CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-277

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-277**
SERIAL NUMBER:	**000 AZ**
DATE RECEIVED BY CENTER:	**12/23/08**
PRODUCT:	**Temodar®**
INTENDED CLINICAL POPULATION:	**Patients with glioblastoma multiforme or refractory anaplastic astrocytoma who are unable to tolerate oral Temodar®**
SPONSOR:	**Schering-Plough**
DOCUMENTS REVIEWED:	**Electronic submission**
REVIEW DIVISION:	**Division of Drug Oncology Products (HFD-150)**
PHARM/TOX REVIEWER:	**Hans Rosenfeldt, Ph.D.**
PHARM/TOX SUPERVISOR:	**Leigh Verbois, Ph.D.**
DIVISION DIRECTOR:	**Robert Justice, M.D.**
PROJECT MANAGER:	**Paul Zimmerman. R. Ph**

Date of review submission to Division File System (DFS): 2/23/09

I. Recommendations

A. Recommendation on approvability

The submitted nonclinical studies evaluated in the Pharmacology/Toxicology review of the original NDA submission adequately support the use of temozolomide (Temodar™) for the treatment of newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and as maintenance therapy and in the treatment of refractory anaplastic astrocytoma.

B. Recommendation for nonclinical studies

The Pharmacology/Toxicology review of the original NDA submission identified additional nonclinical information necessary to qualify the levels of (b) (4) impurities present in the proposed commercial temozolomide formulation, (b) (4)

The Complete Response Letter sent on 11-24-2008 to the sponsor regarding the original submission of this NDA communicated this finding. Specifically, the Complete Response Letter listed the need for the following:

> Perform a rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4) The study should mimic a single cycle of the approved clinical schedule (intravenously daily x 5 every 28 days) and utilize concentrations of (b) (4) which exceed (b) (4) respectively, to adequately qualify these impurities at levels proposed in the current specifications for drug substance and drug product.

In the Cover Letter for the current submission, the sponsor states that technical issues prevent the sponsor from producing a batch of temozolomide that contains a concentration of (b) (4) greater than (b) (4). The sponsor states that the fact that (b) (4) is explosive and the fact that (b) (4) degrades to (b) (4) limits the maximum concentration of (b) (4) possible in a temozolomide batch to "approximately (b) (4)." The review team acknowledged that the tendency of (b) (4) to degrade limits the concentration of (b) (4) achievable in a spiked formulation of temozolomide. Therefore, the following was listed as a postmarketing requirement in the Draft NDA Approval Letter for this NDA during an internal meeting that took place on 2-19-2008:

> Perform a rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4) The study should mimic a single cycle of the approved clinical schedule (intravenously daily x 5 every 28 days) and utilize

concentrations of (b) (4) that are ≥ (b) (4) to adequately qualify these impurities at levels proposed in the current specifications for drug substance and drug product.

The current submission includes a draft protocol for a bridging study of temozolomide spiked with (b) (4) administered intravenously to rats. This protocol is reviewed herein and has been deemed acceptable.

C. Recommendations on labeling

Please refer to the Pharmacology/Toxicology review for the original submission of this NDA. Any changes to the label resulting from the proposed nonclinical study included in the current submission will be described in a subsequent review once the final study report is submitted to the NDA.

Nonclinical Protocol Review

NDA number:	22-277
Review number:	2
Sequence number/date/type of submission:	000 AZ /Dec. 23, 2008/Commercial
Information to sponsor:	Yes
Sponsor and/or agent:	Schering Corp., Kenilworth NJ
Manufacturer for drug substance:	(b) (4)
Reviewer name:	Hans Rosenfeldt, Ph.D.
Division name:	Division of Drug Oncology Products
HFD #:	150
Review completion date:	11/06/2008
Drug:	
Trade name:	Temodar®, Temodal®
Generic name:	temozolomide, methazolastone
Code name:	SCH 52365
Chemical name:	3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide
CAS registry number:	85622-93-1
Molecular formula/molecular weight:	$C_6H_6N_6O_2$/194.15 g/mol
Structure:	

Relevant INDs/NDAs/DMFs: IND (b) (4) IND 44162, IND 68395, NDA 21-029

Drug class: Alkylating drug

Intended clinical population:
Patients with glioma multiforme; patients with anaplastic astrocytoma.

Clinical formulation:

Component	Amt per Vial
Temozolomide	100.0 mg
Mannitol USP	600.0 mg
L-threonine USP	160.0 mg
Polysorbate 80 NF	120.0 mg
Sodium Citrate Dihydrate USP	235 (b) mg
Hydrochloric Acid NF	160.0 mg
Water for Injection USP, q.s.	(b) (4) mL

Route of administration: Intravenous injection over 90 minutes

Proposed Study title: A Single-Cycle (5-Day Dosing) IV Toxicity and Toxicokinetic Study of SCH 52365 (Temozolomide) with Impurities in Rats

Study no.: 08429
Volume #, and page #: M4-2-3-7-6-impurities
Conducting laboratory and location: Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation: March 9, 2009
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: To be determined; projected (b) (4) concentrations in spiked formulation projected to be (b) (4) respectively.

Methods

Doses:

Doses						Number of rats			
			(b) (4)	(b) (4)		Main groups‡		TK groups	
Dose Group	Dose mg/kg	Dose mg/m^2			Vol ml/kg	♂	♀	♂	♀
Control	0	0	(b) (4)		13.6	20	20	9	9
LD	17	102			13.6	20	20	18	18
LD-impurities	17	102			13.6	20	20	18	18
HD	34	204			13.6	20	20	18	18
HD-impurities	34	204			13.6	20	20	18	18

§Approximate value

‡For main groups 10/group necropsied Day 6; 10/group necropsied Day 29 (recovery)

Schedule:	Daily x5, 28-day cycle
Species/strain:	SD Rat
Route and infusion rate:	Intravenous injection
Vehicle:	SCH 52365 Placebo Solution
Age:	Approximately 8 weeks
Weight:	♂: 210-325 g; ♀: 150-225 g
TK Sampling times:	Days 1 and 5; 5, 30 min, 1, 2, 4, 8, 24 h post-dose Placebo: Days 1 and 5; 5 min, 1, 4 h post-dose

Observations and times:

Mortality:	Daily
Clinical signs:	Daily
Body weights:	Weekly
Food consumption:	Weekly
Ophthalmoscopy:	Week -1 and Week 4
EKG:	Not done
Hematology:	Days 4, 28
Clinical chemistry:	Days 4, 28
Urinalysis:	Necropsy (Days 5, 29)
Gross pathology:	Necropsy (Days 5, 29)
Organ weights:	Necropsy (Days 5, 29)
Histopathology:	Necropsy (Days 5, 29)

Important Study Features

- Unscheduled mortalities in Main Study will undergo necropsy
- Unscheduled mortalities in TK groups will receive abbreviated necropsy to determine if death is due to physical trauma or dosing error
- If possible, blood samples will be obtained from unscheduled mortalities in Main Study and animals in TK groups
- Standard hematology paramters will be examined, including erythrocytes, hemoglobin, hematocrit, reticulocytes, platelets, differential leukocyte count, and blood smear morphology
- Standard clinical chemistry parameters will be examined, including liver enzymes, total bilirubin, albumin, globulin, cholesterol, triglycerides, and electrolytes
- Standard urinalysis parameters will be examined, including color, clarity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, osmolality, and volume
- Standard coagulation parameters will be examined, including prothrombin time, activated partial thromboplastin time, and fibrinogen
- Microscopic examination will be performed from all organs/tissues in control and high-dose groups, and in all animals dying preterminally

- Potential target organs identified by the pathologist will be examined microscopically in animals belonging to dose groups other than control or high dose groups.
- Peer review of microscopic findings will be conducted

Histopathology inventory

Study	08429
Species	Rat
Adrenals	X
Aorta	X
Bone with Marrow (Femur)	X
Bone with Marrow (Sternum)	X
Brain	X
Cecum	X
Cervix	
Colon	X
Duodenum	X
Epididymis	X
Esophagus	X
Eye	X
Fallopian tube	
Gall bladder	
Gross lesions	X
Harderian gland	X
Heart	X
Ileum	X
Injection site	X
Jejunum	X
Kidneys	X
Lachrymal gland	
Larynx	X
Liver	X
Lungs	X
Lymph nodes, cervical	
Lymph nodes mandibular	X
Lymph nodes, mesenteric	X
Mammary Gland	X
Nasal cavity	
Optic nerves	
Ovaries	X
Pancreas	X
Parathyroid	X
Peripheral nerve	X
Pituitary	X
Prostate	X

Study	08429
Species	Rat
Rectum	X
Salivary gland	X
Sciatic nerve	X
Seminal vesicles	X
Skeletal muscle	X
Skin	X
Spinal cord	X
Spleen	X
Sternum	X
Stomach	X
Testes	X
Thymus	X
Thyroid	X
Tongue	X
Trachea	X
Urinary bladder	X
Uterus	X
Vagina	X

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The proposed study protocol appears adequate to fulfill the post-marketing requirement described in the Complete Response Letter sent on 11-24-2008 to the sponsor regarding the original submission of this NDA.

Recommendations:

The proposed study should proceed as described in the protocol reviewed herein.

Suggested labeling:

Any changes to the label resulting from the proposed nonclinical study included in the current submission will be described in a subsequent review once the final study report is submitted to the NDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hans Rosenfeldt
2/23/2009 01:46:28 PM
PHARMACOLOGIST

Leigh Verbois
2/23/2009 04:07:09 PM
PHARMACOLOGIST

MEMORANDUM

Date: November 13th, 2008
From: S. Leigh Verbois, Ph.D.
Supervisory Pharmacologist
Division of Drug Oncology Products
To: File for NDA #22-277
TEMODAR for injection (temozolomide)
Re: Approvability of Pharmacology and Toxicology

Non-clinical studies that investigated the pharmacology and toxicology of temozolomide were provided to support NDA 22277 [TEMODAR® for injection for the treatment of newly diagnosed glioblastoma multiforme (GBM) administered concomitantly with radiotherapy and as maintenance therapy and in the treatment of refractory anaplastic astrocytoma] and were reviewed in detail by Hans Rosenfeldt, PhD. The supporting information included studies of IV and/or oral temozolomide that investigated the drug's pharmacology, pharmacokinetic and ADME, safety pharmacology, general toxicology (rat and dog), genetic toxicity (*in vivo* and *in vitro*), and reproductive toxicity in both rats and rabbits. Oral temozolomide is highly bioavailable (~100%), therefore results from studies submitted to support marketing approval for oral temozolomide were relied upon to support approval of the intravenous formulation. The studies cited in the review by Dr. Rosenfeldt consist primarily of original research conducted by the applicant.

The general toxicology studies submitted to the NDA demonstrate that temozolomide is an alkylating drug which causes well defined toxicities in rapidly dividing cells (hematologic and gastrointestinal) in all species independent of route of administration. The current submission included a study which assessed the toxicity associated with (b) (4) impurities (b) (4) The specifications for these impurities are set higher than qualification thresholds set forth by ICH. Although the bioavailability of these impurities is unknown, the study was conducted using oral administration. Since these specifications exceed the qualification of these impurities, and may be associated with clinically significant toxicities when administered IV, a postmarketing study is required. The sponsor should perform a rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4) . This study should mimic a single cycle of the approved clinical schedule (daily x 5 every 28 days) and utilize concentrations of (b) (4) which exceed (b) (4) respectively, to adequately qualify these impurities at levels proposed in the current specifications for drug substance and drug product. The sponsor has provided acceptable timelines for the submission, initiation and completion of a protocol to address this concern.

Temozolomide is a teratogen and a fetotoxin at doses equal to or less than the proposed clinical dose in rats and rabbits. Temozolomide causes resorptions and numerous malformations of the external and internal soft tissue and skeleton in both species and dosing with temozolomide appears to damage the testes in rats and dogs. Temozolomide

is a mutagen and clastogen. Additionally, temozolomide is carcinogenic in rats at doses less than the maximum recommended human dose on a mg/m^2 basis.

Recommendations: I concur with Dr. Rosenfeldt's conclusion that the pharmacology and toxicology data support the approval of NDA 22-277, TEMODAR.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Leigh Verbois
11/13/2008 11:06:10 AM
PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-277**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**1/23/08**
PRODUCT:	**Temodar®**
INTENDED CLINICAL POPULATION:	**Patients with glioblastoma multiforme or refractory anaplastic astrocytoma who are unable to tolerate oral Temodar®**
SPONSOR:	**Schering-Plough**
DOCUMENTS REVIEWED:	**Electronic submission**
REVIEW DIVISION:	**Division of Drug Oncology Products (HFD-150)**
PHARM/TOX REVIEWER:	**Hans Rosenfeldt, Ph.D.**
PHARM/TOX SUPERVISOR:	**Leigh Verbois, Ph.D.**
DIVISION DIRECTOR:	**Robert Justice, M.D.**
PROJECT MANAGER:	**Paul Zimmerman. R. Ph**

Date of review submission to Division File System (DFS): 11/12/2008

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The submitted nonclinical studies adequately support the use of temozolomide (Temodar™) for the treatment of newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and as maintenance therapy and in the treatment of refractory anaplastic astrocytoma.

