# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-277**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| **NDA:** | 22-277/N-000 |
| **BRAND NAME:** | TEMODAR (b) (4) for Injection |
| **GENERIC NAME:** | Temozolomide |
| **DOSAGE FORM/STRENGTH:** | 100 mg Lyophilized Powder in Vials |
| **INDICATIONS:** | Anaplastic Astrocytoma and Newly Diagnosed Glioblastoma Multiforme |
| **SUBMISSION TYPE:** | NDA-Original |
| **APPLICANT:** | Schering-Plough |
| **SUBMISSION DATE:** | 23-Jan-2008 |
| **OCP DIVISION:** | Division of Clinical Pharmacology 5 |
| **DDOP DIVISION:** | Division of Drug Oncology Products |
| **OCP REVIEWER:** | Sophia Abraham, Ph.D. |
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**TABLE OF CONTENTS:**



## 1. Executive Summary

The Applicant seeks approval of a New Drug Application (NDA 22-277/N-000) for TEMODAR (b) (4) for Injection under Section 505b(1) of the Food, Drug, and Cosmetic Act (21 CFR 314.50) for the same indications and at the same dosage and regimens as for the approved oral capsule drug product. TEMODAR (b) (4) for Injection is to be administered intravenously (IV)

over a 1.5-hour infusion at the same dosage and regimen as for the oral capsule product.

The Applicant did not conduct any efficacy and/or safety clinical studies in support of TEMODAR (b) (4) for Injection. The decision for the approval of this NDA submission is solely based on the results obtained from the pivotal bioequivalence Study P02467.

The **pivotal** bioequivalence Study P02467 compared the exposure of the prodrug, temozolomide, and its cytotoxic alkylating active metabolite, *3-methyl-(triazen-1-yl)imidazole-4-carboxamide* (MTIC) following a single dose of temozolomide (150 mg/m$^2$/day) administered either as a 1.5-hour infusion of the new IV formulation (Test) or as the approved oral capsule formulation (Reference) in 22 subjects with primary CNS malignancies in a two-period, crossover design. According the FDA Guidance for Industry on the BA and BE Studies for Orally Administered Drug Products — General Considerations (http://www.fda.gov/cder/guidance/5356fnl.pdf), the new IV dosage form infused over 1.5 hours was found to be bioequivalent to the approved oral formulation (as capsules) at the same dosage and regimen (150 mg/m$^2$/day) with respect to $C_{max}$ and $AUC_{inf}$ for both temozolomide and MTIC based on the data from 21 subjects (one subject was an outlier and was removed from the data analysis). The 90% CIs estimated for the geometric mean $C_{max}$ and $AUC_{inf}$ ratios (IV/PO) were within the bioequivalence range of 80-125% for both temozolomide and MTIC.

In addition, the Applicant revised the current package insert for TEMODAR and submitted it in the PLR format (see Appendix 4.1).

### 1.1 Recommendation

TEMODAR (b) (4) for Injection infused over 1.5 hours is bioequivalent to TEMODAR Oral Capsules at the same dosage and regimen (150 mg/m$^2$/day). Thus, NDA 22-277/N-000 submitted for TEMODAR (b) (4) for Injection is acceptable from the clinical pharmacology perspective. Please forward the detailed OCP Labeling Recommendations as outlined under Section 3 of the review (pp. 20-22) to the Applicant.

### 1.2 Phase 4 Commitments

[None]

### 1.3 SUMMARY OF CLINICAL PHARMACOLOGY

Temozolomide is an imidazole tetrazine derivative of the alkylating agent dacarbazine. Temozolomide is not directly active but undergoes rapid, spontaneous, non-enzymatic conversion at physiologic pH to the cytotoxic compound, monomethyl triazeno imidazole carboxamide (MTIC). Both temozolomide and dacarbazine are prodrugs of MTIC. Unlike dacarbazine, temozolomide does not require metabolic activation by the cytochrome P450. The cytotoxicity of MTIC is primarily due to the alkylation (methylation) of DNA, mainly at the $O^6$ position of guanine. The $O^6$-methylguanine formation inhibits DNA replication through errant repair of the methyladduct which eventually causes cell death via stimulation of p53 and apoptosis.

TEMODAR Capsules (5, 20, 100, and 250 mg strengths) received an accelerated approval for the treatment of refractory anaplastic astrocytoma on 02-Aug-1999 and a full approval for the treatment of newly diagnosed glioblastoma multiforme on 15-Mar-2005 under NDA 21-029. The approved dosage for refractory anaplastic astrocytoma is 150 mg/m$^2$/day orally once daily for 5 consecutive days, repeated every 28 days. Patients with newly diagnosed glioblastoma multiforme are to be administered temozolomide orally at 75 mg/m$^2$ once daily for 42 days concomitantly with focal radiotherapy, followed by maintenance doses of 150 mg/m$^2$/day for 5 days every 28 days for 6 cycles.

The overall clinical pharmacology information on TEMPDAR Oral Capsules was addressed in the original NDA 21-029 submission dated 12-Aug-1998.

The most common non-hematological adverse events associated with TEMODAR were nausea and vomiting (original NDA 21-029). These effects were usually mild to moderate (grade 1 to 2). The incidence of severe nausea and vomiting is around 4% each.

The Applicant has developed a new intravenous (IV) formulation of temozolomide (Viz., "**TEMODAR (b) (4) for Injection**") to be used in patients who cannot swallow the oral capsules (e.g., patients with dysphagia) and in patients who cannot tolerate the oral capsules for other reasons that may occur in association with glioma (e.g., nausea and vomiting). TEMODAR (b) (4) for Injection contains 100 mg/vial of lyophilized powder which is to be reconstituted with Sterile Water for Injection before use. The reconstituted product contains 2.5 mg/mL of temozolomide.

TEMODAR (b) (4) for Injection is to be used for the same indications at the same dosage and regimen as for the oral capsules. In support of the current NDA 22-277 submission for TEMODAR (b) (4) for Injection, the Applicant conducted a **pivotal** bioequivalence study (**Study P02467**) to compare the exposure of temozolomide and its active metabolite, *3-methyl-(triazen-1-yl)imidazole-4-carboxamide* (MTIC) after a 1.5-hour IV infusion of temozolomide to that after the oral capsules. Study P02467 was a Phase 1, randomized, multi-center, open-label, two-period, crossover study in 22 patients with primary CNS malignancies. On Days 1, 2, and 5, patients received 200 mg/m$^2$/day of temozolomide once daily for 5 days of each 28-day treatment cycle. On Days 3 and 4, patients were randomized to receive a single 150 mg/m$^2$/day dose of temozolomide **either** as a **1.5-hour** intravenous infusion (Test) on one day **or** as the approved oral capsule formulation (Reference) on the other day. Based on the data from 21 subjects, the results of this study demonstrated that TEMODAR (b) (4) for Injection infused over 1.5 hours met the bioequivalence criteria when compared to the approved oral capsule formulation at the same dosage and regimen (150 mg/m$^2$/day) with respect to $C_{max}$ and $AUC_{inf}$ for both temozolomide and MTIC. The 90% CIs estimated for the geometric mean $C_{max}$ and $AUC_{inf}$ ratios (IV/PO) were within the bioequivalence range of 80-125% for both temozolomide and MTIC. **Subject 122** (who had MTIC concentrations on Day 4 at or below assay LLOQ for all samples) was considered an outlier and was excluded from the data analysis.

The Applicant also conducted a pilot study (**Study P02466**) to determine the relative bioavailability of IV temozolomide compared to the approved oral capsule in 13 patients with primary CNS malignancies. On Days 1, 2, and 5, patients received 200 mg/m$^2$/day of temozolomide orally once daily for 5 days of each 28-day treatment cycle. On Days 3 and 4, patients were randomized to receive a single 150 mg/m$^2$/day dose of temozolomide either orally on one day or as a **1-hour** IV infusion on the other day. The results of this study showed that the 90% CI estimates for the geometric mean $AUC_{inf}$ ratio (IV/PO) for temozolomide fell within of the acceptable bioequivalence range of 80-125%. However, the corresponding 90% CI estimates for the geometric mean $C_{max}$ ratio (IV/PO) fall outside bioequivalence range (90% CI=100-131%). Based on a population PK analysis and simulations of data obtained in this study, it was demonstrated that a **1.5-hour** IV infusion of temozolomide would have a comparable $C_{max}$ value to that after the oral formulation (see Pharmacometric Review, pp. 35). Therefore, the 1.5-hour IV infusion was used in the pivotal bioequivalence **Study P02467**.

## 2. Question-Based Review (QBR)

**The following questions were addressed in support of the current NDA 22-277 submission for the new IV formulation. For any other questions, please refer to the original NDA 21-029 submission dated 12-Aug-1998.**

- **What is the new formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?**

The new dosage form is known as "TEMODAR (b) (4) for Injection". It will be available for marketing as a 100 mg lyophilized powder in vials. Each vial will be reconstituted with Sterile Water for Injection at the time of use. Upon reconstitution, TEMODAR (b) (4) for Injection is stable for up to 14 hours at room temperature including the infusion time. The reconstituted solution contains 2.5 mg/mL of temozolomide. The composition of TEMODAR (b) (4) for Injection is provided in Table 1.

**TABLE 1. Composition of Temozolomide (b) (4) for Injection**

| | Amount per Vial | Function |
|---|---|---|
| **Active Ingredient** | | |
| Temozolomide | 100.0 mg | Active |
| **Inactive Ingredients** | | |
| Mannitol USP | 600.0 mg | (b) (4) |
| 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. ad | (b) (4) mL | |

*(b) (4)

- **What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**

No efficacy and/or safety clinical studies were conducted for the new IV dosage form. The decision for the approval of this NDA is solely based on the results obtained from the pivotal bioequivalence (BE) Study P02467.

