of guanine with additional alkylation at the N-7 position. The final degradation product, AIC, is an intermediate in the biosynthetic pathway to purines and, ultimately, to nucleic acids.

Temozolomide has an uncomplicated and well-defined pharmacokinetic profile. Plasma concentrations increase in direct proportion to dose in a predictable and clearance are independent of dose and are predictable and reproducible in clinical use. reproducible manner in adults. Compared to adults, children had higher plasma temozolomide concentrations, probably due to their higher body surface area to weight ratio. Children (age 3-17 years) showed the same predictable pharmacokinetic profile as adults. Temozolomide does not accumulate in plasma after multiple (5-day) daily doses. Preliminary data from patients confirmed animal findings that temozolomide readily crosses the blood-brain barrier; its concentration in the cerebral spinal fluid is approximately 30% of that in plasma. In adult patients, clearance is not affected by factors such as age, hepatic or renal function, or by commonly used medications such as steroids, anticonvulsants, antiemetics, and H 2 -receptor antagonists. In addition, administration of temozolomide does not interfere with metabolism of other drugs.

Promising preliminary clinical results with temozolomide were demonstrated in studies conducted by the Cancer Research Campaign (CRC) group which initially studied temozolomide in the UK. Results reported in published CRC Phase I and II studies demonstrated clinical activity in glioma with an acceptable toxicity profile. Based on these encouraging preliminary results, Schering-Plough pursued development of temozolomide.

In 1993, a clinical registration program was initiated by SPRI to establish the safety and efficacy of temozolomide in the treatment of adult patients with recurrent high-grade gliomas The program included 412 temozolomide treated relapsed high grade glioma patients (the intent to treat populations [ITT]) registered in three multicenter trials (Table 3). These trials included the pivotal randomized controlled trial in GBM (C94-091/I96-

058), a large, supportive uncontrolled trial in GBM (I94-122) and a large, pivotal trial in AA (C/I94-123). One hundred thirteen were registered to receive the control drug; procarbazine in C94-091. These three multicenter studies, combined, represent the largest clinical trial database ever reported for a single agent in the treatment of recurrent malignant gliomas. The three adult trials all had similar designs and similar patient eligibility criteria. The primary objective of these studies, as stated by SPRI, was to show that the lower boundary of the 95% Confidence Interval (CI) of progression-free survival at 6 months was higher than 10%. The primary efficacy endpoint was assessed in all patients by imaging with gadolinium-enhanced-MRI, using strict radiologic scanning technique criteria and a central independent review of all scans. Assessment of disease progression was based both on measurable tumor changes identified on radiologic scan and on clinical neurologic examination. Overall survival and health-related quality of life (HQL), using the standard EORTC QLQC-30+3 core cancer module and a validated Brain Cancer Module (BCM 20), were defined as secondary endpoints. The three trials, enrolling a total of 525 patients, are summarized in table 3 Efficacy Studies of Temozolomide for the Treatment of Glioma.

Table 3 Efficacy Studies of Temozolomide for the Treatment of Glioma

Study No./ No. of Sites	Indication	Treatment	ITT Population	Dose	Treatment a Cycle Length
19 US sites 2 non-US sites	Glioma in Adults	TMZ PCB	112 113	200 mg/m 2 /day or 150 mg/m 2 /day (PO) 150 mg/m 2 /day or 125 mg/m 2 /day (PO)	5 days every 28 days 28 days every 56 days
26 Non-US sites	Glioma in Adults	TMZ	138	200 mg/m 2 /day or 150 mg/m 2 /day (PO)	5 days every 28 days
C/I94-123 15 US sites 17 non-US sites	Glioma in Adults	TMZ	162	200 mg/m 2 /day or 150 mg/m 2 /day (PO)	5 days every 28 days

ITT=intent to treat; TMZ=temozolomide; PCB=procarbazine.
Treatment continued until unacceptable toxicity, evidence of disease progression or a maximum of 2 years.

Doses selected for use in these studies were based on the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) determined in Phase I studies. The recommended starting dose of temozolomide for adults is 200 mg/m2/day (1000 mg/m2 total) for patients who have not received prior chemotherapy and 150 mg/m2/day (750 mg/m2 total) for patients who have received prior chemotherapy, Treatment was administered in equally divided doses over 5 days, repeated every 28 days. Procarbazine was administered orally, daily for 28 consecutive days (Days 1-28) at a starting dose of 150 mg/m2/day for patients who had not previously received chemotherapy or 125 mg/m2/day for patients who had received any previous chemotherapy. Treatment cycles could be repeated every 56 days following the first daily dose of PCB. Study drug (TMZ or PCB) could be administered for a maximum of 2 years from initial treatment until the occurrence of either unacceptable toxicity or evidence of disease progression.