B. Recommendation for nonclinical studies

Additional nonclinical studies are necessary given that clinical and nonclinical studies submitted with this NDA do not directly test intravenous exposures of impurities, (b) (4) at levels that are comparable to the proposed clinical formulation. The sponsor has submitted one oral toxicity study in rats of temozolomide spiked with enhanced levels of (b) (4) but this study relies on the unknown bioavailability of (b) (4) administered by this route.

The sponsor should directly test the toxicity profile of intravenous temozolomide spiked with (b) (4) The sponsor should conduct a rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4). This study should mimic a single cycle of the approved clinical schedule (daily x5 every 28 days) and utilize concentrations of (b) (4) which exceed (b) (4) respectively, to adequately qualify these impurities at levels proposed in the current specifications for drug substance and drug product, respectively.

C. Recommendations on labeling

Highlights section of the label
The sponsor proposed:
INDICATIONS AND USAGE
TEMODAR is an alkylating (b) (4) indicated for the treatment of adult patients with:

FDA Recommends: TEMODAR is an alkylating drug indicated for the treatment of adult patients with:

Rationale:
Per CFR, this statement should include the pharmacologic classification, which is "alkylating drug", not "alkylating (b) (4) "

Highlights section of the label
The sponsor proposed:
WARNINGS AND PRECAUTIONS
(b) (4)

FDA Recommends:
Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving TEMODAR. (5.5, 8.1)

Rationale: The Office of New Drugs (OND) Pregnancy Labeling Outline recommends this language in the warnings and precautions part of the Highlights section of the label for Pregnancy Category D drugs.

The sponsor proposed:
5 WARNINGS AND PRECAUTIONS
(b) (4)

FDA Recommends:
5 WARNINGS AND PRECAUTIONS

Use in Pregnancy
Temodar can cause fetal harm when administered to a pregnant woman. Administration of TEMODAR to rats and rabbits during organogenesis at 0.38 and 0.75 times the maximum recommended human dose (75 and 150 mg/m^2), respectively, caused numerous fetal malformations of the external organs, soft tissues, and skeleton in both species [See Use in Specific Populations (8.1)].

Rationale: The OND Pregnancy Labeling Outline recommends this language in the warnings and precautions section of the label for Pregnancy Category D drugs.

The sponsor proposed:
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category D

(b) (4)

Temozolomide may cause fetal harm when administered to a pregnant woman. Five consecutive days of oral administration of (b) (4) in rabbits during the period of organogenesis (b) (4)

(b) (4) caused numerous malformations of the external organs, soft tissues, and skeleton in both species. Doses of (b) (4) in rats and rabbits also caused embryolethality as indicated by increased resorptions. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TEMODAR®.

FDA recommends:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. [See Warnings and Precautions (5.5)]

TEMODAR® can cause fetal harm when administered to a pregnant woman. Five consecutive days of oral temozolomide administration of 0.38 and 0.75 times the highest recommended human dose (75 and 150 mg/m^2) in rats and rabbits, respectively during the period of organogenesis caused numerous malformations of the external and internal soft tissues and skeleton in both species. Doses equivalent to 0.75 times the highest recommended human dose (150 mg/m^2) caused embryolethality in rats and rabbits as indicated by increased resorptions. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TEMODAR.

Rationale:

(b) (4)

This section was brought into compliance with CFR language.

The sponsor proposed:

8 USE IN SPECIFIC POPULATIONS

8.3 Nursing Mothers

(b) (4)

FDA Recommends:

8 USE IN SPECIFIC POPULATIONS

8.3 Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for temozolomide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Rationale: This section was brought into compliance with CFR language.

The sponsor proposed:
12 CLINICAL PHARMACOLOGY

12 Mechanism of Action
(b) (4)

FDA recommends:
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.

Rationale (b) (4)

The sponsor proposed:
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
(b) (4)

(b) (4)

(b) (4)

FDA recommends:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Temozolomide is carcinogenic in rats at doses less than the maximum recommended human dose. Temozolomide induced mammary carcinomas in both males and females at doses 0.13 to 0.63 times the maximum human dose (25 to 125 mg/m^2) when administered orally on 5 consecutive days every 28 days for 6 cycles. Temozolomide also induced fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate, carcinomas of the seminal vesicles, schwannomas of the heart, optic nerve, and harderian gland, and adenomas of the skin, lung, pituitary, and thyroid at doses 0.5 times the maximum daily dose. Mammary tumors were also induced following 3 cycles of temozolomide at the maximum recommended daily dose.

Temozolimide is a mutagen and a clastogen. In a reverse bacterial mutagenesis assay (Ames assay), temozolomide increased revertant frequency in the absence and presence of metabolic activation. Temozolimide was clastogenic in human lymphocytes in the presence and absence of metabolic activation.

Temozolomide impairs male fertility. Temozolomide caused syncytial cells/immature sperm formation at 0.25 and 0.63 times of the maximum recommended human dose (50 and 125 mg/m^2) in rats and dogs, respectively and testicular atrophy in dogs at 0.63 times the maximum recommended human dose (125 mg/m^2).

Rationale: (b) (4)

The language in this section was clarified.

The sponsor proposed:

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

(b) (4)

FDA recommends:

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

Toxicology studies in rats and dogs identified a low incidence of hemorrhage, degeneration and necrosis of the retina at temozolomide doses equal to or greater than 0.63 times the maximum recommended human dose (125 mg/m^2).

Rationale: (b) (4)

The purpose of this section is to provide toxicological data that provides important information to the prescriber. (b) (4)

(b) (4)

The sponsor proposed:

15 REFERENCES

(b) (4)

(b) (4)

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4) **TEMODAR Capsules**

TEMODAR® (temozolomide) Capsules are supplied in amber glass bottles with child-resistant polypropylene caps containing the following capsule strengths:

TEMODAR Capsules 5 mg:
5-count - NDC 0085-3004-02
14-count - NDC 0085-3004-01
TEMODAR Capsules 20 mg:
5-count - NDC 0085-1519-02
14-count - NDC 0085-1519-01
TEMODAR Capsules 100 mg:
5-count - NDC 0085-1366-02
14-count - NDC 0085-1366-01
TEMODAR Capsules 140 mg:
5-count - NDC 0085-1425-01
14-count - NDC 0085-1425-02
TEMODAR Capsules 180 mg:
5-count - NDC 0085-1430-01
14-count - NDC 0085-1430-02
TEMODAR Capsules 250 mg:
5-count - NDC 0085-1417-01

Store TEMODAR capsules at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)
[see USP Controlled Room Temperature].

(b) (4)

16.2 TEMODAR (b) (4) for Injection

TEMODAR (temozolomide) (b) (4) for Injection is supplied in single-use glass vials containing 100 mg temozolomide.

TEMODAR (b) (4) for Injection 100 mg
NDC XXXX-XXXX-XX

Store TEMODAR (b) (4) for Injection refrigerated at 2°C-8°C (36°F-46°F).9,10

(b) (4)

FDA Recommends:

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

Care should be exercised in the handling and preparation of TEMODAR. Vials and capsules should not be opened. If vials or capsules are accidentally opened or damaged, rigorous precautions should be taken with the contents to avoid inhalation or contact with the skin or mucous membranes. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or capsules. Procedures for proper handling and disposal of anticancer drugs should be considered[1-4]. Several guidelines on this subject have been published.

(b) (4)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The sponsor holds NDA 21-029 for the tablet formulation of temozolomide. Toxicology studies submitted with NDA 21-029 include repeat-dose studies performed in dogs and rats. Although the submitted toxicology studies were done via the oral route, temozolomide is nearly 100% bioavailable in both dogs and rats therefore allowing these toxicology studies to support an application for temozolomide dosing via the intravenous route.

Temozolomide end-organ toxicity occurred mainly in the hematopoietic and male reproductive organs, although the gastrointestinal tract, liver, kidney, retina, brain and lung were also affected at a lesser frequency.

Non-clinical studies indicate that temozolomide is teratogenic, embryotoxic, mutagenic, clastogenic, and carcinogenic.

B. Pharmacologic activity

Temozolomide undergoes a non-enzymatic conversion to 5-(3-methyl-1-triazen) imidazole-4-carboxamide (MTIC) at physiological pH. MTIC alkylates DNA at the O^6 and N^7 positions of guanine.

C. Nonclinical safety issues relevant to clinical use

Temozolomide toxicity in mice, rats, and dogs occurred in hematopoietic organs, male reproductive organs, and the retina at doses less than or equal to 125 mg/m^2, 0.63 times the maximum recommended clinical dose.. Temozolomide hematopoietic toxicity was manifested as white and red blood cell decreases in both rats and dogs, although this toxicity improved after the first cycle of treatment. At doses greater than 125 mg/m^2 temozolomide toxicity also occurred in the gastrointestinal tract, liver, kidney, brain and lung.

Primary clinical signs in rats and dogs were similar and indicated gastrointestinal toxicity and carcinogenesis. Primary clinical signs in rats also indicated neurological, kidney, and eye toxicities. These clinical signs included cold to touch, hunched posture, limited use of swollen limbs, swollen thoracic/cervical/abdominal/inguinal regions, thin appearance, convulsion, red urine, mucoid feces, corneal abrasions, exopthalmus, eye ulceration and hair loss. Tissue masses in cervical and abdominal regions were observed at doses $\geq$ 50 mg/m^2. Primary clinical signs in dogs indicated anemia in addition to gastrointestinal toxicity and carcinogenesis. These clinical signs included vomiting, fecal changes, pale gums, diminished appetite, and hypoactivity. Higher doses of temozolomide caused dehydration, anorexia, and prostration. One male dosed with 125 mg/m^2 temozolomide had a tissue mass in the scrotum.

Histopathological changes in rats and dogs treated with temozolomide included signs of necrosis, hemorrhage and atrophy in the gastrointestinal tract, liver and kidney necrosis, and bone marrow depletion. Pathology studies in rats and dogs

also noted a low incidence of hemorrhage and degeneration of the retina at doses of 125 mg/m^2 or greater when administered on a daily x5 every 28-days schedule.

Intravenous administration of temozolomide does not significantly change the range of end-organ temozolomide toxicities when compared to oral administration. However, the intravenous formulation of temozolomide did produce mild to moderate venous irritation in rats and rabbits. Much of this local irritation correlated with the intravenous formulation as opposed to temozolomide itself when compared to saline control.

Temozolimide is a mutagen and a clastogen. Temozolomide mutagenicity was demonstrated with *in vitro* reverse mutation (Ames) assays in bacteria and temozolomide clastogenicity in mammalian cells was demonstrated with assays using human peripheral blood lymphocytes.

Temozolomide is carcinogenic in rats at doses greater than 25 mg/m^2. Tumor masses developed in rats treated with greater than 50 mg/m^2 temozolomide after three months of treatment. Tumor masses developed in rats treated with greater than 25 mg/m^2 temozolomide after six months of treatment. At 25 – 50 mg/m^2 rats developed mammary carcinomas in both sexes, while rats treated with temozolomide doses equal to or greater than 125 mg/m^2 developed a wide spectrum of neoplasms, including mammary carcinomas, fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate, carcinomas of the seminal vesicles, schwannomas of the heart, optic nerve, and harderian gland, and adenomas of the skin, lung, pituitary, and thyroid gland.

Temozolomide impairs male fertility in rats and dogs via increases in syncytial cells/immature sperm, and testicular atrophy. Testicular atrophy occurred at doses equal to or greater than 50 mg/m^2 in rats and 125 mg/m^2 in dogs.

Temozolomide is teratogenic and embryotoxic. Five consecutive days of oral temozolomide administration of 75 and 150 mg/m^2 (0.38 and 0.75 times the highest recommended human dose) in rats and rabbits, respectively during the period of organogenesis caused numerous malformations of the external and internal soft tissues and skeleton in both species. A dose of 150 mg/m^2 caused embryolethality in rats and rabbits as indicated by increased resorptions.

Specifications for an impurity,(b) (4) and a degradant,(b) (4) have been set outside the threshold for qualification. The drug substance specification for(b) (4) has been set at(b) (4) However, this process impurity has only been qualified to(b) (4) (Batch #7812-090) for intravenous administration. The drug product specification for(b) (4) has been set at(b) (4) with additional degradant increases of up to(b) (4) following reconstitution; this degradant has only been qualified to(b) (4) when administered intravenously.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-277
Review number: 1
Sequence number/date/type of submission: 000/January 23, 2008/Commercial
Information to sponsor: Yes
Sponsor and/or agent: Schering Corp., Kenilworth NJ
Manufacturer for drug substance: (b) (4)

Reviewer name: Hans Rosenfeldt, Ph.D.
Division name: Division of Drug Oncology Products
HFD #: 150
Review completion date: 11/06/2008
Drug:

- Trade name: Temodar®, Temodal®
- Generic name: temozolomide, methazolastone
- Code name: SCH 52365
- Chemical name: 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide
- CAS registry number: 85622-93-1
- Molecular formula/molecular weight: $C_6H_6N_6O_2$/194.15 g/mol
- Structure:

Relevant INDs/NDAs/DMFs: IND (b) (4), IND 44162, IND 68395, NDA 21-029

Drug class: Alkylating drug

Intended clinical population:
Patients with glioma multiforme; patients with anaplastic astrocytoma.