In support of the new IV dosage form (TEMODAR (b) (4) for Injection), the Applicant submitted a pivotal and pilot BE studies (**Studies P02467 and P02466, respectively**) comparing the new intravenous (IV) formulation (TEMODAR (b) (4) for Injection) to the approved oral Capsule formulation.

- **Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Both temozolomide and its active metabolite, *3-methyl-(triazen-1-yl)imidazole-4-carboxamide* (MTIC), were measured in plasma samples collected in the two bioequivalence Studies P02466 and P02467.

- **What is the relative bioavailability of the new IV formulation to the approved oral capsule formulation?**

The Applicant conducted two bioequivalence studies, a pivotal (P02467) and a pilot (P02466) studies.

**Pivotal Bioequivalence Study P02467:**

This was a randomized, multi-center, open-label, two-period, crossover, Phase 1 study in 22 patients with primary CNS malignancies (10 females and 12 males). Patients were randomized to receive either of the following two treatment sequences separated by a 24-hour washout period:

- **Treatment A:** Oral temozolomide 200 mg/m$^2$/day on Days 1, 2, and 5
  **IV** temozolomide 150 mg/m$^2$/day over a 1.5-hour infusion on Day 3
  **Oral** temozolomide 150 mg/m$^2$/day on Day 4
- **Treatment B:** Oral temozolomide 200 mg/m$^2$/day on Days 1, 2, and 5
  **Oral** temozolomide 150 mg/m$^2$/day on Day 3
  **IV** temozolomide 150 mg/m$^2$/day over a 1.5-hour infusion on Day 4

As temozolomide has a short half-life of approximately 1.8 hours and there is no accumulation in plasma after once-daily dosing (Original NDA), the 24-hour washout period (approximately 12 half lives between each dose) used in this study was sufficient to assure no carryover effect prior to the next dose. The pharmacokinetics (PK) of temozolomide and its active metabolite, MTIC, were assessed on Day 3 and Day 4. On PK sampling days (Days 3 and 4), patients were fasted for a minimum of 8 hours before each dose and continued fasting for 4 hours afterward. On PK sampling days (Days 3 and 4), concomitant medications were delayed for 4 hours post-dose. On

Days 3 and 4, blood samples were collected pre-dosing and up to 8 hours after dosing. Plasma samples were assayed for temozolomide and MTIC using a validated High-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay method (see Section 2.6 of this review).

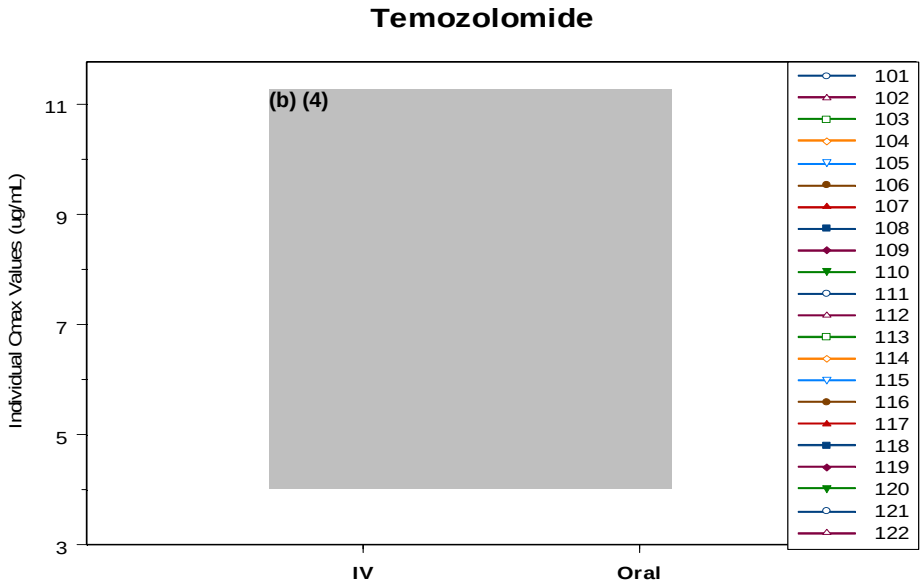
Of the 22 patients enrolled and randomized to receive the study drug, nineteen (19) were considered to be evaluable for PK and the other three (Subject #: 107, 121, and 122) were excluded from the PK analysis due to protocol's deviations (see below).

- **Subject 107:** A female patient who had pre-dose temozolomide and MTIC concentrations of 45% and 15%, respectively, of the corresponding $C_{max}$ values for unknown reasons on Day 4.
- **Subject 121:** A female patient who had drug administered in 3 non-continuous infusions. Thus, she did not receive the nominal dose (±10%) within the nominal (continuous) 1.5-hour infusion.
- **Subject 122:** A female patient who had MTIC concentrations on Day 4 at or below assay LLOQ for all samples.

The target sample size was 20 subjects. Assuming an intrasubject coefficient of variation (%CV) of 20%, a sample size of 20 subjects was selected to provide at least 90% power for the 90% CI of the ratio of the treatment means for derived PK parameters to fall within the 80% to 125% confidence range. The Applicant included 19 patients in the PK and statistical evaluations in this study.

**Results:**
Individual $C_{max}$ and $AUC_{inf}$ values versus treatments in all patients (including Subjects 107, 121, and 122) are shown in Figure 1 and 2. The mean plasma concentration/time profiles are shown in Figure 3. The mean PK parameters for temozolomide and MTIC are shown in Tables 2-7.