Clinical formulation:

Component	Amt per Vial
Temozolomide	100.0 mg
Mannitol USP	600.0 mg
L-threonine USP	160.0 mg
Polysorbate 80 NF	120.0 mg
Sodium Citrate Dihydrate USP	235 (b) mg
Hydrochloric Acid NF	160.0 mg
Water for Injection USP, q.s.	(b) (4) mL

Route of administration: Intravenous injection over 90 minutes

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:
Repeat-Dose Toxicity

Study #	Title
01350	Single-Cycle (Five Day Dosing) IV Toxicity and Toxicokinetic Study of SCH 52365 (Temozolomide) in Rats
03451	A Single-Cycle (5-Day Dosing) Oral Gavage Toxicity Study of SCH 52365 with Impurities in Rats

Reproductive Toxicology

Study #	Title
03450	Embryo-Fetal Developmental Toxicity and Toxicokinetic Study of SCH 52365 Administered Orally by Gavage In Rabbits
03471	Fertility and Early Embryonic Developmental Toxicity Study of SCH 52365 Administered Orally by Gavage in Rats
03487	A Pre- and Postnatal Development Toxicity and Maternal Function Study of SCH 52365 Administered Orally by Gavage in Rats

Local Tolerance

Study #	Title
01349	Three-day IV Irritation Screening Study of SCH 52365 (Temozolomide) IV Formulations in Rats
02042	Intra-arterial Tolerance Study of SCH 52365 IV Formulation in Rabbits
02044	Intravenous Tolerance Study of SCH 52365 IV Formulation in Rabbits
02267	SN 02267; Exploratory Intravenous Tolerance Study of SCH 52365 IV Placebo in Rabbits
02512	Intravenous Tolerance Study of SCH 52365 Placebo and Dacarbazine in Rabbits

Studies not reviewed within this submission:
Pharmacokinetics

Study #	Title
01573	SCH 52365: Validation of a High Performance Liquid Chromatographic-Tandem Mass Spectrometric (LC-MS/MS) Method for the Determination of SCH 52365 Concentrations in Rat Plasma

Genetic Toxicology

Study #	Title
03453	Mouse Bone Marrow Erythrocyte Micronucleus Study of SCH 52365 (Temozolomide)
03452	Chromosome Aberration Study of SCH 52365 (Temozolomide) with Impurities in Human Peripheral Blood Lymphocytes
03454	*Salmonella-Escherichia*/Mammalian-Microsome Reverse Mutation Assay of SCH 52365 (Temozolomide) with Impurities

Local Tolerance

Study #	Title
02041	Subcutaneous Irritation Study of SCH 52365 IV Formulation in Rats
02043	Muscle Irritation Study of SCH 52365 IV Formulation in Rabbits

Special Toxicology

Study #	Title
01470	*In Vitro* Hemolytic Assay for SCH 52365 in Rat Blood (Non-GLP)
03322	*In Vitro* Hemolysis Assay of SCH 52365 Intravenous Formulation in Human Blood

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Temozolomide is an imidazotetrazinone that is structurally related to dacarbazine (DTIC) and mitozolomide. Temozolomide undergoes a non-enzymatic conversion to 5-(3-methyl-1-triazeno) imidazole-4-carboxamide (MTIC) at physiological pH. MTIC alkylates DNA primarily at the O^6 and N^7 positions of guanine. *In vitro* and *in vivo* nonclinical studies show that temozolomide has activity against several tumor cell lines, including cell lines derived from human CNS tumors that have been implanted intracranially. Cell culture experiments indicate that some temozolomide metabolites and degradants such as (b) (4) are also pharmacologically active.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Studies submitted with NDA 21-029 and in the current submission have investigated the pharmacokinetics and excretion of temozolomide in the mouse, rat, dog and human. With the exception of studies conducted using mice, dosing in these studies was measured as a body surface area dose (not mg/kg body weight).

Due to the instability of temozolomide in plasma at room temperature ($t_{1/2}$ = 15 minutes), samples were acidified at collection. MTIC, a major temozolomide degradant and active moiety, is unstable in acidified plasma ($t_{1/2}$ = 5.5 minutes). Thus, the two components could not be analyzed concurrently.

AUC and C_{max} for rat, dog and human were within a factor of 2 of each other. Mouse AUC was 3-fold greater than rat when normalized by dose. In the rat and dog, the C_{max} levels were similar by both HPLC and radiolabel measurement. However, the AUC values measured by the two techniques differed greatly. Since temozolomide is extensively metabolized, this discrepancy is not unexpected.

Oral bioavailability of temozolomide was close to 100% in mice, rats, and dogs. Biologically relevant differences in ADME parameters were not noted between genders in any species tested, nor were parameters dependent on duration of dosing. AUC was linear with doses over a range of 25 to 1000 mg/m^2 in both rats and dogs. Human data correlated well with other species both in C_{max} and AUC levels. No significant accumulation of parent drug was seen between day 1 and day 5 with oral dosing. In addition, a study submitted with the current application showed no temozolomide accumulation between day 1 and day 4 in rats receiving intravenous doses of temozolomide).

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:
The toxicology program submitted with NDA 21-029 included studies using mice, rats, and dogs. At doses less than or equal to 125 mg/m^2 administered orally, toxicity occurred in hematopoietic organs, male reproductive organs and the retina. Temozolomide toxicity also occurred in the gastrointestinal tract, liver, kidney, brain and lung at doses greater than 125 mg/m^2. Histopathological changes in rats and dogs treated with temozolomide included signs of necrosis, hemorrhage and atrophy in the gastrointestinal tract, liver and kidney necrosis, and bone marrow depletion. Toxicology studies in rats and dogs also noted a low incidence of hemorrhage and degeneration of the retina.

The current submission includes a repeat-dose study using intravenous administration of temozolomide in rats. Toxicities identified in this study included histopathological signs of hypocellularity and lymphocyte depletion in lymphoid organs, single cell necrosis in the GI tract, and degeneration/atrophy of the seminiferous tubules in the testes. Hematology results in this study were consistent with the histopathological signs observed in the lymphoid organs and included decreases in white blood cells, lymphocytes, and neutrophils. Red blood cell decreases in this study were slight but, dose-dependent decreases in reticulocyte levels show that this cell lineage was also affected by temozolomide administration. These toxicities are consistent with those seen in the toxicology studies using oral administration. Thus, intravenous administration of

temozolomide does not significantly change the range of end-organ temozolomide toxicities when compared to oral administration.

The current application includes a study to qualify the levels of (b) (4) impurities present in the proposed clinical formulation: (b) (4) a process impurity, and (b) (4) a degradant of temozolomide. Although the bioavailability of these impurities is unknown, this study was conducted using oral administration. (b) (4) is present in the drug substance at levels up to (b) (4), which is greater than the qualification threshold of 0.15% limit set out by ICH-Q3A for a drug that is to be administered at levels greater than 2 g/day. The drug product specification lists (b) (4) as a degradant impurity in the drug product at a level of (b) (4) at release but levels reach up to (b) (4) 14 hours after reconstitution for intravenous administration. These (b) (4) levels are greater than the qualification threshold of 0.2% limit set out by ICH-Q3B for a product that is to be administered at a total daily intake of 100 mg to 2 g. Since completed studies submitted with this NDA did not use drug batches that contained (b) (4) at levels comparable to those presented in the proposed specification, the sponsor should conduct a non-clinical study to qualify these impurities.

Maximum Exposures* to (b) (4) according Drug Lot/Batch

			Drug Substance		Drug Product	
		Impurity:	(b) (4)			
Batch/Lot	Route	Species	%	max dose (mg/m^2)	%	max dose (mg/m^2)
78012-090 (tox)	IV	rat	(b) (4)		(b) (4)	
79229-058	IV	human				
5D005	IV	human				
5E006	IV	human				
NDA 21-029 approved specification	Oral	human				
NDA 22-277 proposed specification	IV	human				
NDA 22-277 proposed 14 after reconstitution	IV	human				

*Exposures based on a maximum dose of 200 mg/m

Genetic toxicology:
Temozolimide is a mutagen and a clastogen. In a reverse bacterial mutagenesis assay (Ames assay), temozolomide increased revertant frequency in the absence and presence of metabolic activation. *In vitro* clastogenicity assays with human peripheral blood lymphocytes determined that temozolomide is a clastogen in the absence and presence of metabolic activation.

Carcinogenicity:
Temozolomide is carcinogenic in rats at doses equivalent to less than the maximum recommended human dose. Rats treated with an oral dose of 200 mg/m^2 temozolomide

(equivalent to the maximum recommended daily human dose) on 5 consecutive days every 28 days for 3 cycles developed mammary carcinomas in both males and females. Rats treated for 6 cycles with oral doses of 25, 50, and 125 mg/m^2 (0.13 to 0.5 times the maximum recommended daily human dose), developed mammary carcinomas at all doses and also had a wide spectrum of other neoplasms at the high dose. These neoplasms included fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate, carcinomas of the seminal vesicles, schwannomas of the heart, optic nerve, and harderian gland, and adenomas of the skin, lung, pituitary, and thyroid gland.

Reproductive toxicology:
Temozolomide impairs male fertility. Rats and dogs exhibited syncytial cells/immature sperm, and testicular atrophy after oral administration of 50 mg/m^2 in rats and 125 mg/m^2 in dogs (0.25 and 0.63 times of the maximum recommended human dose).

Temozolomide is teratogenic and embryotoxic. Five consecutive days of oral temozolomide administration of 75 and 150 mg/m^2 (0.38 and 0.75 times the maximum recommended human dose) in rats and rabbits, respectively during the period of organogenesis caused numerous malformations of the external and internal soft tissues and skeleton in both species. A dose of 150 mg/m^2 caused embryolethality in rats and rabbits as indicated by increased resorptions.

Local Tolerance
The intravenous formulation of temozolomide produced mild to moderate venous irritation in rats and rabbits. Much of this local irritation correlated with the intravenous formulation as opposed to temozolomide itself when compared to saline control.

2.6.6.3 Repeat-dose toxicity

Study title: Single-Cycle (Five-Day Dosing) IV Toxicity and Toxicokinetic Study of SCH 52365 (Temozolomide) in Rats

Key study findings:
- Primary end-organ toxicities observed in lymphoid organs, the GI tract, and in the testes
- Toxicities identified in this study are not significantly different than those observed in studies of temozolomide administered via the oral route

Study no.: 01350
Volume #, and page #: Electronic submission
Conducting laboratory and location: Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation: March 6, 2002
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: Batch No. 78012-090; 104.9%

Placebo Control:

Batch 78012-147

Component	Amt per Vial
Mannitol USP	(b) (4)
L-threonine USP	
Polysorbate 80 NF	
Sodium Citrate Dihydrate USP	
Hydrochloric Acid NF	
Water for Injection USP, q.s.	

Methods

Doses:

Doses				Number of rats			
				Main groups‡		TK groups	
Dose Group	Dose mg/kg	Dose† mg/m^2	Vol ml/kg	♂	♀	♂	♀
Control	0	0	13.6	20	20	--	--
Placebo	0	0	13.6	20	20	--	-
LD	4.25	25	13.6	20	20	21	21
MD	17	100	13.6	20	20	21	21
HD	34	200	13.6	20	20	21	21

(b) (4)

‡For main groups 10/group necropsied Day 6; 10/group necropsied Day 28 (recovery)

*Levels of (b) (4) present in the drug substance calculated from the COA

Schedule:	Daily x5, 28-day cycle
Species/strain:	SD Rat
Route and infusion rate:	Intravenous injection
Vehicle:	0.9% Sodium Chloride for Injection, USP
Age:	6 weeks
Weight:	♂: 141 – 208 g; ♀: 125 – 180 g
TK Sampling times:	5, 30 min, 1, 2, 4, 8 h post-dose on Days 1, 5; Also 24 h time-point after Day 5 dose

Observations and times:

Mortality:	Daily
Clinical signs:	Daily
Body weights:	Weekly
Food consumption:	Weekly
Ophthalmoscopy:	Predose, During Week 4
EKG:	Not done
Hematology:	Necropsy (Days 5, 28)
Clinical chemistry:	Necropsy (Days 5, 28)
Urinalysis:	Necropsy (Days 5, 28)
Gross pathology:	Necropsy (Days 5, 28)
Organ weights:	See histopathology table

Histopathology: Adequate Battery: Yes; Peer review: No

Results

Mortality:

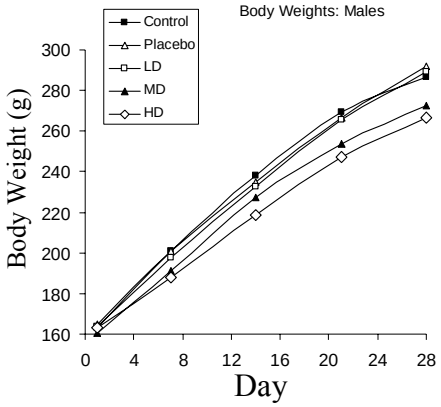
Day	Animal Number	Sex	Dose Level mg/m^2	Sponsor attribution
28	155	F	Control	Found dead; complications of jugular bleeding procedure
0	1035	M	25*	Found dead; cause not determined