**FIGURE 1. Individual $C_{max}$ Values Following IN and PO administration of Temozolomide to 22 Patients**



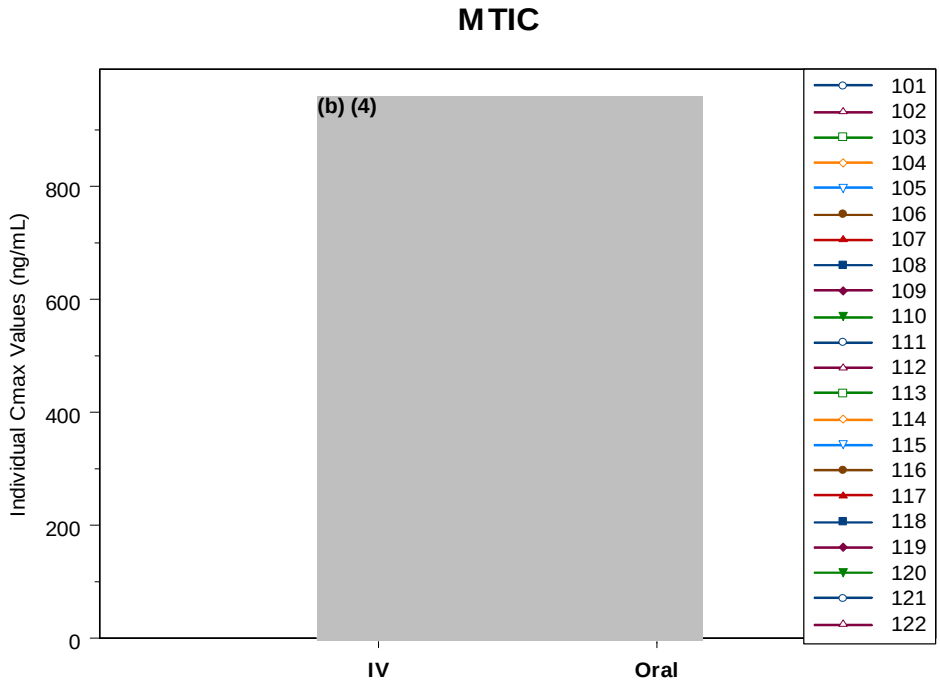



**FIGURE 2. Individual $AUC_{inf}$ Values Following IN and PO administration of Temozolomide to 22 Patients**

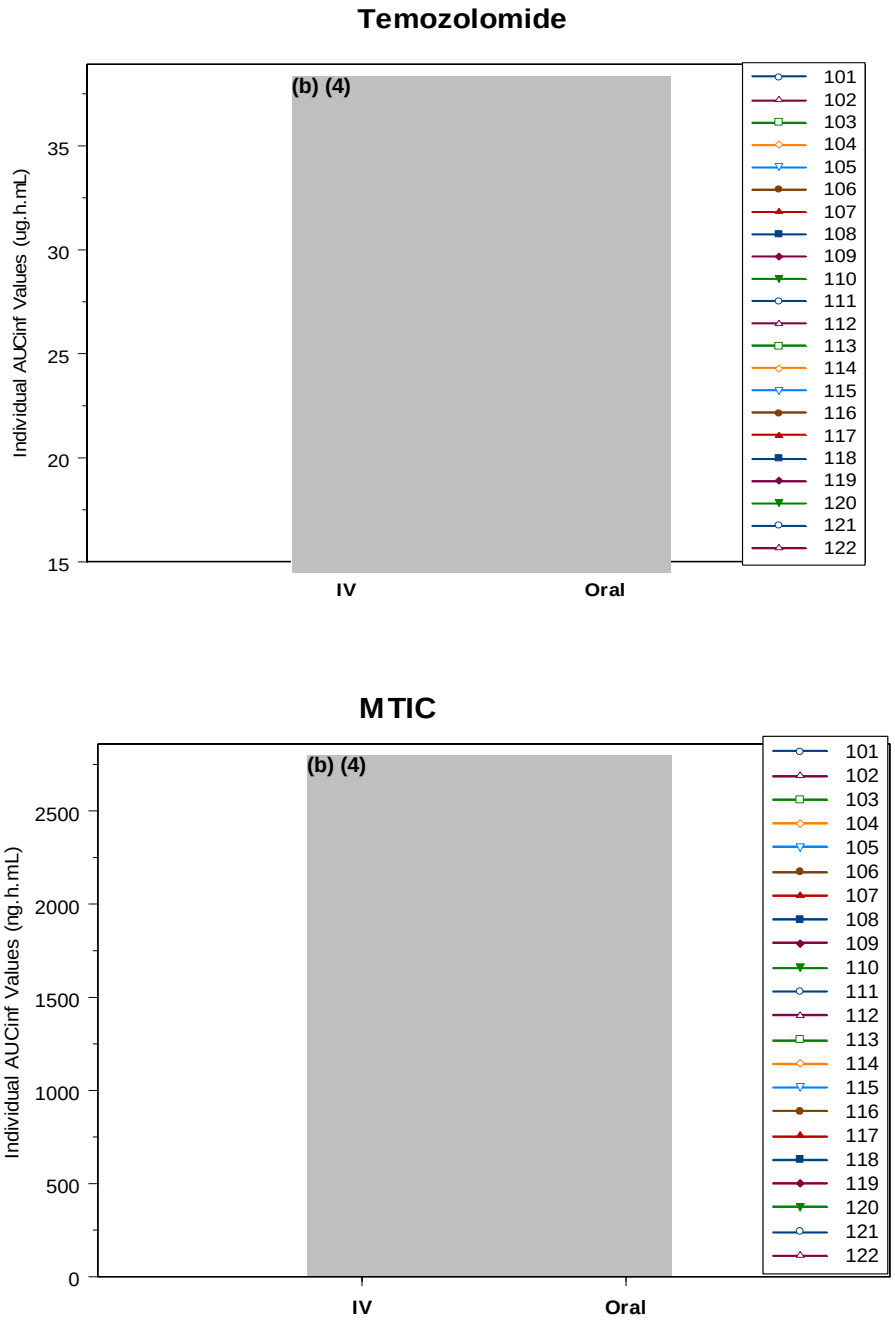


**TABLE 2. Individual $C_{max}$, $AUC_{0-t}$, and $AUC_{inf}$ Values for Subjects 107, 121, and 122**

| | Temozolomide | | | | | |
|---|---|---|---|---|---|---|
| | IV | | | PO | | |
| Subject No. | $C_{max}$ (µg/mL) | $AUC_{0-t}$ (µg h/mL) | $AUC_{inf}$ (µg h/mL) | $C_{max}$ (µg/mL) | $AUC_{0-t}$ µg.h/mL) | $AUC_{inf}$ (µg.h/mL) |
| 107 | (b) (4) | | | | | |
| 121 | | | | | | |
| 122 | | | | | | |

**TABLE 3. Individual $C_{max}$, $AUC_{0-t}$, and $AUC_{inf}$ Values for Subjects 107, 121, and 122**

| | MTIC | | | | | |
|---|---|---|---|---|---|---|
| | IV | | | PO | | |
| Subject No. | $C_{max}$ (ng/mL) | $AUC_{0-t}$ (ng h/mL) | $AUC_{inf}$ (ng h/mL) | $C_{max}$ (ng/mL) | $AUC_{0-t}$ (ng h/mL) | $AUC_{inf}$ (ng h/mL) |
| 107 | (b) (4) | | | | | |
| 121 | | | | | | |
| 122 | | | | | | |

NA=Not available

**Subject 107:** A female patient who had pre-dose temozolomide and MTIC concentrations of 45% and 15%, respectively, of the corresponding $C_{max}$ values for unknown reasons on Day 4.

**Subject 121:** A female patient who had drug administered in 3 non-continuous infusions. Thus, she did not receive the nominal dose (±10%) within the nominal (continuous) 1.5-hour infusion.

**Subject 122:** A female patient who had MTIC concentrations on Day 4 at or below assay LLOQ for all samples.

**FIGURE 3. Mean Plasma Concentration/Time Profiles after a Single 150 mg/m$^2$ Dose of Temozolomide either as a 1.5-Hour IV Infusion or Oral Capsules (Excluding Subjects 107, 121, and 122)**

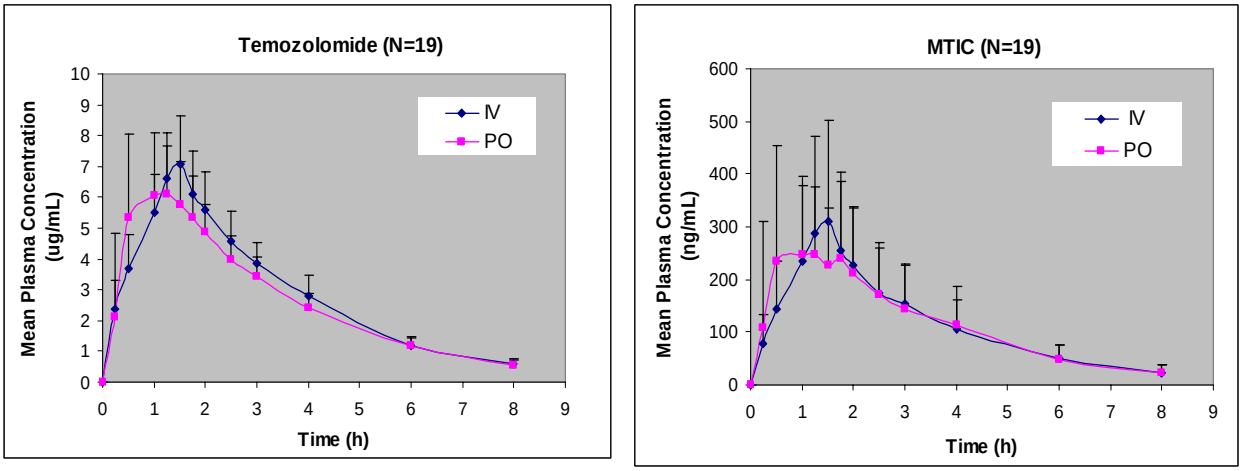


**TABLE 4. Arithmetic Mean±SD (%CV) PK Parameters for Temozolomide Following IV and Oral Administrations of a single 150 mg/m$^2$ Dose of Temozolomide in 19 Subjects**

| PK Parameter | Temozolomide | |
|---|---|---|
| | 1.5-hour IV Infusion | PO |
| $C_{max}$ (µg/mL) | 7.4±1.6 (21%) | 7.7±1.4 (19%) |
| *$T_{max}$ (h) | 1.5 (0.92-2.0) | 1.0 (0.25-2.0) |
| $AUC_{0-t}$ (µg•h/mL) | 23.4±4.1 (18%) | 22.0±3.2 (14%) |
| $AUC_{inf}$ (µg•h/mL) | 25.0±4.5 (18%) | 23.6±3.4 (15%) |
| t½ (h) | 1.8±0.22 (12%) | 1.9±0.26 (13%) |
| CL(/F) (L/h/ m$^2$) | 6.2±1.1 (17%) | 6.5±0.98 (15%) |
| $V_d$(/F) (L/m$^2$) | 16.0±2.5 (15%) | 17.7±2.6 (15%) |

*Median (range)

**TABLE 5. Arithmetic Mean±SD (%CV) PK Parameters for MTIC Following IV and Oral Administrations of a single 150 mg/m$^2$ Dose of Temozolomide in 19 Subjects**

| PK Parameter | MTIC | |
|---|---|---|
| | 1.5-hour IV Infusion | PO |
| $C_{max}$ (ng/mL) | 320±194 (61%) | 333±207 (62%) |
| *$T_{max}$ (h) | 1.5 (1.25-1.75) | 1.0 (0.25-2.0) |
| $AUC_{0-t}$ (ng•h/mL) | 941±502 (53%) | 944±567 (60%) |
| $AUC_{inf}$ (ng•h/mL) | 1004±546 (54%) | 1003±605 (60%) |
| t½ (h) | 1.8±0.29 (16%) | 1.8±0.19 (11%) |

*Median (range)

The results of this study showed that plasma concentrations of temozolomide and its active metabolite, MTIC, decline rapidly following both IV and oral administrations. Mean elimination half-lives are 1.8 hours for both temozolomide and MTIC. The systemic exposure of MTIC is low with a mean $AUC_{(metabolite/parent)}$ ratio of 4%.

Temozolomide is rapidly and completely absorbed following oral administration with a mean absolute bioavailability value of 95±7%,

The apparent volume of distribution and apparent plasma clearance values for temozolomide following oral administration are comparable to those obtained following IV administration at same dosage and regimen (150 mg/m$^2$/day).

**TABLE 6. Geometric Mean Ratios and 90% Confidence Intervals (CI) for Temozolomide in 19 Subjects**

| | Geometric Mean | | | |
|---|---|---|---|---|
| **PK Parameter** | **IV (N=19)** | **PO (N=19)** | **Ratio (IV/PO)** | **90% CI** |
| $C_{max}$ (μg/mL) | 7.28 | 7.53 | 0.97 | 91-102% |
| $AUC_{0-t}$ (μg•h/mL) | 23.13 | 21.82 | 1.06 | 103-109% |
| $AUC_{inf}$ (μg•h/mL) | 24.63 | 23.38 | 1.05 | 102-108% |

**TABLE 7. Geometric Mean Ratios and 90% Confidence Intervals (CI) for MTIC in 19 Subjects**

| | Geometric Mean | | | |
|---|---|---|---|---|
| **PK Parameter** | **IV (N=19)** | **PO (N=19)** | **Ratio (IV/PO)** | **90% CI** |
| $C_{max}$ (ng/mL) | 275 | 282 | 0.98 | 90-105% |
| $AUC_{0-t}$ (ng•h/mL) | 837 | 815 | 1.03 | 97-108% |
| $AUC_{inf}$ (ng•h/mL) | 890 | 863 | 1.03 | 98-108% |

Based on data from 19 subjects, the new IV formulation is equivalent to the approved oral capsule formulation at same dosage and regimen with respect to $C_{max}$, $AUC_{0-t}$, and $AUC_{inf}$ for both temozolomide and MTIC. The 90% CIs for the geometric mean $C_{max}$, $AUC_{0-t}$, and $AUC_{inf}$ ratios (IV/PO) were within the acceptable BE range of 80-125%.

**The PK data were reanalyzed by the reviewer** for both temozolomide and MTIC. The point estimates and the 90% confidence intervals (CI) were determined for all subjects participated in the study (N=22) and after separately excluding Subjects #107, 121, or 122 (total N=21). The results are shown in Tables 8-15.