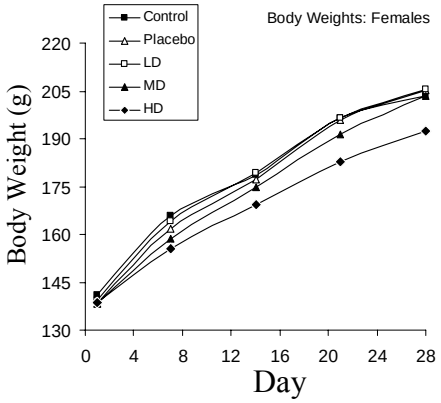
*Toxicokinetic group; only abbreviated necropsy performed

Clinical signs:

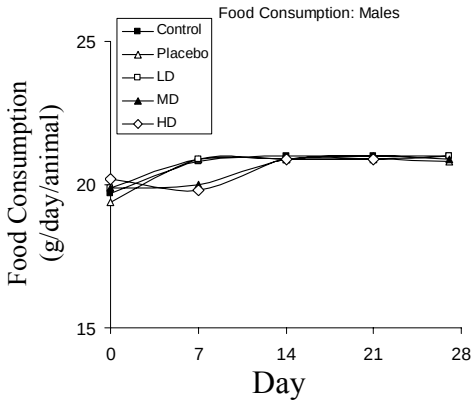
Sign		Control		Placebo		25 mg/m^2		100 mg/m^2		200 mg/m^2	
		M	F	M	F	M	F	M	F	M	F
	Group Size:	10/*10*	**1**/9/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*
		Preterminal/Terminal/*Recovery*									
Hair loss		--	--	--	--	--	--	*9*	--	3/*10*	*10*
Urogenital Staining		--	--	--	--	--	--	--	--	2	--
Found Dead, after bleeding		--	**1**	--	--	--	--	--	--	--	--

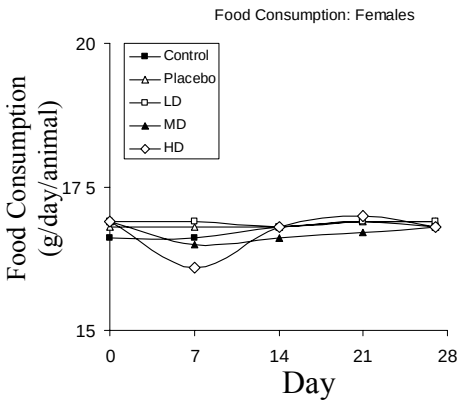
Body weights:





Food consumption:





Ophthalmoscopy: No significant changes

Hematology:

Parameter	Sex	Control	Placebo	25 mg/m^2	100 mg/m^2	200 mg/m^2
Terminal *Recovery*						
WBC	M	9.3 x 10^3/µL *10.3 x 10^3/µL*	--	--	-27%	-54% *-32%*
	F	7.7 x 10^3/µL	--	--	--	-40%
Neutrophils	M	0.64 x 10^3/µL	--	--	--	-60%
	F	0.62 x 10^3/µL	--	--	--	-50%
Eosinophils	M	0.9 x 10^3/µL	--	--	--	-67%
	F	0.12 x 10^3/µL	--	--	-50%	-75%
Lymphocytes	M	8.1 x 10^3/µL *8.58 x 10^3/µL*	--	--	-26%	-54% *-34%*
	F	6.6 x 10^3/µL	--	--	--	-34%
Reticulocytes	M	0.4 x 10^6/µL	--	--	-67%	-93%
	F	0.3 x 10^6/µL	--	--	-65%	-94%

Clinical chemistry: No significant differences

Urinalysis: No significant differences

Gross pathology:

Macro-scopic Signs		Control		Placebo		25 mg/m^2		100 mg/m^2		200 mg/m^2	
		M	F	M	F	M	F	M	F	M	F
	Group Size:	10/*10*	**1**/9/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*
	Grade	**Preterminal**/Terminal/*Recovery*									
Urine staining, uro-genital	Present	--	--	--	--	--	--	1	--	2	--
Prostate Gland, small	Mild	--	--	--	--	--	--	--	--	1	--
	All	--	--	--	--	--	--	--	--	1	--
Thymus, dis-color-ation,, dark red	Severe	--	--	--	--	--	--	--	--	1	--
	All	--	--	--	--	--	--	--	--	1	--
Thymus, small	Min.	--	1	--	--	--	1	--	2	--	3
	Mild	--	--	--	--	--	--	6	1	5	2
	Mod.	--	--	--	--	--	--	1	7	4	5
	All	--	--	--	--	--	--	7	10	9	10
Kidney, hydro-nephro-sis	Min.	--	--	--	--	--	--	--	--	1	--
	All	--	--	--	--	--	--	--	--	1	--
Neck, hemo-rrhage	Present	--	**1**	--	--	--	--	--	--	--	--
Skin,	Min.	--	--	--	--	--	--	1	--	8	3

Macro-scopic Signs		Control		Placebo		25 mg/m^2		100 mg/m^2		200 mg/m^2	
		M	F	M	F	M	F	M	F	M	F
	Group Size:	10/*10*	**1**/9/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*
	Grade	**Preterminal**/Terminal/*Recovery*									
hypotri-chosis	Mild	--	--	--	--	--	--	--	--	--	6
	Mod.	--	--	--	--	--	--	--	--	--	1
	All	--	--	--	--	--	--	1	--	8	10
Uterus, small	Mod.	--	--	--	--	--	--	--	--	--	1
	All	--	--	--	--	--	--	--	--	--	1

Organ weights:

Parameter	Sex	Control	Placebo	25 mg/m^2	100 mg/m^2	200 mg/m^2
		Terminal *Recovery*				
Thymus	M	0.64 g	--	-32%	-74%	-75%
	F	0.54 g	--	-22%	-70%	-74%
Spleen	M	0.52 g *0.65 g*	--	--	--	-27% *-24%*
	F	0.45 g	--	--	--	-16%
Prostate Gland	M	0.33 g	--	--	--	*-21%*
Testes	M	2.4 g	--	--	--	*-25%*

Histopathology:

Micro-scopic Signs		Control		Placebo		25 mg/m^2		100 mg/m^2		200 mg/m^2	
		M	F	M	F	M	F	M	F	M	F
	Group Size:	10/*10*	**1**/9/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*
	Grade	Terminal/*Recovery*									
Bone marrow, hypo-cellula-rity	Min.	--	--	--	--	--	--	--	--	1	--
	Mild	--	--	--	--	--	--	--	--	9	3
	Mod.	--	--	--	--	--	--	--	--	--	6
	Severe	--	--	--	--	--	--	--	--	--	1
	All	--	--	--	--	--	--	--	--	10	10
Epidi-dymis, debris, luminal, in -creased	Min.	--	--	--	--	6	--	9/*5*	--	8/*2*	--
	Mild	--	--	--	--	2	--	1	--	2	--
	All	--	--	--	--	8	--	10/*5*	--	10/*2*	--
Large Intestine lymph-oid deple-tion	Min.	--	--	--	--	--	--	--	--	4	2
	All	--	--	--	--	--	--	--	--	4	2
Large Intestine Apopt-osis, crypt	Min.	--	--	--	--	--	--	--	--	6	4
	All	--	--	--	--	--	--	--	--	6	4
Lymph	Min.	--	--	--	--	--	--	--	--	10	6

Micro-scopic Signs		Control		Placebo		25 mg/m^2		100 mg/m^2		200 mg/m^2	
		M	F	M	F	M	F	M	F	M	F
	Group Size:	10/*10*	**1**/9/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*
	Grade	Terminal/*Recovery*									
Node, Mandi-bular, lymph-oid deple-tion	All	--	--	--	--	--	--	--	--	10	6
Lymph Node, Mesente ric, lymph-oid deple-tion	Min.	--	--	--	--	--	--	--	--	10	6
	All	--	--	--	--	--	--	--	--	10	6
Mam-mary gland, single cell necrosis	Min.	--	--	--	--	--	--	--	--	--	5
	All	--	--	--	--	--	--	--	--	--	5
Skin, single cell necrosis, hair follicle	Min.	--	--	--	--	--	--	--	--	6/*2*	10
	Mild	--	--	--	--	--	--	--	--	4	--
	All	--	--	--	--	--	--	--	--	10/*2*	10
Small Intestine lymph-oid deple-tion	Min.	--	--	--	--	--	--	--	--	9	6
	Mild	--	--	--	--	--	--	--	--	1	--
	All	--	--	--	--	--	--	--	--	10	6
Small Intestine apopt-osis, crypt	Min.	--	--	--	--	--	--	--	--	8	6
	All	--	--	--	--	--	--	--	--	8	6
Spleen, lymph-oid deplet-ion	Min.	--	--	--	--	8/*5*	1	2/*9*	4	5/*9*	7
	Mild	--	--	--	--	1	--	--	--	4	--
	All	--	--	--	--	9/*5*	1	2/*9*	4	9/*9*	7
Testes, degene-ration, semini-ferous	Min.	--	--	--	--	5	--	9	--	8	--
	Mild	--	--	--	--	--	--	*10*	--	2	--
	All	--	--	--	--	5	--	9/*10*	--	10	--
Testes, atrophy, semini-ferous tubule	Min.	--	--	--	--	--	--	--	--	*4*	--
	Mild	--	--	--	--	--	--	--	--	*5*	--
	Mod.	--	--	--	--	--	--	--	--	*1*	--
	All	--	--	--	--	--	--	--	--	*10*	--
Testes, sperma-	Min.	--	--	--	--	--	--	*8*	--	*5*	--
	Mild	--	--	--	--	--	--	*2*	--	*5*	--

Micro-scopic Signs		Control		Placebo		25 mg/m^2		100 mg/m^2		200 mg/m^2	
		M	F	M	F	M	F	M	F	M	F
	Group Size:	10/*10*	**1**/9/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*
	Grade	Terminal/*Recovery*									
tid giant cells in-creased	All	--	--	--	--	--	--	*10*	--	*10*	--
Thymus, lymph-oid deple-tion	Min.	--	--	--	--	10	5	--	--	--	--
	Mild	--	--	--	--	--	--	--	--	--	1
	Mod.	--	--	--	--	--	--	10	10	10	7
	Severe	--	--	--	--	--	--	--	--	--	2
	All	--	--	--	--	10	5	10	10	10	10

Toxicokinetics:

Parameter	Sex	25 mg/m^2	100 mg/m^2	200 mg/m^2
		Day 1 **Day4**		
C_{max} (µg/ml)	M	6.50 **5.78**	22.2 **23.0**	52.7 **44.8**
	F	6.43 **6.03**	24.4 **25.2**	47.9 **52.8**
AUC (µg*h/ml)	M	11.1 **9.57**	43.6 **39.9**	85.8 **75.8**
	F	10.6 **8.64**	39.7 **37.5**	82.4 **75.1**
$t_{1/2}$ (h)	M	1.11 **0.90**	1.04 **1.12**	1.10 **1.26**
	F	0.99 **1.23**	1.07 **1.10**	1.04 **1.09**
V (mL/kg)	M	609 **577**	588 **690**	630 **816**
	F	575 **868**	717 **627**	618 **713**
CL (ml/hr/kg)	M	382 **444**	390 **426**	396 **449**
	F	401 **488**	428 **453**	413 **453**
R (Accumulation Ratio)	M	NA **0.917**	NA **0.917**	NA **0.883**
	F	NA **0.822**	NA **0.945**	NA **0.911**

NA = Not applicable

Study title: A Single-Cycle (5-Day Dosing) Oral Gavage Toxicity Study of SCH 52365 with Impurities in Rats

Key study findings:

- No significant toxicological differences between temozolomide formulation and a temozolomide formulation spiked with (b)(4) and (b)(4)
- This study confirms previously identified end-organ toxicities in lymphoid organs, the GI tract, and in the testes

Study no.: 03451
Volume #, and page #: Electronic submission
Conducting laboratory and location: (b)(4)
Date of study initiation: March 9, 2004
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: H05481; 99.6% (Formulation spiked with (b)(4)); H05482; 99.9%

Methods

Doses:

Doses							Number of rats			
Dose Group	Lot #	Dose* mg/kg	Dose† mg/m^2	(b)(4)		Vol ml/m^2	Main groups‡		TK groups	
							♂	♀	♂	♀
Cont	--	0	0			35	20	20	--	--
LD	H05481	4.2	25			35	20	20	3	3
MD	H05481	16.7	100			35	20	20	3	3
HD1	H05481	33.3	200			35	20	20	3	3
HD2	H05482	33.3	200			35	20	20	3	3

*Estimated. The mg/kg dosage calculated as 1/6th of mg/m^2 dosage.
†Doses based on the individual animal body surface area calculated from most recent body weight. Surface area calculated as follows: S = (K x w$^{2/3}$) /10^4 where S = surface area (m^2), w = body weight (g) and K = constant for estimating surface area = 9.0.
‡For main groups 10/group necropsied Day 6; 10/group necropsied Day 28 (recovery)

Schedule:	Daily x5, 28-day cycle
Species/strain:	SD Rat
Route and infusion rate:	Oral gavage
Vehicle:	0.5% Methylcellulose
Age:	Approximately 8 weeks
Weight:	♂: 251 – 298 g; ♀: 172 – 215 g
TK Sampling times:	Days 1 and 5; 1 h post-dose

Observations and times:

Mortality: Twice daily

Clinical signs: Daily
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: Predose, Day 5, During Week 4
EKG: Not done
Hematology: Necropsy (Days 6, 29)
Clinical chemistry: Necropsy (Days 6, 29)
Urinalysis: Necropsy (Days 6, 29)
Gross pathology: Necropsy (Days 6, 29)
Organ weights: See histopathology table
Histopathology: Adequate Battery: Yes
Peer review: No

Results

Mortality:

Day	Animal Number	Sex	Dose Level mg/m^2	Sponsor attribution
28	4514	F	200†	Found dead after blood collection

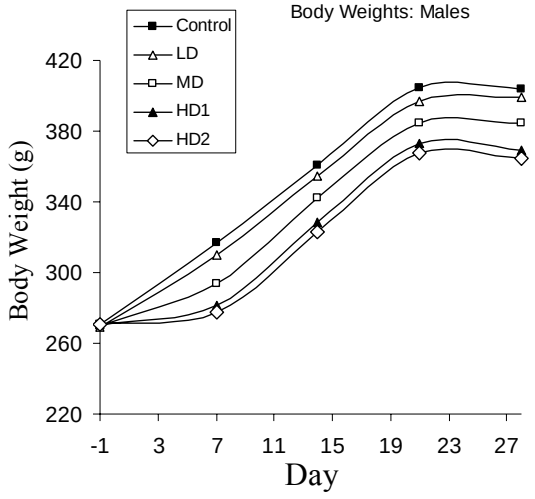
†Formulation spiked with (b) (4)

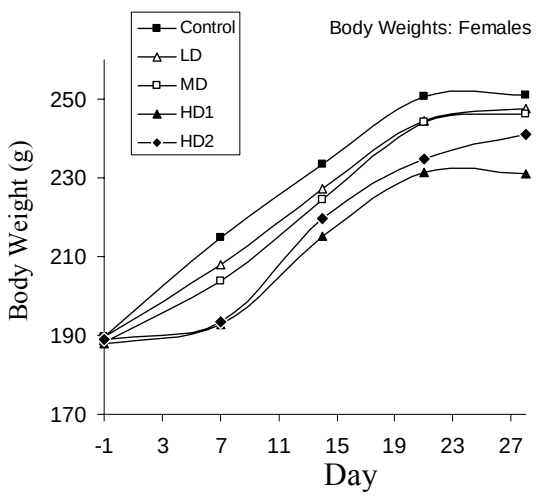
Clinical signs:

Sign	Sex	Control	25 mg/m^2†	100 mg/m^2†	200 mg/m^2†	200 mg/m^2
Total Number of Observations over 28 days						
Fur, thin cover	M	37	32	59	117	106
	F	24	18	77	105	83
Skin, lesion	M	--	--	--	2	1
	F	--	--	--	--	--
Skin, scab	M	2	2	3	9	5
	F	0	4	1	4	1
Skin, Blue	M	--	--	--	--	--
	F	--	--	--	--	1

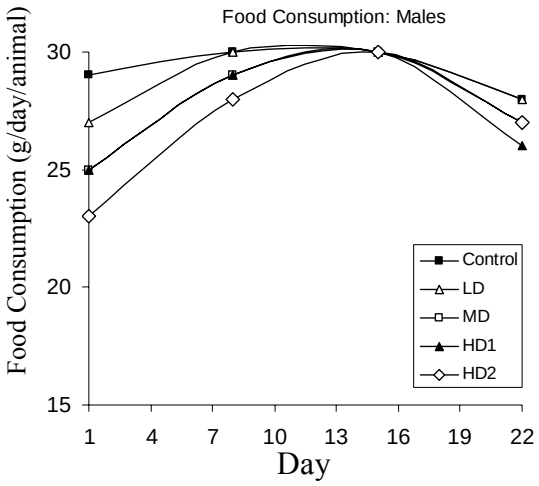
†Formulation spiked with (b) (4)

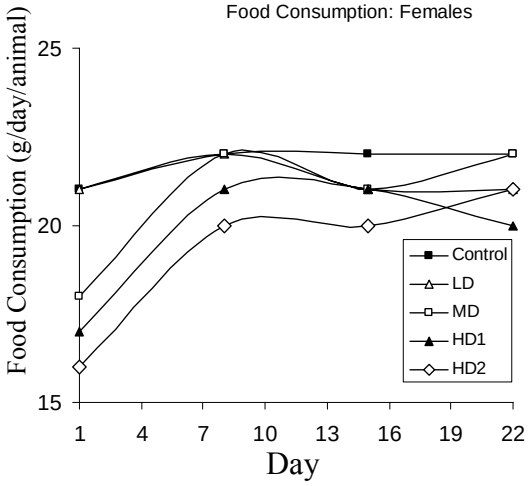
Body weights:





Food consumption:





Ophthalmoscopy:

Sign	Sex	Control	25 mg/m^2†	100 mg/m^2†	200 mg/m^2†	200 mg/m^2
Terminal/*Recovery*						
Superficial Punctate Keratopathy	M	--	1/*1*	*3*	--	*1*
	F	--	--	--	--	*2*

†Formulation spiked with **(b) (4)**

Hematology:

Parameter	Sex	Control	25 mg/m^2†	100 mg/m^2†	200 mg/m^2†	200 mg/m^2
Terminal						
WBC	M	10.7 x 10^3/µL	--	-31%	-47%	-48%
	F	8.7 x 10^3/µL	--	-24%	-57%	-44%
Neutrophils	M	1.3 x 10^3/µL	--	-65%	-67%	-69%
	F	0.94 x 10^3/µL	-38%	-54%	-49%	-55%
Lymphocytes	M	9.0 x 10^3/µL	--	--	-44%	-46%
	F	7.5 x 10^3/µL	--	--	-59%	43%
Basophils	M	3.3 x 10^1/µL	--	--	-48%	-48%
	F	3.3 x 10^1/µL	--	--	-76%	-55%
Reticulocytes	M	374 x 10^9/µL	--	-69%	-95%	-92%
	F	289 x 10^9/µL	--	-76%	-96%	-96%

†Formulation spiked with **(b) (4)**

Clinical chemistry: No significant changes

Urinalysis: No significant changes

Gross pathology:

Micro-scopic Signs		Control		25 mg/m^2†		100 mg/m^2†		200 mg/m^2†		200 mg/m^2	
		M	F	M	F	M	F	M	F	M	F
	Group Size:	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*
	Grade	Terminal/*Recovery*									
Liver, area pale	Present	--	--	--	2	--	3	--	2	--	1
Lymph node, man-dibular, dark foci	Present	--	--	--	--	--	--	--	--	1	--
Sub-cuta-neous tissue, clot	Present	--	--	--	--	--	--	1	--	1	--

†Formulation spiked with [redacted]

Organ weights

Absolute weights presented. Changes in organ weight also evident when corrected by body weight.

Parameter	Sex	Control	25 mg/m^2†	100 mg/m^2†	200 mg/m^2†	200 mg/m^2
Terminal/Recovery						
Spleen	M	0.60 g	--	--	-20%	-21%
	F	0.50 g	--	--	-27%	-28%
Thymus	M	0.46 g	-21%	-72%	-71%	-74%
	F	0.45 g	-25%	-78%	-78%	-75%
Testis	M	3.3 g	--	--	-16%	-21%

†Formulation spiked with [redacted]

Histopathology:

Micro-scopic Signs		Control		25 mg/m^2†		100 mg/m^2†		200 mg/m^2†		200 mg/m^2	
		M	F	M	F	M	F	M	F	M	F
	Group Size:	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*
	Grade	Terminal/*Recovery*									
Thymus, atrophy cortical	Min.	--	--	3	6	--	--	--	--	--	--
	Mild	--	--	7	3	--	--	--	--	--	1
	Mod.	--	--	--	--	10	10	10	9	10	9
	All	--	--	10	9	10	10	10	9	10	10
Spleen, lymph-oid de-pletion	Min.	--	--	6	3	6/*2*	8	9/*1*	4/*2*	3/*1*	6/*3*
	Mild	--	--	1	1	3	--	--	2	6	3
	All	--	--	7	4	9/*2*	8	9/*1*	6/*2*	9/*1*	9/*3*
Bone marrow, hypocell ularity, myeloid	Min.	--	--	--	--	2	6	2	--	3	5
	Mild	--	--	--	--	--	1	7	7	6	2
	Mod.	--	--	--	--	--	--	1	3	1	3
	All	--	--	--	--	2	7	10	10	10	10
Bone	Min.	--	--	2	6	4	4	--	--	--	--

Micro-scopic Signs		Control		25 mg/m^2†		100 mg/m^2†		200 mg/m^2†		200 mg/m^2	
		M	F	M	F	M	F	M	F	M	F
	Group Size:	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*	10/*10*
	Grade	Terminal/*Recovery*									
marrow, hypocellularity, erythroid	Mild	--	--	--	--	6	5	8	1	1	6
	Mod.	--	--	--	--	--	1	2	9	9	4
	All	--	--	2	6	10	10	10	10	10	10
Small Intestine single cell necrosis	Min.	--	--	--	--	3	3	9	7	6	6
	Mild	--	--	--	--	--	--	--	2	--	1
	All	--	--	--	--	3	3	9	9	6	7
Large Intestine single cell necrosis	Min.	--	--	--	--	6	7	5	7	7	4
	Mild	--	--	--	--	--	--	--	--	--	1
	All	--	--	--	--	6	7	5	7	7	5
Testis, degeneration, spermatid	Min.	--	--	--	--	8	--	7	--	8	--
	Mild	--	--	--	--	1	--	3	--	2	--
	All	--	--	--	--	9	--	10	--	10	--

Toxicokinetics:

Parameter	Sex	Control	25 mg/m^2†	100 mg/m^2†	200 mg/m^2†	200 mg/m^2
			Day 1 **Day5**			
Temozolomide concentration 1 h after dosing (µg/ml)	M	--	2.16 **2.13**	10.2 **11.2**	20.6 **19.5**	21.9 **24.2**
	F	--	2.96 **2.99**	10.3 **10.8**	21.3 **19.5**	20.3 **20.5**

Histopathology inventory

Study	03451	01350
Species	Rat	Rat
Adrenals	X*	X*
Aorta	X	X
Bone Marrow smear	X	X
Bone (femur)	X	X
Brain	X*	X*
Cecum	X	X
Cervix		
Colon	X	X
Duodenum	X	X
Epididymis	X*	X*
Esophagus	X	X

Eye	X	X
Fallopian tube		
Gall bladder		
Gross lesions		
Harderian gland	X	X
Heart	X*	X*
Ileum	X	X
Injection site		
Jejunum	X	X
Kidneys	X*	X*
Lachrymal gland		
Larynx		
Liver	X*	X*
Lungs	X*	X*
Lymph nodes, cervical		
Lymph nodes mandibular	X	X
Lymph nodes, mesenteric	X	X
Mammary Gland	X	X
Nasal cavity		
Optic nerves	X	X
Ovaries	X*	X*
Pancreas	X	X
Parathyroid		
Peripheral nerve	X	X
Pharynx		
Pituitary	X*	X*
Prostate	X*	X*
Rectum	X	X
Salivary gland	X*	X*
Sciatic nerve	X	X
Seminal vesicles	X	X
Skeletal muscle	X	X
Skin	X	X
Spinal cord	X	X
Spleen	X	X
Sternum	X	X
Stomach	X	X
Testes	X*	X*
Thymus	X*	X*
Thyroid	X*	X*
Tongue		
Trachea	X	X
Urinary bladder	X	X
Uterus	X*	X*
Vagina	X	X
Zymbal gland		

X, histopathology performed
*, organ weight obtained

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Study title: Fertility and Early Embryonic Developmental Toxicity Study of SCH 52365 Administered Orally by Gavage in Rats

Key study findings:

- Temozolomide adversely affected body weights and food consumption at 150 mg/m^2 in males and at 50 and 150 mg/m^2 in females
- No temozolomide effect on female fertility with doses up to 150 mg/m^2 administered preimplantation
- Dose-dependent increase on post-implantation loss and non-viable embryos

Study no.: 03471
Volume #, and page #: Electronic submission
Conducting laboratory and location: (b) (4)

Date of study initiation: February 5, 2004
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: H05482, 99.9%
Methods

Doses: (b) (4)

	Doses			Number of rats	
				Main groups	
Dose Group	Dose* mg/kg	Dose† mg/m^2	Vol ml/m^2	♂	♀
Cont	0	0	35	25	25
LD	0.8	5	35	25	25
MD	8.3	50	35	25	25
HD	25	150	35	25	25