**TABLE 8. Geometric Mean Ratios and 90% Confidence Intervals (CI) for Temozolomide (All Subjects)**

| | Geometric Mean | | | |
|---|---|---|---|---|
| **PK Parameter** | **IV (N=22)** | **PO (N=22)** | **Ratio (IV/PO)** | **90% CI** |
| $C_{max}$ (μg/mL) | 7.28 | 7.63 | 0.95 | 89-103% |
| $AUC_{0-t}$ (μg•h/mL) | 23.36 | 22.28 | 1.05 | 101-109% |
| $AUC_{inf}$ (μg•h/mL) | 24.85 | 23.85 | 1.04 | 100-108% |

**TABLE 9. Geometric Mean Ratios and 90% Confidence Intervals (CI) for MTIC (All Subjects)**

| | Geometric Mean | | | |
|---|---|---|---|---|
| **PK Parameter** | **IV (N=22)** | **PO (N=22)** | **Ratio (IV/PO)** | **90% CI** |
| $C_{max}$ (ng/mL) | 233 | 293 | 0.79 | 54-116% |
| $AUC_{0-t}$ (ng•h/mL) | 609 | 850 | 0.72 | 38-132% |
| *$AUC_{inf}$ (ng•h/mL) | 926 | 902 | 1.00 | 98-107% |

*Subject 122 had no $AUC_{inf}$ value (see Table 3)

**TABLE 10. Geometric Mean Ratios and 90% Confidence Intervals (CI) for Temozolomide (Excluding Subject 107)**

| | Geometric Mean | | | |
|---|---|---|---|---|
| **PK Parameter** | **IV (N=21)** | **PO (N=21)** | **Ratio (IV/PO)** | **90% CI** |
| $C_{max}$ (μg/mL) | 7.29 | 7.78 | 0.97 | 87-101% |
| $AUC_{0-t}$ (μg•h/mL) | 23.47 | 22.53 | 1.01 | 100-108% |
| $AUC_{inf}$ (μg•h/mL) | 24.14 | 24.97 | 0.99 | 99-108% |

**TABLE 11. Geometric Mean Ratios and 90% Confidence Intervals (CI) for MTIC (Excluding Subject 107)**

| | Geometric Mean | | | |
|---|---|---|---|---|
| **PK Parameter** | **IV (N=21)** | **PO (N=21)** | **Ratio (IV/PO)** | **90% CI** |
| $C_{max}$ (ng/mL) | 239 | 301 | 0.96 | 53-118% |
| $AUC_{0-t}$ (ng•h/mL) | 628 | 868 | 0.95 | 37-138% |
| $AUC_{inf}$ (ng•h/mL) | 951 | 920 | 1.00 | 99-108% |

*Subject 122 had no $AUC_{inf}$ value (see Table 3)

**TABLE 12. Geometric Mean Ratios and 90% Confidence Intervals (CI) for Temozolomide (Excluding Subject 121)**

| | Geometric Mean | | | |
|---|---|---|---|---|
| **PK Parameter** | **IV (N=21)** | **PO (N=21)** | **Ratio (IV/PO)** | **90% CI** |
| $C_{max}$ (μg/mL) | 7.21 | 7.51 | 0.96 | 89-104% |
| $AUC_{0-t}$ (μg•h/mL) | 22.96 | 21.86 | 1.05 | 101-109% |
| $AUC_{inf}$ (μg•h/mL) | 24.41 | 23.41 | 1.04 | 99-108% |

**TABLE 13. Geometric Mean Ratios and 90% Confidence Intervals (CI) for MTIC (Excluding Subject 121)**

| | Geometric Mean | | | |
|---|---|---|---|---|
| **PK Parameter** | **IV (N=21)** | **PO (N=21)** | **Ratio (IV/PO)** | **90% CI** |
| $C_{max}$ (ng/mL) | 225 | 286 | 0.78 | 52-117% |
| $AUC_{0-t}$ (ng•h/mL) | 588 | 826 | 0.71 | 37-136% |
| $AUC_{inf}$ (ng•h/mL) | 894 | 875 | 1.02 | 97-107% |

*Subject 122 had no $AUC_{inf}$ value (see Table 3)

**TABLE 14. Geometric Mean Ratios and 90% Confidence Intervals (CI) for Temozolomide (Excluding Subject 122)**

| | Geometric Mean | | | |
|---|---|---|---|---|
| **PK Parameter** | **IV (N=21)** | **PO (N=21)** | **Ratio (IV/PO)** | **90% CI** |
| $C_{max}$ (μg/mL) | 7.37 | 7.51 | 0.99 | 92-104% |
| $AUC_{0-t}$ (μg•h/mL) | 23.45 | 21.99 | 1.02 | 103-109% |
| $AUC_{inf}$ (μg•h/mL) | 24.95 | 23.55 | 1.02 | 102-109% |

**TABLE 15. Geometric Mean Ratios and 90% Confidence Intervals (CI) for MTIC (Excluding Subject 122)**

| | Geometric Mean | | | |
|---|---|---|---|---|
| **PK Parameter** | **IV (N=21)** | **PO (N=21)** | **Ratio (IV/PO)** | **90% CI** |
| $C_{max}$ (ng/mL) | 278 | 282 | 0.99 | 92-106% |
| $AUC_{0-t}$ (ng•h/mL) | 840 | 821 | 1.00 | 97-107% |
| $AUC_{inf}$ (ng•h/mL) | 894 | 871 | 1.00 | 98-107% |

When either all subjects were included in the data analysis or each of Subjects 107 and 121 was separately excluded from the data analysis, the new IV formulation was equivalent to the approved oral capsule formulation with respect to $C_{max}$, $AUC_{0-t}$, and $AUC_{inf}$ of temozolomide. The 90% CIs for the geometric mean $C_{max}$, $AUC_{0-t}$, and $AUC_{inf}$ ratios (IV/PO) for **temozolomide** were within the acceptable BE range of 80-125%.

The 90% CIs for the geometric mean $C_{max}$ and $AUC_{0-t}$ for **MTIC** were outside the acceptable BE range whether the analysis was performed on the data from all subjects or after excluding the data from Subjects 107 and 121. The 90% CI for the geometric mean $AUC_{inf}$ ratio (IV/PO) for **MTIC** was within the acceptable BE range of 80-125%. However, this was due to the fact that there was no $AUC_{inf}$ value estimated for MTIC for Subject 122 (see Table 3, Subject 122).

When Subject 122 was only excluded from the data analysis (total N=21), the new IV formulation was found to be equivalent to the approved oral capsule formulation with respect to $C_{max}$, $AUC_{0-t}$, and $AUC_{inf}$ for **both temozolomide and MTIC**. The 90% CIs for the geometric mean $C_{max}$, $AUC_{0-t}$, and $AUC_{inf}$ for both temozolomide and MTIC were within the acceptable BE range of 85-125%.

The FDA Guidance for Industry on the BA and BE Studies for Orally Administered Drug Products — General Considerations (http://www.fda.gov/cder/guidance/5356fnl.pdf) states that:

***"For BE studies, measurement of only the parent drug released from the dosage form, rather than the metabolite, is generally recommended."***

However, because temozolomide is a prodrug of the cytotoxic compound, MTIC, bioequivalence should be established for both compounds. We can conclude that TEMODAR (b) (4) for Injection infused over 1.5 hours at the same dosage and regimen is bioequivalent to the approved oral capsule formulation based on data from 21 subjects (after excluding Subject 122). The 90% CIs estimated for the geometric mean $C_{max}$, $AUC_{0-t}$, and $AUC_{inf}$ ratios (IV/PO) were within the bioequivalence range of 80-125% for **both temozolomide and MTIC**.

**Pilot Bioequivalence Study P02466:**

This was a pilot, Phase 1 study in 13 patients with primary CNS malignancies (10 male and 3 female). The objectives and study design for Study P02466 were exactly identical to those for the pivotal bioequivalence (BE) Study P024067 except that a 1-hour infusion was used in Study P02466 for the new IV formulation instead of 1.5-hour infusion. The Applicant used a 1.5-hour infusion in the pivotal BE Study P02467 based on population PK and simulations analyses of PK data obtained from the pilot BE Study P02466. The Applicant claims that these simulations demonstrated that the 1.5-hour infusion would have a comparable $C_{max}$ value to that observed after the approved oral capsule formulation (see the Pharmacometrics Review, pp. 35).

**Results:**

In this study, 13 patients were available for PK and statistical evaluations. However, the PK data for one subject for MTIC were excluded from these analyses for both oral and IV treatments because of improper sample procurement at the study site. The mean plasma concentration/time profiles are shown in Figure 4. The mean PK parameters for temozolomide and MTIC are shown in Tables 12-15.