*Estimated. The mg/kg dosage calculated as 1/6 of mg/m^2 dosage.
†Doses based on the individual animal body surface area calculated from most recent body weight. Surface area calculated as follows: $S = (K \times w^{2/3}) /10^4$ where S = surface area (m^2), w = body weight (g) and K = constant for estimating surface area = 9.0.
‡Levels of (b) (4) present in the drug substance calculated from the COA

Species/strain: SD Rat
Number/sex/group: 25/sex/dose
Route, formulation, volume, and infusion rate: Oral gavage; 0.4% (w/v) aqueous methylcellulose

Satellite groups used for toxicokinetics: None
Study design:

- Male study: pre-cohabitation Days 1-62
- Female study: pre-cohabitation Days 1-29
- Cohabitation: 1 male and 1 female from same dose group placed together for 14 days or positive evidence of mating
- Males dosed once daily pre-cohabitation Days 1-5, 29-33, 57-61
- Females dosed once daily pre-cohabitation Days 1-5
- Females dosed once daily during cohabitation Days 29-33

Parameters and endpoints evaluated:

- Number and distribution of corpora lutea, implantation sites, viable and non-viable embryos
- Placentae examined for size, color, shape
- Pre-coital interval
- Male Mating Index (%)
- Male Fertility Index (%)
- Female Mating Index (%)
- Female Fertility Index (%)

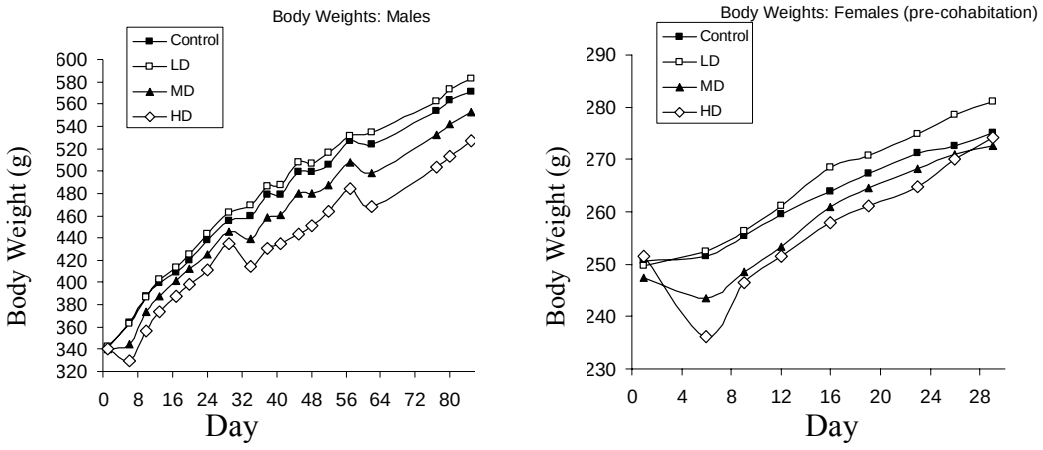
Results

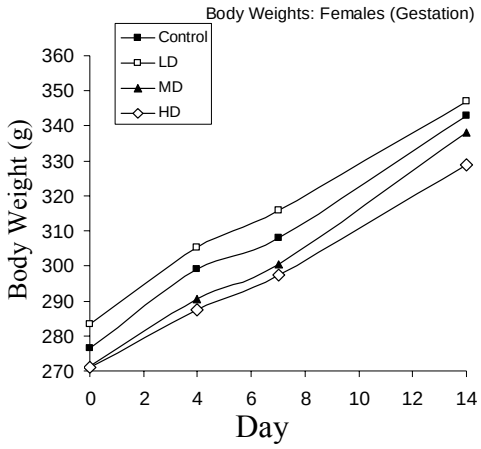
Mortality: None

Clinical signs:

Sign	Sex	Control	5 mg/m^2	50 mg/m^2	150 mg/m^2
Females only: Pre-cohabitation/**Gestation** 25 rats/sex/group					
Sparse hair coat	M	--	--	--	25
	F	**1**	--	--	17/**22**
Soft/liquid feces	M	2	6	8	10
	F	--	--	--	--
Red peri-oral substance	M	3	3	3	10
	F	--	--	--	--
Red substance in cage pan	M	--	--	--	5
	F	--	--	--	--

Body weight:





Food consumption:

Sign	Sex	Control	5 mg/m^2	50 mg/m^2	150 mg/m^2
Food Consumption (g/day); pre-cohabitation					
Days 1-6	M	27.3	27.8	23.8	21.1**
	F	20.0	19.2	17.8**	15.4**
Days 6-29	M	28.5	29.6	28.5	28.1
	F	20.4	21	20.4	20.5
Days 29-34	M	28.6	29.6	26.9	23.7**
	F	20.4	20.7	20.0	19.6
Days 34-57	M	29.4	30.6	29.2	28.9
	F	--	--	--	--
Days 57-62	M	28.5	29.5	26.7	25.9**
	F	--	--	--	--

**Statistically difference from control ($p \leq 0.01$)

Toxicokinetics:
Not conducted

Necropsy:
No treatment-related effects observed.

Fertility parameters:
No treatment-related effects observed on estrous cycle, corpora lutea, implantations, preimplantation loss, pregnancy rate, or fertility index.

The following reproductive parameters increased with dose:

Parameter	Sex	Control	5 mg/m^2	50 mg/m^2	150 mg/m^2
Mean No. Non-viable Embryos	F	0.9±0.8	1.0±0.7	2.5±2.7	6.1±4.9
Post-implantation Loss	F	5.4%±4.8	6.9%±7.4	16.4%±17.6	38.7%±30.9**

**Significantly different from Control ($p \leq 0.01$)

Embryofetal development

Study title: Embryo-Fetal Developmental Toxicity and Toxicokinetic Study of SCH 52365 Administered Orally by Gavage in Rabbits

Key study findings:

- Temozolomide induced external, visceral, and skeletal abnormalities
- Most abnormalities occurred at the 125 mg/m^2 dose level
- Some skeletal abnormalities occurred at the 5 and 50 mg/m^2 dose level
- Temozolomide had no effect in number of corpora lutea, the rate of implantation, the rate of preimplantation loss, litter size, placental appearance, or number of live fetuses.

Study no.: 03450
Volume #, and page #: Electronic submission
Conducting laboratory and location: (b) (4)

Date of study initiation: February 27, 2004
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: H05482, 99.9%

Methods

Doses: (b) (4)

Doses				No. of rabbits
				Main groups∫
Dose Group	Dose* mg/kg	Dose† mg/m^2	Vol ml/m^2	♀
Cont	0	0	35	20
LD	0.8	5	35	20
MD	8.3	50	35	20
HD	20.8	125	35	20

*Estimated. The mg/kg dosage calculated as 1/6 of mg/m^2 dosage.
†Doses based on the individual animal body surface area calculated from most recent body weight. Surface area calculated as follows: $S = (K \times w^{2/3}) /10^4$ where S = surface area (m^2), w = body weight (g) and K = constant for estimating surface area = 9.0.
‡Levels of (b) (4) present calculated from COA
∫Four rabbits in each group were used for Toxicokinetic analysis

Species/strain: New Zealand White rabbit
Number/sex/group: 20/dose
Route, formulation, volume, and infusion rate: Oral gavage
Satellite groups used for toxicokinetics: None
Study design:

- Females dosed once daily on gestation days 8-12

Parameters and endpoints evaluated:

- Uteri of pregnant females with at least one viable fetus were removed and weighed
- Numbers and distribution of corpora lutea, implantation sites, fetuses (live and dead) resorptions (early and late) were determined
- Late resorptions were subjected to gross external examination and discarded
- Placentae were examined for abnormal size, and, color and shape

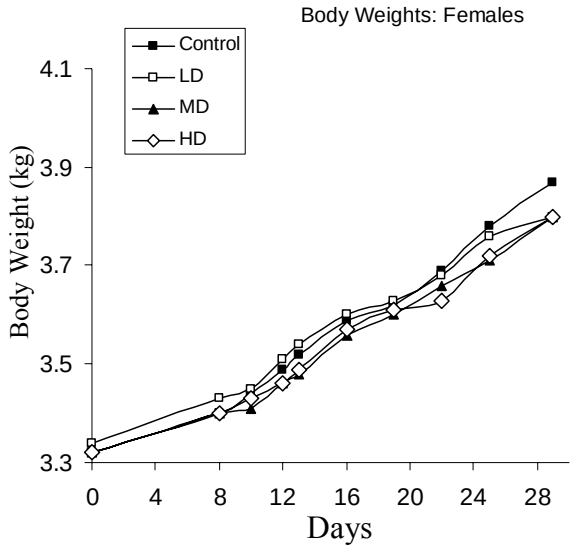
Results

Mortality (dams): No maternal deaths

Clinical signs (dams):

Sign	Sex	Control	5 mg/m^2	50 mg/m^2	125 mg/m^2
20 rabbits/group					
Abortion	F	--	--	1	--
Scab	F	--	--	--	1

Body weight (dams):



Food consumption (dams):

Day	Sex	Control	5 mg/m^2	50 mg/m^2	125g/m^2
Food Consumption (g/day)					
Days 8-10	F	148.1	151.4	146.4	150
Days 11-12	F	152.9	152.2	144.5	146.7
Days 13-16	F	152.1	144.1	138.6	146.6
Days 16-19	F	152.1	145.8	146.5	149.8
Days 19-22	F	152.9	143	147	147.7
Days 22-25	F	145.8	121.5	141.5	146.9
Days 25-29	F	126.6	112	124.1	134.1

Toxicokinetics:

Parameter	Sex	25 mg/m^2	50 mg/m^2	125 mg/m^2
Day 12				
C_{max} (µg/ml)	F	0.165	2.10	4.31
AUC (µg*h/ml)	F	0.669	7.15	17.7
T_{max} (h)	F	1.13	1.50	1.25

Terminal and necroscopic evaluations: No effect in number of corpora lutea, implantation loss, preimplantation loss, litter size, placental appearance, or number of live fetuses. No dead fetuses observed. No change in early or late resorptions or postimplantation loss.

Offspring:

External Examination

%Change in live fetal body weight relative to control:

%Change in live fetal body weight relative to control			
Control	5 mg/m^2	50 mg/m^2	125 mg/m^2
42.32 g	--	--	-31%

There were no differences between male and female fetuses

Finding		Control	5 mg/m^2	50 mg/m^2	125 mg/m^2
Head, domed	Litter Incidence	--	--	--	90%
	Fetal Incidence		--	--	88%
Head. meningocele	Litter Incidence	--	--	--	2%
	Fetal Incidence		--	--	3%
Eye, bulge depressed	Litter Incidence	--	--	--	16%
	Fetal Incidence		--	--	58%
Snout, short	Litter Incidence	--	--	--	85%
	Fetal Incidence		--	--	62%
Snout, cleft	Litter Incidence	--	--	--	5%
	Fetal Incidence		--	--	0.6%
Palate, cleft	Litter Incidence	--	--	--	85%
	Fetal Incidence		--	--	25%
Limbs, digits absent	Litter Incidence	--	--	--	100%
	Fetal Incidence		--	--	66%
Limbs, toenails absent	Litter Incidence	--	--	--	95%
	Fetal Incidence		--	--	37%
Limbs, rotated medially	Litter Incidence	--	--	--	75%
	Fetal Incidence		--	--	32%
Limbs, short	Litter Incidence	--	--	--	80%
	Fetal Incidence		--	--	36%
Limbs, flexed upward	Litter Incidence	--	--	--	70%
	Fetal Incidence		--	--	20%
Limbs, digits splayed	Litter Incidence	--	--	--	20%
	Fetal Incidence		--	--	3%
Limbs,	Litter Incidence	--	--	--	45%

Finding		Control	5 mg/m^2	50 mg/m^2	125 mg/m^2
flexed backward	Fetal Incidence		--	--	12%
Limbs, flexed downward	Litter Incidence	--	--	6%	85%
	Fetal Incidence		--	1%	44%
Limbs, digits fused	Litter Incidence	--	--	--	50%
	Fetal Incidence		--	--	10%
Limbs, extra digit	Litter Incidence	--	--	--	65%
	Fetal Incidence		--	--	8%
Limbs, rotated laterally	Litter Incidence	--	--	--	15%
	Fetal Incidence		--	--	2%
Tail, short	Litter Incidence	--	--	--	90%
	Fetal Incidence		--	--	60%
Tail, absent	Litter Incidence	--	--	--	80%
	Fetal Incidence		--	--	37%
Body, fleshy protrusion	Litter Incidence	--	--	--	5%
	Fetal Incidence		--	--	1%
Body, umbilical hernia	Litter Incidence	--	--	--	35%
	Fetal Incidence		--	--	7.5%
Body, edema	Litter Incidence	--	--	--	5%
	Fetal Incidence		--	--	1%
Body, trunk short	Litter Incidence	--	--	--	15%
	Fetal Incidence		--	--	3%