**FIGURE 4. Mean Plasma Concentration/Time Profiles after a Single 150 mgm$^2$ Dose of Temozolomide either as a 1-Hour IV Infusion or Oral Capsules**

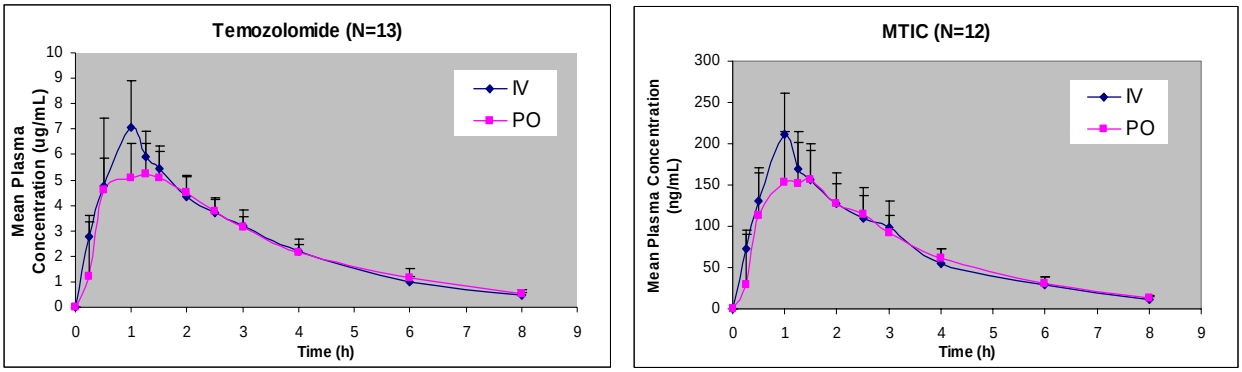


**TABLE 12. Arithmetic Mean±SD (%CV) PK Parameters for Temozolomide Following IV and Oral Administrations of a single 150 mg/m$^2$ Dose of Temozolomide in 13 Patients**

| PK Parameter | Temozolomide | |
|---|---|---|
| | 1-Hour IV Infusion | PO |
| $C_{max}$ (µg/mL) | 7.3±1.4 (19%) | 6.4±1.6 (25%) |
| *$T_{max}$ (h) | 1.0 (1.0-1.25) | 1.0 (0.25-2.0) |
| $AUC_{0-t}$ (µg h/mL) | 20.5±3.1 (15%) | 19.6±2.3 (12%) |
| $AUC_{inf}$ (µg.h/mL) | 21.9±3.5 (16%) | 21.0±2.5 (12%) |
| t½ (h) | 1.76±0.15 (8%) | 1.85±0.17 (9%) |
| CL(/F) (L/h/ m$^2$) | 7.0±1.2 (17%) | 7.25±0.95 (13%) |
| $V_d$(/F) (L/m$^2$) | 17.9±3.2 (18%) | 17.4±3.2 (17%) |

*Median (range)

**TABLE 13. Arithmetic Mean±SD (%CV) PK Parameters for MTIC Following IV and Oral Administrations of a single 150 mg/m$^2$ Dose of Temozolomide in 12 Patients**

| PK Parameter | MTIC | |
|---|---|---|
| | 1-Hour IV Infusion | PO |
| $C_{max}$ (ng/mL) | 218±48 (22%) | 184±45 (25%) |
| *$T_{max}$ (h) | 1.0 (1.0-1.5) | 1.06 (0.5-1.5) |
| $AUC_{inf}$ (ng h/mL) | 630±99 (16%) | 595±89 (15%) |
| t½ (h) | 1.73±0.28 (16%) | 1.72±0.20 (11%) |

*Median (range)

**TABLE 14. Geometric Mean Ratios and 90% Confidence Intervals (CI) for Temozolomide**

| | Geometric Mean | | | |
|---|---|---|---|---|
| PK Parameter | IV (N=13) | PO (N=13) | Ratio (IV/PO) | 90% CI |
| $C_{max}$ (µg/mL) | 7.1 | 6.2 | 1.14 | 100-131% |
| $AUC_{inf}$ (µg*h/mL) | 21.8 | 20.9 | 1.03 | 97-112% |

**TABLE 15. Geometric Mean Ratios and 90% Confidence Intervals (CI) for MTIC**

| | Geometric Mean | | | |
|---|---|---|---|---|
| **PK Parameter** | **IV (N=12)** | **PO (N=12)** | **Ratio (IV/PO)** | **90% CI** |
| $C_{max}$ (ng/mL) | 214 | 179 | 1.19 | 105-136% |
| $AUC_{inf}$ (ng*h/mL) | 607 | 580 | 1.04 | 99-111% |

The results of this study demonstrated that at the same dosage and regimen, the IV formulation infused over 1 hour is equivalent to the approved oral capsule formulation only with respect to $AUC_{inf}$. However, $C_{max}$ failed to meet the BE criteria. Following a 1-hour IV infusion, the 90% CIs of the geometric mean $AUC_{inf}$ ratio (IV/PO) were within the bioequivalence range of 80-125% for both temozolomide and MTIC. However, the 90% CIs of the geometric mean $C_{max}$ ratios (IV/PO) for both temozolomide and MTIC fell outside of the bioequivalence range: 90%CI=100-131% and 105-136%, respectively.

# 2 QUESTION BASED REVIEW

## *2.1 General Attributes of the Drug*

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?
2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?
2.1.3 What are the proposed dosage(s) and route(s) of administration?

## *2.2 General clinical pharmacology*

2.2.1 What are the design features of the clinical studies used to support dosing or claims?
2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD) and how are they measured in clinical pharmacology and clinical studies?
2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

### 2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?
2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?
2.2.4.3 Does this drug prolong the QT or QTc interval?
2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

2.2.5.3 What are the characteristics of drug absorption?

2.2.5.4 What are the characteristics of drug distribution?

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

2.2.5.6 What are the characteristics of drug metabolism?

2.2.5.7 What are the characteristics of drug excretion?

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

2.2.5.9 How do the PK parameters change with time following chronic dosing?

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

### *2.3 Intrinsic Factors*

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?

### *2.4 Extrinsic Factors*

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

#### 2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

***2.5 General Biopharmaceutics***

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

2.5.4 When would a fed BE study be appropriate and was one conducted?

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

***2.5 Analytical Section***

**2.5.2 How are the active moieties identified and measured in the plasma in the clinical pharmacology studies?**

Temozolomide and its active metabolite, MTIC, were the active moieties measured in plasma samples.

**2.5.3 Which metabolites have been selected for analysis and why?**

The active metabolite, MTIC, was measured in plasma samples from Studies P02466 and P02467.

### 2.5.4 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total (unbound+bound) concentrations of the parent drug and active metabolite were measured in plasma samples from Studies P02466 and P02467.

### 2.6.4 What bioanalytical methods are used to assess concentrations?

A validated high-performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method was used to analyze plasma samples for both temozolomide and MTIC using ethazolastone and dacarbazime as the internal standards, respectively.

#### 2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

**Standard curves were linear over the following concentration ranges:**

Temozolomide: 0.02 - 30 μg/ml

MTIC: 5.0 - 4000 ng/ml

#### 2.6.4.2 What is the lower limit of quantification (LLOQ)?

**The LLOQ was:**

Temozolomide: 0.02 μg/ml

MTIC: 5.0 ng/ml

#### 2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Temozolomide:

The intra-assay and inter-assay precision ranged from 1.5-10.2% and at all tested Quality Control (QC) Sample concentrations (0.05, 1.0, and 24 μg/mL). The intra-assay and inter-assay accuracy ranged from -13.8% to 6.4% at all QC concentration at the tested QC Sample concentrations (0.05, 1.0, and 24 μg/mL).

MTIC:

The intra-assay and inter-assay precision ranged from 1.5-6.3% at all tested Quality Control (QC) Sample concentrations (12, 200, and 3000 ng/mL). The intra-assay and inter-assay accuracy ranged from -7.8% to 5.9% at all QC concentration at the tested QC Sample concentrations (12, 200, and 3000 ng/mL).

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### 4.2 Pharmacometrics Review

## PHARMACOMETRICS REVIEW

| | |
|---|---|
| NDA: | 22-277 |
| Submission Date | 23-Jan-2008 |
| Type of Submission | NDA/N-000 |
| Generic Name | Temozolomide |
| Brand Name | Temodar |
| Dosage Form | Powder for Injection 100 mg/vial |
| Sponsor | Schering-Plough Research Institute |
| Primary PM Reviewer | Young Jin Moon, Ph.D. |
| Secondary PM Reviewer | Christoffer W. Tornoe, Ph.D. |
| OCPB Team Leader | Brian Booth, Ph.D. |
| PDUFA Date | |

**SCH 52365: POPULATION PHARMACOKINETIC (PK) MODELING AND SIMULATION OF TEMOZOLOMIDE FOR IV ADMINISTRATION**

## 1. INTRODUCTION

### 1.1 Background

Temozolomide (TMZ, SCH 52365) is an approved orally active imidazotetrazine cytotoxic alkylating agent under Schering's NDA 21-029. Due to the unsuitability of oral (PO) administration of TMZ for some patients, an IV formulation of TMZ is being developed.

### 1.2 Pharmacokinetics

Monomethyl triazenoimidazole carboxamide (MTIC) is the active moiety and the primary metabolite. MTIC is formed by non-enzymatic pH-dependant hydrolysis of TMZ. TMZ is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. In an absolute bioavailability study the mean (n = 5 patients) oral bioavailability was calculated as 109% and as such, it was anticipated that the two formulations, IV and oral, would be bioequivalent. It is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. It is weakly bound to human plasma proteins (15%). About 38% of the administered TMZ total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces.

### 1.3 Aims of analysis

• To develop a population PK model that describes the oral and IV PK profiles and variability estimates for both TMZ and MTIC.

• To investigate the feasibility of the bioequivalence approach for the registration of the TMZ IV.

• To design an optimal bioequivalence trial comparing the oral and IV administration of TMZ.

## 2. COMMENTS ON SPONSOR'S PK ANALYSIS

• The sponsor developed a population PK model using existing data to choose the most optimal design for a bioequivalence study. Based on results of the present analysis, the sponsor conducted a pivotal bioequivalent study (P02467), and this has met the criteria (AUC, $C_{max}$ 80-125%) as described for both TMZ and MTIC.

• Overall, the sponsor's method and interpretation of population PK analyses do not seem like a best practice. Nonetheless, the reason why the bioequivalence study was successful is probably because individual prediction (Figure 5) might be good enough to predict the power for bioequivalence.

• They should have investigated the reason why FOCE did not work and tried to fix the problem instead of using FO.

• The sponsor's method of covariate selection was not appropriate. Modeling should have been conducted based on mechanistic understanding of the system. Although previous population PK study found that BSA and gender correlate with clearance of TMZ, the sponsor did not explore the effect of BSA or gender on clearance.

• Model selection was based on goodness of fit plots (GOF) instead of using mechanism based understanding and using both objective function value and GOF.

• Each individual data plot which includes observed concentrations, the individual prediction line and the population prediction line should have been looked at. Visual predictive check should have been performed, as well.

## 3. DATA

### 3.1 I95-018- For oral (PO) population PK model

Study I95-018 was an international, multicenter, randomized, active-controlled, parallel group Phase III study designed to determine the efficacy and safety of TMZ (SCH 52365) as compared to dacarbazine in the treatment of patients with advanced metastatic malignant melanoma (N = 21). A treatment cycle for TMZ was once-daily 200 mg/$m^2$ oral administration for 5 days.

Blood samples were collected on Day 4 during the first treatment cycle at pre-dose and at 15, 30, 45 min, and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hr on Day 4 of Cycle 1. Body surface area (BSA) was the only covariate investigated in this population PK analysis.

### 3.2 I95-007- External validation dataset

Study I95-007 was an open-label, single center, randomized, crossover trial that investigated the effect of gastric pH on the oral bioavailability of TMZ by comparing the PK of TMZ administered alone to that when administered with Ranitidine in patients with advanced cancer (N = 15). TMZ

was administered after a 4 hour fast at a starting dose level of 150 mg/m$^2$/day on Days 1 through 5 of Cycle 1.

Blood samples were collected to determine TMZ and MTIC concentrations at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hr post-dose on Days 2 and 5 of Cycle 1.

## 4. RESULTS

In study I95-018, seventeen patients out of the 21 TMZ patients in the PK study were considered evaluable (Figure 1). The lower limit of quantification (LOQ) was set at 0.02 µg/mL for TMZ and 0.005 µg/mL for MTIC. Below the limit of quantification samples were excluded.

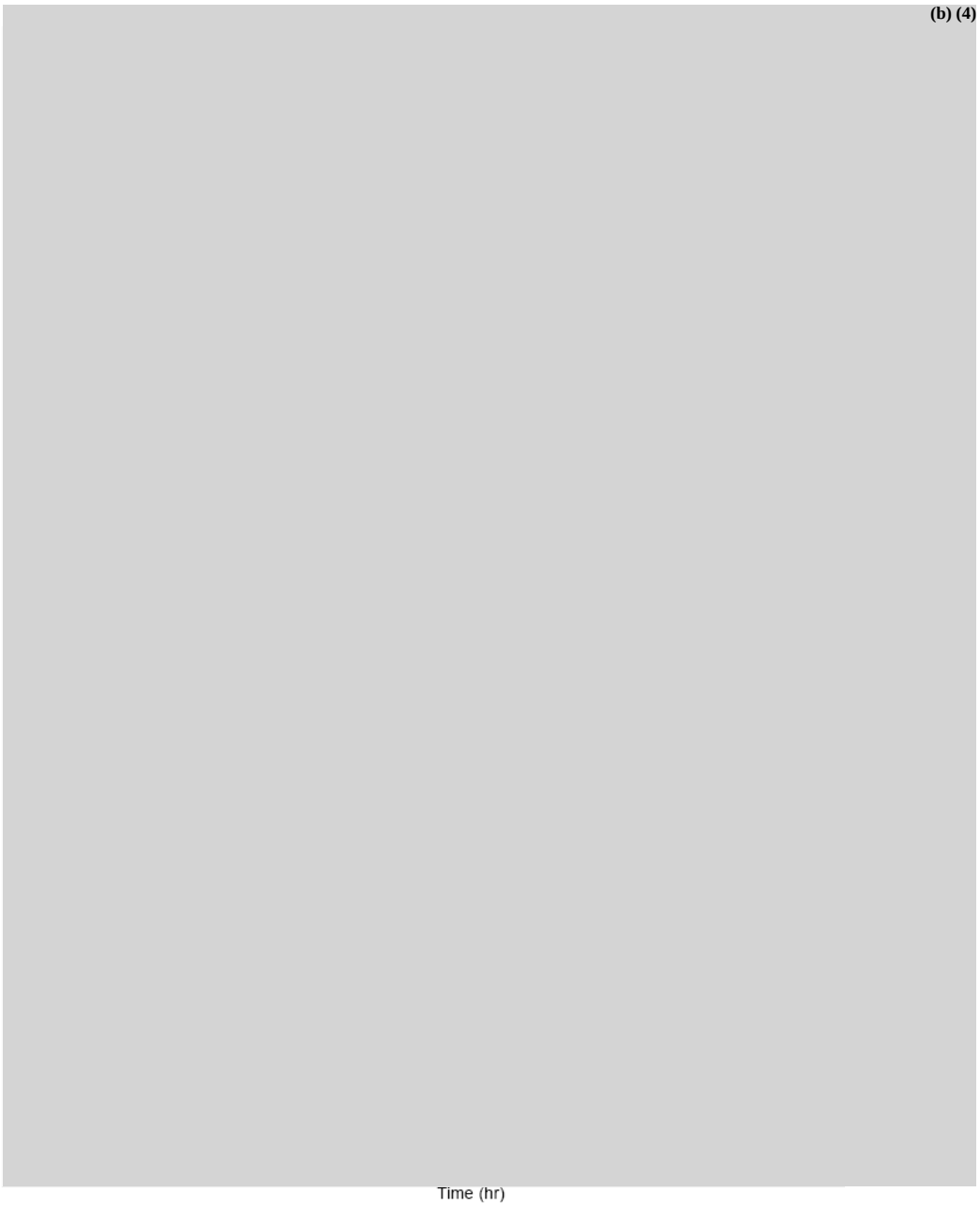


**Figure 1** Concentration-time profiles of TMZ and MTIC for patients enrolled in study I95-018

Model selection was based on the goodness of fit plots (GOF), standard error estimates of the PK parameters, and estimates of inter-occasion (intra-subject) variability. Since the First Order Conditional Estimation (FOCE) method in NONMEM did not result in a successful NONMEM run with the models tested, the First Order (FO) method was used.

### 4.1 Basic Structural Model and Variability Models

Since plasma concentrations of both TMZ and MTIC declined monoexponentially (Figure 1), a one-compartment model was chosen. The absorption of TMZ was modeled using first order kinetics. Since pH-dependent hydrolysis is unlikely to be saturable, a first order process was used to describe the conversion of TMZ to MTIC. The GOF plots for the basic structural model are presented in Figure 2.

(b) (4)

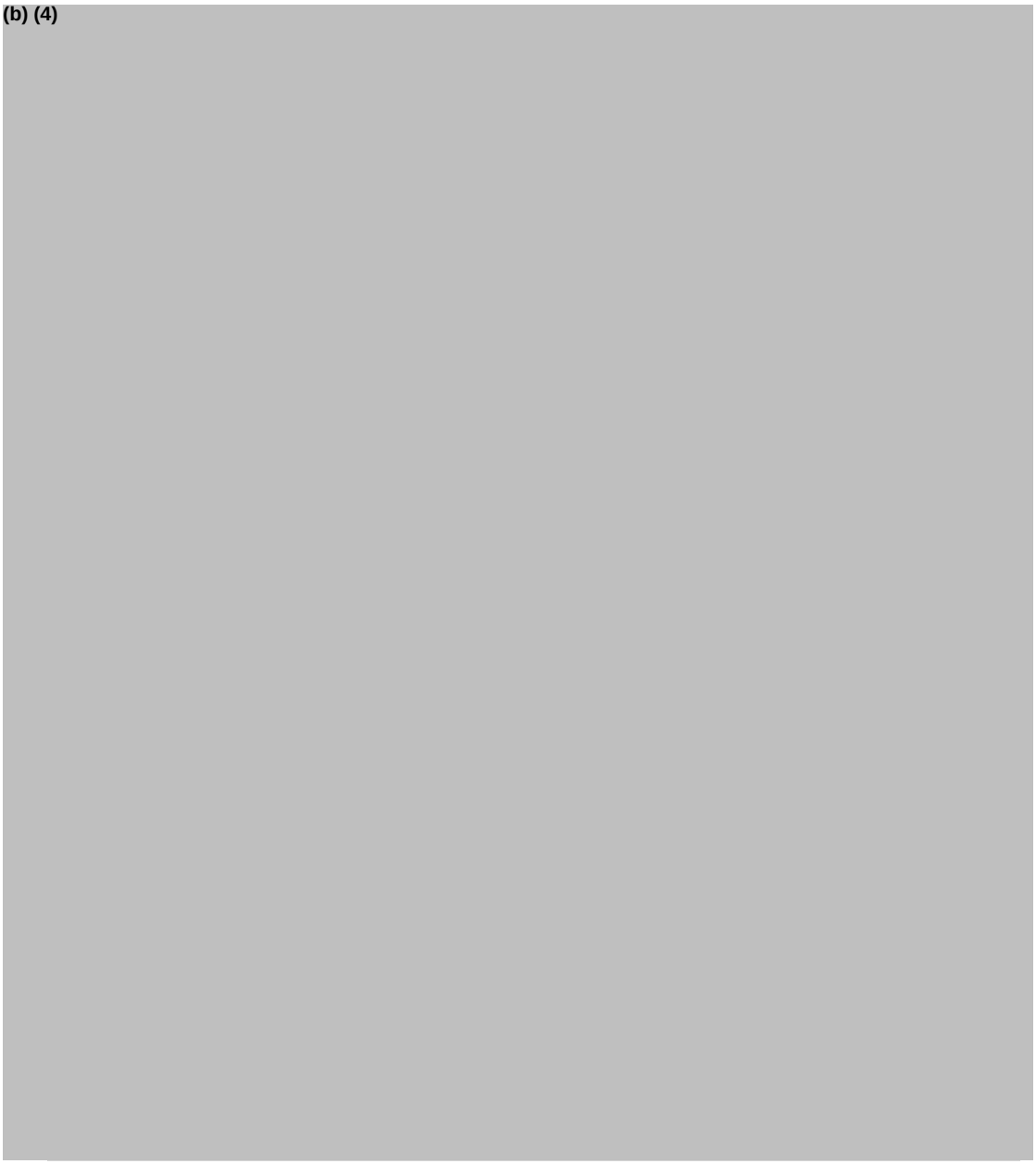

**Figure 2** Goodness of fit plots for the basic structural model for TMZ

Trend is observed in plot of residuals vs. observed concentrations of TMZ (red circle). Weighted

residuals are biased into the negative values for both TMZ and MTIC. Larger residuals are observed in earlier time points (0-2 hours) in plot of residuals vs. time.