Visceral Examination

Finding		Control	5 mg/m^2	50 mg/m^2	125 mg/m^2
Eyes, small	Litter Incidence	--	--	--	85%
	Fetal Incidence		--	--	32%
Brain, dilated ventricles, moderate	Litter Incidence	--	--	--	45%
	Fetal Incidence	--	--	--	10%
Brain, dilated ventricles, slight	Litter Incidence	--	--	--	90%
	Fetal Incidence		--	--	23%
Brain, Irregular shape	Litter Incidence	--	--	--	60%
	Fetal Incidence		--	--	17%
Brain, dilated, ventricles, extreme	Litter Incidence	--	--	--	20%
	Fetal Incidence		--	--	3%
Heart, Interventricular septal defect	Litter Incidence	--	--	--	10%
	Fetal Incidence		--	--	1%
Heart,	Litter Incidence	--	--	--	5%

Finding		Control	5 mg/m^2	50 mg/m^2	125 mg/m^2
Ventricle wall thick	Fetal Incidence		--	--	1%
Heart, Non-patent valve	Litter Incidence	--	--	--	5%
	Fetal Incidence		--	--	1%
Vessels, dilated aortic arch	Litter Incidence	--	--	--	5%
	Fetal Incidence		--	--	1%
Vessels, persistent truncus arteriosis	Litter Incidence	--	--	--	5%
	Fetal Incidence		--	--	1%
Diaphragm, diaphragm-matic hernia	Litter Incidence	--	--	--	20%
	Fetal Incidence		--	--	2%
Liver, thick	Litter Incidence	--	--	--	10%
	Fetal Incidence		--	--	3%
Kidneys, absent	Litter Incidence	--	--	--	20%
	Fetal Incidence		--	--	3%
Kidneys, small	Litter Incidence	--	--	--	10%
	Fetal Incidence		--	--	2%
Kidneys, dialated, marked	Litter Incidence	--	--	--	10%
	Fetal Incidence		--	--	1%
Kidneys, low set	Litter Incidence	--	--	--	5%
	Fetal Incidence		--	--	1%
Intestines, portion protruded through umbilicus	Litter Incidence	--	--	--	35%
	Fetal Incidence		--	--	8%
Gallbladder, absent	Litter Incidence	--	--	--	10%
	Fetal Incidence		--	--	1%
Ureter, absent	Litter Incidence	--	--	--	20%
	Fetal Incidence		--	--	3%
Ureters, dilated, moderate	Litter Incidence	--	--	--	10%
	Fetal Incidence		--	--	1%
Ureter, dilated, marked	Litter Incidence	--	--	--	5%
	Fetal Incidence		--	--	2%

Skeletal Examination

Finding		Control	5 mg/m^2	50 mg/m^2	125 mg/m^2
Skull, nasals, fused	Litter Incidence	--	--	--	56%
	Fetal Incidence		--	--	14%
Skull, suture irregular	Litter Incidence	--	--	--	44%
	Fetal Incidence		--	--	5%
Skull, incomplete-ly ossified	Litter Incidence	--	--	--	11%
	Fetal Incidence		--	--	2%

Finding		Control	5 mg/m^2	50 mg/m^2	125 mg/m^2
Skull, nasal and frontal fused	Litter Incidence	--	--	25%	100%
	Fetal Incidence		--	7%	85%
Skull, frontals, contained an interfrontal	Litter Incidence	--	5%	25%	44%
	Fetal Incidence		1%	4%	8%
Skull, anterior fontanelle, irregularly shaped	Litter Incidence	--	--	--	67%
	Fetal Incidence		--	--	10%
Skull, Eye Socket, Small	Litter Incidence	--	--	--	100%
	Fetal Incidence		--	--	31%
Skull, frontals, contained an intrafrontal	Litter Incidence	--	--	--	11%
	Fetal Incidence		--	--	1%
Skull, tympanic ring not ossified	Litter Incidence	--	--	--	11%
	Fetal Incidence		--	--	1%
Skull, palate, incomplete-ly ossified	Litter Incidence	--	--	--	78%
	Fetal Incidence		--	--	16%

Prenatal and postnatal development

Study title: A Pre- and Postnatal Development Toxicity and Maternal Function Study of SCH 52365 Administered Orally by Gavage in Rat

Key study findings:

- Temozolomide reduced litter size and pup survival at 75 mg/m^2
- Temozolomide reduced pup body weights at 75 mg/m^2
- Temozolomide caused malformations in pups at 75 mg/m^2
- Temozolomide did not affect the number of pups born or the % male ratio at doses up to 75 mg/m^2

Study no.: 03487
Volume #, and page #: Electronic submission
Conducting laboratory and location: (b) (4)
Date of study initiation: March 15, 2004
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: H05482; 99.9%

Methods

Doses:

Doses				Number of Rats
				Main groups
Dose Group	Dose* mg/kg	Dose† mg/m^2	Vol ml/m^2	♀
Cont	0	0	35	25
LD	0.8	5	35	25
MD	4.2	25	35	25
HD	20.8	75	35	25

*Estimated. The mg/kg dosage calculated as $1/6^{th}$ of mg/m^2 dosage.
†Doses based on the individual animal body surface area calculated from most recent body weight. Surface area calculated as follows: $S = (K \times w^{2/3}) /10^4$ where S = surface area (m^2), w = body weight (g) and K = constant for estimating surface area = 9.0.
‡Levels of (b) (4) present in the drug substance calculated from the COA

Species/strain: SD Rats
Number/sex/group: 25/dose
Route, formulation, volume, and infusion rate: Oral gavage
Satellite groups used for toxicokinetics: None
Study design:

- Females dosed once daily Days 8-12, 21-25 of gestation

Parameters and endpoints evaluated:

- Clinical Observations
  F_0: Daily beginning gestation Day 0
  F_1: Daily Postnatal Days 0-21

- Body weights (F_0 only)
  Gestation Days 0, 6, 8, 13, 15, 18 and 20
  Lactation Days 1, 5, 10, 14, 17, 21

- Food Consumption (F_0 only)
  Gestation Days 0, 6, 8, 13, 15, 18 and 20
  Lactation Days 1, 5, 10, 14, 17, 21

- Necropsy (F0 and F1)
  Lactation Day 21
  Post-Natal Days 4, 21
  Pup External/Visceral Investigation

- Reproductive Parameters: Number and distribution of former implantation sites

- Pup Body Weight (F1): Postnatal days 1, 4, 7, 10, 14, 17, 21

- Pup Sex Determination (F1): Postnatal days 0, 4, 21

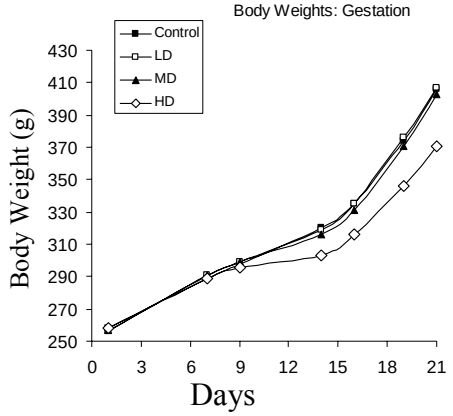
- Developmental Landmarks (F1)
  Surface Righting Response: evaluated daily beginning Postnatal Day 5
  Incisor eruption: evaluated daily beginning Postnatal Day 7

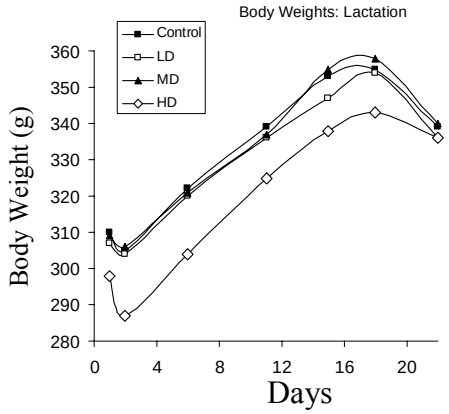
Results

F0 in-life:
Mortality: All F_0 females survived to scheduled necropsy

Body Weight:
F_0 females treated with 75 mg/m^2 temozolomide had statistically lower body weights than control over the periods of gestation and lactation.

Maternal Body Weights during gestation and lactation:





Food Consumption:

Day	Control	5 mg/m^2	50 mg/m^2	75 mg/m^2
Food Consumption (g/day)				
Days 0-6	21	22	22	22
Days 6-8	23	23	24	23
Days 8-13	24	24	22	20
Days 13-15	25	25	25	24
Days 15-18	26	27	27	25
Days 18-20	27	27	27	26

F_0 necropsy:
Females which Failed to Deliver:
Control female #50421 and LD (5 mg/m^2) female #50363: no significant findings

Females with Total Litter Loss:
HD (75 mg/m^2) female #50396 had total litter loss on Postnatal Day 3. No significant findings were found during necropsy

Females Necropsied on Day 21 of Lactation Period

Macroscopic Findings		Control	5 mg/m^2	50 mg/m^2	75 mg/m^2
	Group Size:	25	25	25	25
Ovaries, discolor-ation, dark red		--	--	--	1
Abdominal Cavity, thick red contents		--	--	--	1

F_1 physical development:

Viability:

No significant differences in number born or % males per litter.

%Litter Size/Group				
Parameter	Control	5 mg/m^2	50 mg/m^2	75 mg/m^2
Live Litter Size	14.6	--	--	-27%

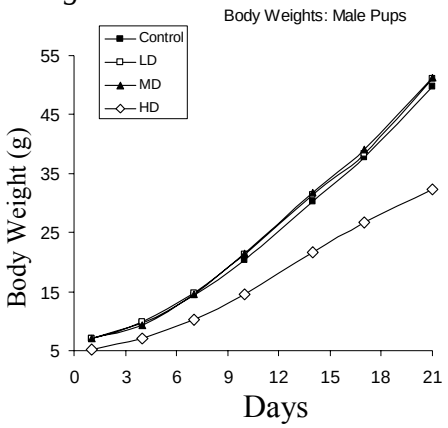
Postnatal survival per litter

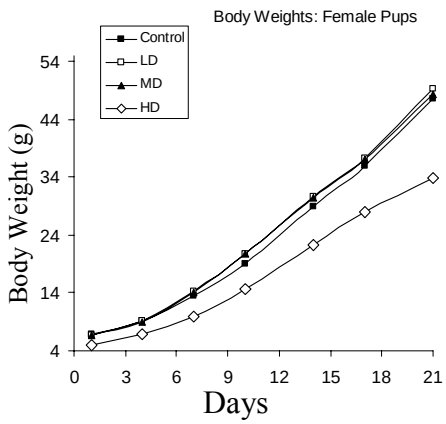
Day	Control	5 mg/m^2	50 mg/m^2	75 mg/m^2
Day 0	99%	98%	99%	75%
Day 1-4	99.5%	98.7%	99.5%	88%
Day 7-14	100%	100%	100%	97%

Pup clinical signs

Sign	Control	5 mg/m^2	50 mg/m^2	75 mg/m^2
Found dead	8	13	10	106
Euthanized	--	--	--	1
Missing	2	6	2	34
Malrotated Limb	--	1	--	45
Spinal column deviated left	--	--	--	1
Gasping	--	--	--	3
Cyanotic	--	--	--	7
Labored respiration	--	--	--	3
Fleshy protrusion from mouth	--	--	--	1

Pup Weights:





Incisor eruption:

Parameter	Sex	Control	5 mg/m^2	50 mg/m^2	75 mg/m^2
Frequency of Incisor eruption Postnatal Day 9	M	11.6%	--	--	20%
	F	--	--	--	--

Necropsy

Macroscopic Findings	Control	5 mg/m^2	50 mg/m^2	75 mg/m^2
	Preterminal/Terminal			
Stomach, milk not present	**8**	**13**	**10**	**106**
Tarsal Flexure	--	--	**1**	**5**
Diaphragmatic hernia	--	--	--	**8**
Renal Papilla not developed	--	--	--	**3**
Brain, hydrocephaly	--	--	--	7
Brain, small	--	--	--	6
Kidney, dilated pelvis	3	1	5	14
Malrotated limb	--	1	--	20

F_1 behavioral evaluation:
No significant changes in surface righting response

F_1 reproduction:
Not conducted

F_2 findings:
Not conducted

2.6.6.7 Local tolerance

2.6.6.8 Special toxicology studies
Study title: Three-day IV Irritation screening study of SCH 52365 (Temozolomide) IV Formulations in Rats

Key study findings:

- Histopathology results from tail injection sites show that all temozolomide formulations used in this study produced more venous irritation than saline control

Study no.: 01349
Volume #, and page #: Electronic submission
Conducting laboratory and location: Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation: September 24, 2001
GLP compliance: No
QA reports: No

Drug, lot #, and % purity:

Batch No.	Purity
55612-003	96.02%
55612-024	99.37%
55612-034	98.55%
55612-053	Not provided

Formulation/vehicle:
Batch No. 55612-053; Placebo Batch No. 55338-078 (without temozolomide): Composition not provided

Batch No. 55612-003; Placebo Batch No. 55338-074 (without temozolomide)

Excipient	Concentration (mg/mL)
SCH 52365	2.50
Sodium Citrate dihydrate	5.88
Hydrochloric acid, NF	2.09
Mannitol	15.0
Polysorbate 80	3.00
L-Histidine	2.00
Water for Injection	1.00