(b) (4)

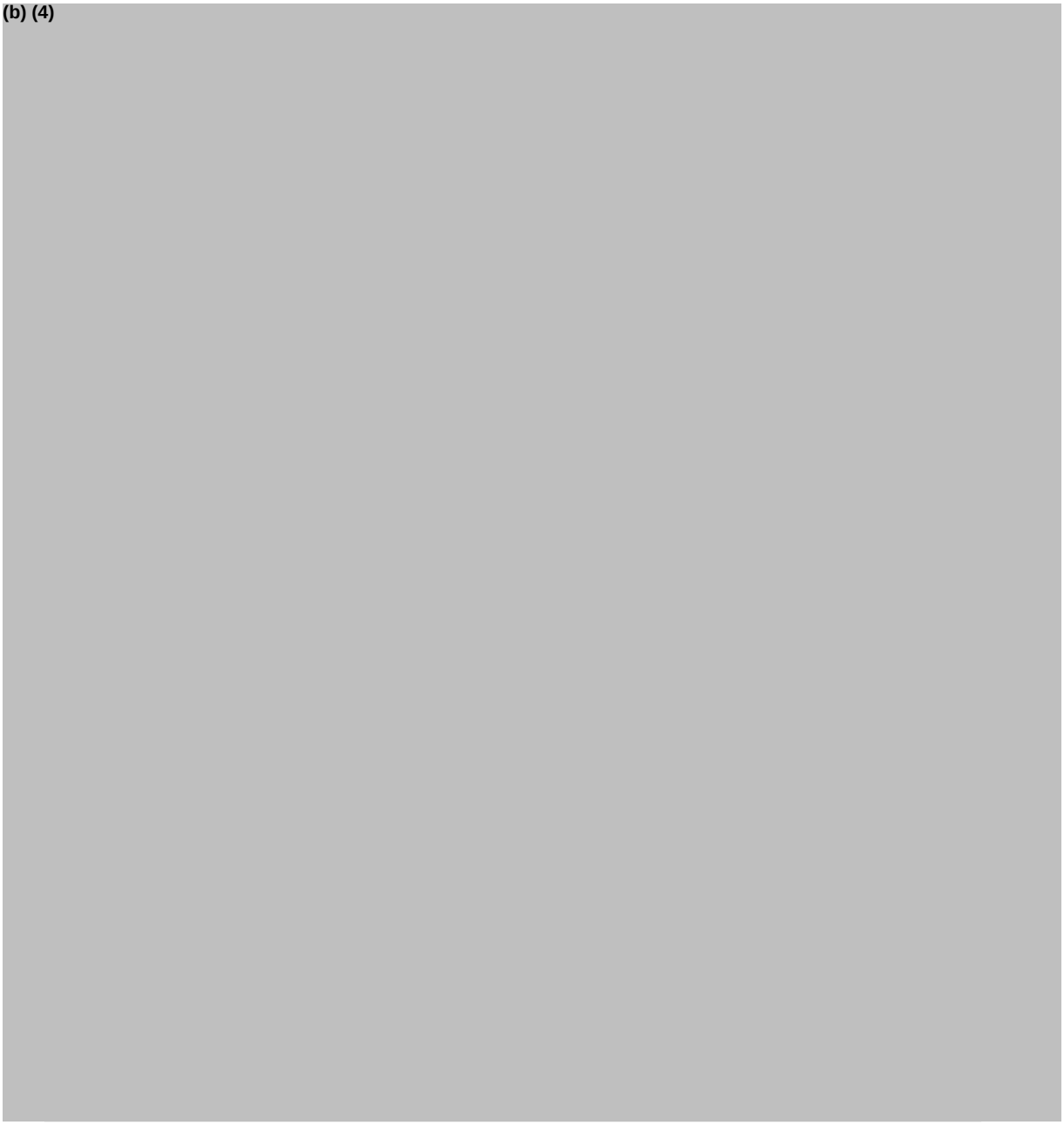

**Figure 2** (continued) Goodness of fit plots for the basic structural model for MTIC

Trends are also observed in plots of residuals vs. observed concentration and weighted residuals vs. observed concentration of MTIC (red circles).

The residual error was introduced into the model as additive and proportional models. Although the sponsor stated that proportional model was superior based on improved GOF plots, the reviewer does not see much improvement with proportional error (Figure 3 and Figure 4). Data points at 24 hr are missing (red circles in Figure 3 and Figure 4).


**Figure 3** Weighted residuals versus time plots comparing additive (Top) and proportional (Bottom) residual (Intra-Subject) variability models for TMZ

(b) (4)

**Figure 4** Weighted residuals versus time plots comparing additive (Top) and proportional (Bottom) residual (Intra-Subject) variability models for MTIC

PK parameters obtained by the sponsor for basic structural model are in Table 1.

**Table 1** Population PK Parameter Estimates for the Basic Structural Model

| PK Parameter | Description | Value (± Std. Error) |
|---|---|---|
| ka ($hr^{-1}$) | Absorption rate constant | 3.55 (1.11) |
| kT ($hr^{-1}$) | Elimination rate constant, TMZ | 0.360 (0.00721) |
| kM ($hr^{-1}$) | Elimination rate constant, MTIC | 15.3 (4.04) |
| V (L) | Apparent volume of distribution, TMZ | 26.4 (1.2) |
| V2 (L) | Apparent volume of distribution, MTIC | 24.6 (6.27) |
| ETA(1)[a] | Inter-subject variability on ka | 1.22, or ~ 122% (0.595) |
| ETA(2)[a] | Inter-subject variability on kT | 0.124 or ~ 12.4% (0.00113) |
| ETA(3)[a] | Inter-subject variability on kM | 0.395 or ~ 39.5% (0.025) |
| ETA(4)[a] | Inter-subject variability on V | 0.157 or ~ 15.7% (0.0131) |
| EPS(1)[b] | Residual Error on TMZ concentrations | 0.223 or 22.3% (0.012) |
| EPS(2)[b] | Residual Error on MTIC concentrations | 0.377 or 37.7% (0.0358) |

a: ETA(1) to ETA(4) were calculated by taking the square root from the OMEGA variance estimates in NONMEM output.

b: EPS(1) and EPS(2) were calculated by taking the square root from the SIGMA variance estimates in NONMEM output.

### 4.2 Covariate selection and final model

Following the visual inspection (Figure 4), BSA was introduced into the population PK model (Vi = TVV*BSA) and the goodness of fit plots, inter-subject variability estimates and residual variability estimates were compared to the model without BSA. BSA values for the TMZ PK group ranged from 1.37 to 2.23 $m^2$. BSA was also tested on Km, but this did not improve the diagnostic plots, standard error of Km, and the estimate of the inter-subject variability of Km. The different model runs (a run log) can be found in Appendix.

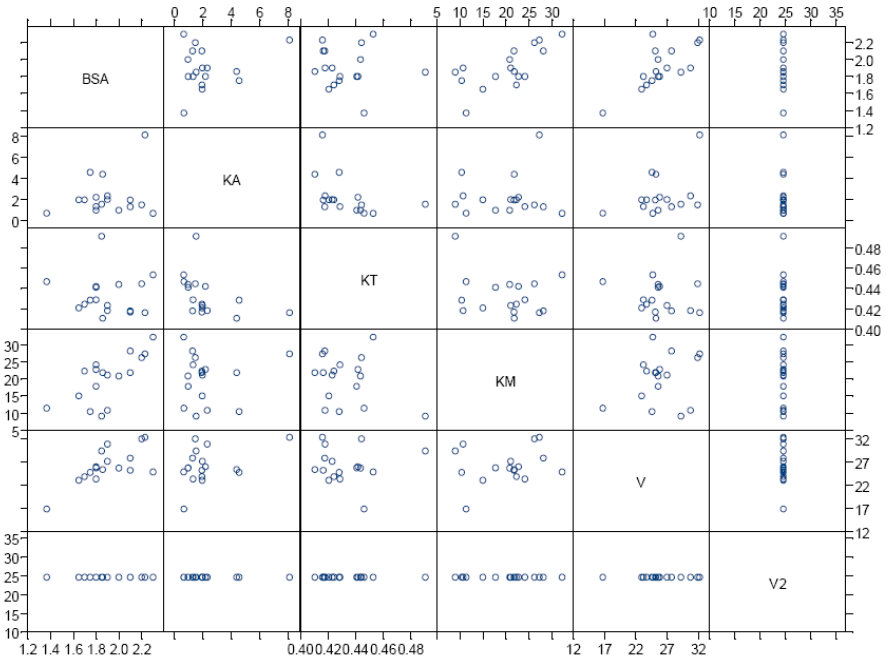


**Figure 4** Scatter plot correlating BSA with all PK parameters from the final basic structural model

The addition of BSA to the basic structural population PK model decreased the estimate of the inter-subject variability of the volume of distribution of TMZ (Table 2).