Batch No. 55612-024; Placebo Batch No. 55338-076 (without temozolomide)

Excipient	Concentration (mg/mL)
SCH 52365	2.50
Sodium Citrate dihydrate	5.88
Hydrochloric acid, NF	1.48
Mannitol	10.0
Urea	5.00
Water for Injection	1.00

Batch No 55612-034; Placebo Batch No. 55338-082 (without temozolomide)

Excipient	Concentration (mg/mL)
SCH 52365	2.50
Sodium Citrate dihydrate	5.88
Hydrochloric acid, NF	1.48
Mannitol	15.0
Polysorbate 80	3.00
L-Asparagine	4.00
Water for Injection	1.00

Batch No. 55612-053; Placebo Batch No. 55338-078 (without temozolomide)

Excipient	Concentration (mg/mL)
SCH 52365	2.50
Sodium Citrate dihydrate	5.88
Hydrochloric acid, NF	1.48
Mannitol	15.0
Polysorbate 80	3.00
L-Threonine	4.00
Water for Injection	1.00

Methods

Study design:

Doses:

Group Number	Formulation	Batch No.	Volume (mL)	Active Agent (mg/kg)	No. of Male Rats
C1	0.9% Sodium Chloride	--	13.6	0	5
C2	Placebo IV Formulation	55338-074	13.6	0	5
T2	Temozolomide IV Formulation	55612-003	13.6	34	5
C3	Placebo IV Formulation	55338-076	13.6	0	5
T3	Temozolomide IV Formulation	55612-024	13.6	34	5
C4†	Placebo IV Formulation	55338-082	13.6	0	5
T4†	Temozolomide IV Formulation	55612-034	13.6	34	5
C5	Placebo IV Formulation	55338-078	13.6	0	5
T5	Temozolomide IV Formulation	55621-053	13.6	34	5

†Clinical Temodar batches based on this formulation

Schedule: Daily x3
Species/strain: SD Rat
Route and infusion rate: Intravenous bolus injection (tail vein)
Vehicle: See Formulation/Vehicle section above
Age: 6 weeks old
Weight: ♂: 150.9 – 190.3 g

Observation and Times:

Clinical signs: Daily
Body Weight: Week -1, Days 0, 3
Food Consumption: Week -1, Days 0, 3
Gross Pathology: Abdominal, thoracic, cranial cavities; injection site
Histopathology: Injection sites (tails)

Results:

Mortality:

Day	Animal Number	Sex	Group	Sponsor attribution
1	102M	M	C1 (Saline)	Died after dosing
1	3005M	M	C3 (Placebo)	Died 2 h after dosing

Clinical Signs No significant findings

Gross Pathology: No significant findings

Histopathology:

	Group:	C1	C2	T2	C3	T3	C4†	T4†	C5	T5
Microscopic Finding	Grade	All findings for injection sites only (tail vein) **Injection site 1**/Injection site 2/*Injection site 3*								
Cellular infiltration, mixed cell	minimal	**1**	1	1/*1*	**3**/1	2	**3**	--	*1*	--
	mild	--	--	--	--	--	--	--	--	*1*
Cellular infiltration, neutrophilic	minimal	1	2	2	--	--	--	2	**1**	**1**/1/*2*
Proliferation, intimal	minimal	--	--	**1**	--	--	--	--	--	--
Necrosis, vascular, focal	minimal	--	--	1/*1*	***1/1***	--	*1*	--	--	*1*
Inflammation, Fibrinous, perivascular	minimal	--	--	**1**	**1**	--	--	--	--	--
Hemorrhage, perivascular	minimal	--	1	--	**1**/1/*1*	--	--	1	--	1
	mild	--	2	--	--	--	--	--	--	--

†Clinical Temodar batches based on this formulation

Study title: Intra-arterial tolerance study of SCH 52365 IV Formulation in Rabbits (Study #02042)

Key study findings:

- Drug product not used in this study because administration of placebo formulation had to be stopped due to ethical concerns
- Placebo IV formulation caused significant clinical observations (struggling and vocalization)
- Both saline and placebo intra-arterial injections produced significant intra-arterial irritation

---

Study title: Intravenous tolerance study of SCH 52365 IV Formulation in Rabbits
Key study findings:

- Temodar IV formulation and placebo IV formulation caused minimal to mild venous irritation
- Rabbits injected with temodar IV formulation and placebo IV formulation exhibited clinical symptoms of injection site irritation
- Saline and positive control, cefotoxin, caused no detectable irritation.

Study no.: 02044
Volume #, and page #: Electronic submission
Conducting laboratory and location: (b) (4)
Date of study initiation: March 15, 2002
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: Batch No. 78012/104.9%
Formulation/vehicle:

SCH 52365 Placebo Powder for Injection

Component	Amt per Vial
Mannitol USP	(b) (4)
L-threonine USP	
Polysorbate 80 NF	
Sodium Citrate Dihydrate USP	
Hydrochloric Acid NF	
Water for Injection USP, q.s.	

Methods
Study design:
Doses:

Group Number	Formulation	Volume (mL)	Active Agent (mg)	No. of Male Rabbits
1	0.9% Sodium Chloride	0.5	0	4
2	Placebo IV Formulation	0.5	0	4
3	Temozolomide IV Formulation	0.5	1.25	4
4	Cefoxitin	0.5	100	4

Schedule: Single dose
Species/strain: New Zealand White Rabbit
Route and infusion rate: Intravenous bolus injection (marginal vein)
Vehicle: See Formulation/Vehicle section above
Age: Approximately 15 weeks
Weight: ♂: 2.1 – 2.6 kg

Observation and Times:
Clinical signs: 1, 2 and 24 h post-dose
Intravenous Irritation: 1, 2 and 24 h post-dose
Gross Pathology: Scheduled euthanasia
Histopathology: Scheduled euthanasia

Venous irritation grading scale used:

Grade	Clinical Sign
0	Normal, no change other than associated injection trauma
1	Slightly reddened, irritation is limited to area of artery distal to the injection site, not more than 25% of the area of the ear
2	Red without swelling but involving 25 to 100% of the area of the ear
3	Deep red to purple with discernible swelling
4	Pronounced purple discoloration and swelling

Results:
Mortality: All dosed animals survived to scheduled euthanasia

Clinical Signs:

Sign	Saline	Placebo	Temozolomide	Cefotoxin
Total Occurrence/No. of animals				
Injection site sensitive to touch	--	--	1/1	--
Struggled during dosing	--	2/2	4/4	--

Intravenous Irritation:

	Group:	Saline			Placebo			Temozolomide			Cefotoxin		
	Timepoint (h):	1	2	24	1	2	24	1	2	24	1	2	24
Sign		No. Animals Affected (4 animals/group)											
Grade 1 Intravenous Irritation		--	--	--	--	--	2	1	1	2	--	--	--
Grade 2 Intravenous Irritation		--	--	--	--	--	1	--	2	--	--	--	--

Gross Pathology:

Microscopic Findings		Saline	Placebo	Temozolomide	Cefotoxin
	Grade	No. Animals Affected (4 animals/group)			
Injection site, discolored, purple	Present	--	--	1	--

Histopathology: No significant findings

Study title: Exploratory Intravenous Tolerance Study of SCH 52365 Placebo in Rabbits
Key study findings:

- The study refers to previous study #2044, which used a SCH 52365 Placebo IV Formulation with a pH of 4
- The present study tests a new SCH 52365 Placebo IV formulation with a pH of 7
- No venous irritation detected in two rabbits injected with new pH 7 formulation

Study no.: 02267
Volume #, and page #: Electronic submission
Conducting laboratory and location: Schering-Plough Research Institute, Lafayette, NJ

Date of study initiation: October 1, 2002
GLP compliance: No
QA reports: No
Drug, lot #, and % purity: No drug used; Placebo formulation only
Formulation/vehicle:
SCH 52365 Placebo Powder for Injection pH 7.

Component	Amt per Vial
Mannitol USP	(b) (4)
L-threonine USP	
Polysorbate 80 NF	
Sodium Citrate Dihydrate USP	
Hydrochloric Acid NF†	
Water for Injection USP, q.s.	

†The sponsor states that placebo formulation was exactly as the formulation used in study 2044. However, the pH in the present study was manipulated, and some change in HCL concentration or the addition of a base, such as NaOH, must have taken place. How pH was changed in the present study's formulation is not specified.

Methods
Doses:

Group Number	Formulation	Volume (mL)	Active Agent (mg)	No. of Female Rabbits
1	Placebo IV Formulation	0.5	0	2

Schedule: Single dose
Species/strain: New Zealand White Rabbit
Route and infusion rate: Intravenous bolus injection (marginal vein)
Vehicle: See Formulation/Vehicle section above
Age: Adult (age not specified)
Weight: ♂: 2 – 5 kg

Observation and Times:
Clinical signs: Day of injection
Body Weight: Day of injection
Intravenous Irritation: Immediately after injection

Results: No reaction was observed in either rabbit after injection with pH 7 Temodar Placebo

Study title: Intravenous Tolerance Study of SCH 52365 Placebo and Dacarbazine in Rabbits

Key study findings:

- Clinical signs of struggling during dosing were observed for SCH 52365 Placebo formulation and positive control (dacarbazine)
- No significant differences in irritation were found in gross pathology or histopathology between SCH 52365 Placebo formulation, the positive control, dacarbazine, and the saline negative control

Study no.: 02512
Volume #, and page #: Electronic submission
Conducting laboratory and location: (b) (4)
Date of study initiation: August 14, 2002
GLP compliance: No
QA reports: Yes
Drug, lot #, and % purity: Batch 78012-147; % purity not provided
Formulation/vehicle:
Saline control: 0.9% Sodium Chloride for Injection, U.S.P.

SCH 52365 Placebo Powder for Injection

Component	Amt per Vial
Mannitol USP	(b) (4)
L-threonine USP	
Polysorbate 80 NF	
Sodium Citrate Dihydrate USP	
Hydrochloric Acid NF	
Water for Injection USP, q.s.	

Methods
Study design:
Doses:

Group Number	Formulation	Volume (mL)	Active Agent (mg)	No. of Male Rabbits
1	0.9% Sodium Chloride	0.5	0	4
2	Placebo IV Formulation	0.5	0	4
3	Dacarbazine	0.5	5	4

Schedule: Single dose
Species/strain: New Zealand White Rabbit
Route and infusion rate: Intravenous bolus injection (marginal vein)
Vehicle: See Formulation/Vehicle section above
Age: Approximately 13 weeks
Weight: ♂: 2.5 – 2.8 kg

Observation and Times:

Clinical signs: 1, 2 and 24 h post-dose
Body Weight: Day 1
Gross Pathology: Scheduled euthanasia
Histopathology: Scheduled euthanasia

Venous irritation grading scale used:

Grade	Clinical Sign
0	Normal, no change other than associated injection trauma
1	Slightly reddened, irritation is limited to area of artery distal to the injection site, not more than 25% of the area of the ear
2	Red without swelling but involving 25 to 100% of the area of the ear
3	Deep red to purple with discernible swelling
4	Pronounced purple discoloration and swelling

Results:

Mortality: All animals survived to scheduled euthanasia
Clinical Signs:

Sign	Saline	Placebo	Decarbazine
No. Animals (4 Aimals/Group)			
Struggled during dosing	--	3	3
Vocalization	--	--	1

Body Weights: No significant changes
Gross Pathology: No significant changes
Histopathology: Injection site only (no significant findings)

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

This application depends heavily on the pharmacology/toxicology program submitted with NDA 21-029 for the tablet formulation of temozolomide. Although these nonclinical studies were done via the oral route, temozolomide is nearly 100% bioavailable in dogs, rats, and humans, therefore allowing these toxicology studies to support an application for temozolomide dosing via the intravenous route.

The nonclinical studies reviewed herein include the venous irritation studies required for a change in route from oral to intravenous dosing. A repeat-dose study of intravenous temozolomide in the rat was also reviewed. The data submitted by the sponsor demonstrates that while some mild to moderate venous irritation occurs with intravenous administration of temozolomide, no new toxicities arise in comparison to oral administration.

Additional repeat-dose studies included with this application were reviewed because of the presence of (b) (4) impurities, (b) (4) in the proposed clinical specification. It is important to note that none of the non-clinical or clinical studies submitted with this NDA used drug batches that contained (b) (4) at levels comparable to those presented in the proposed clinical specification. The sponsor should conduct a rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4). This study should mimic a single cycle of the approved clinical schedule (daily x5 every 28 days) and utilize concentrations of (b) (4) which exceed (b) (4) respectively, to adequately qualify these impurities at levels proposed in the current specifications for drug substance and drug product, respectively.

Unresolved toxicology issues: Qualification of (b) (4)

Recommendations:
The submitted nonclinical studies adequately support the use of temozolomide (Temodar™) for the treatment of newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and as maintenance therapy and in the treatment of refractory anaplastic astrocytoma.

Suggested labeling:
Proposed changes to the label are included in the Executive Summary on page 3 of this review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hans Rosenfeldt
11/12/2008 04:03:22 PM
PHARMACOLOGIST

Leigh Verbois
11/12/2008 04:05:02 PM
PHARMACOLOGIST