**Table 2** Population PK Parameter Estimates for the Final Covariate Model

| PK Parameter (units) | Description | Value (± Std. Error) |
|---|---|---|
| ka ($hr^{-1}$) | Absorption rate constant | 3.75 (1.12) |
| kT ($hr^{-1}$) | Elimination rate constant, TMZ | 0.358 (0.00832) |
| kM ($hr^{-1}$) | Elimination rate constant, MTIC | 13.4 (2.71) |
| V slope ($L/m^2$) | The slope of the apparent volume of distribution relationship with BSA, TMZ | 14.5 (0.434) |
| V2 (L) | Apparent volume of distribution, MTIC | 27.9 (5.23) |
| ETA(1)[a] | Inter-subject variability on ka | 1.24, or ~ 124% (0.680) |
| ETA(2)[a] | Inter-subject variability on kT | 0.126 or ~ 12.6% (0.0012) |
| ETA(3)[a] | Inter-subject variability on kM | 0.392 or ~ 39.2% (0.0256) |
| ETA(4)[a] | Inter-subject variability on V | 0.053 or ~ 5.3% (0.00305) |
| EPS(1)[b] | Residual Error on TMZ concentrations | 0.235 or 23.5% (0.0175) |
| EPS(2)[b] | Residual Error on MTIC concentrations | 0.373 or 37.3% (0.0363) |

a: ETA(1) to ETA(4) were calculated by taking the square root from the OMEGA variance estimates in NONMEM output.

b: EPS(1) and EPS(2) were calculated by taking the square root from the SIGMA variance estimates in NONMEM output.

The GOF plots for the final covariate model are included in Figure 5.

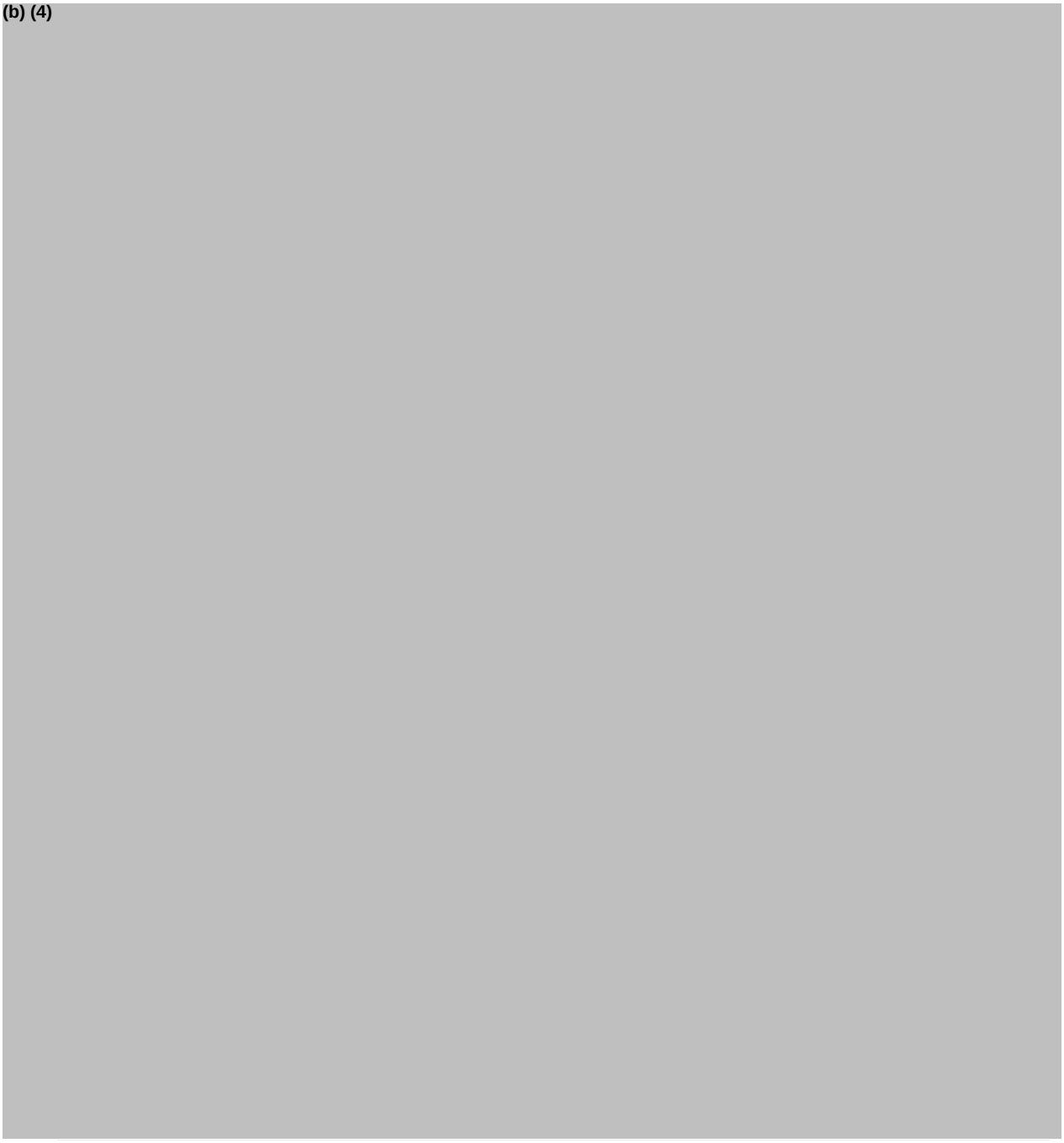


**Figure 5** Goodness of fit plots for TMZ: final covariate model

Predicted concentration vs. observed concentration plots and residuals vs. observed concentration of TMZ contain unexplained pattern which was not shown in basic structural model (Figure 2). Trend

seen before (Figure 2) still remained in plot of residuals vs. observed concentration of TMZ (red circle). Biased weighted residuals into the negative values still remained for both TMZ and MTIC. Larger residuals are observed in earlier time points (0-2 hours) in plot of residuals vs. time. The reason for those observations needs to be explored.

(b) (4)

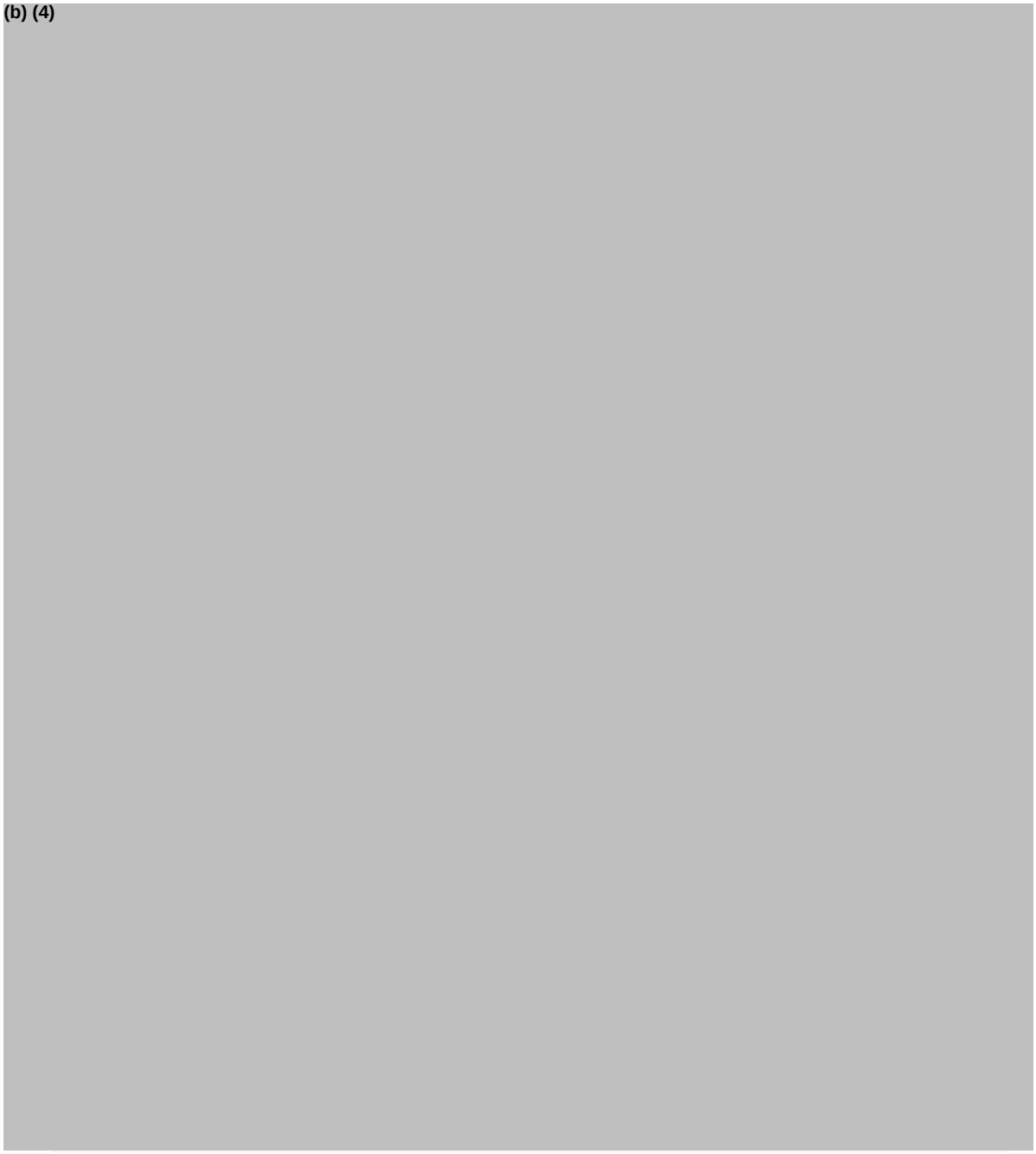

**Figure 5** (continued) Goodness of fit plots for MTIC: final covariate model

Trends still remained in plots of residuals vs. observed concentration and weighted residuals vs.

observed concentration of MTIC (red circles). The residual error models tested were additive and proportional. Combined error model should have been tested, too. This may be because data themselves have some extreme cases (especially MTIC data have a large variability (Figure 1)). Most of MTIC data were available up to 8 hours (Figure 1).

### 4.3 Simulation and comparison to the validation dataset

In study I95-007, data from 12 patients were used.

Model evaluation was focused on the ability of the model to predict or describe $C_{max}$ and AUC values, the two parameters used for BE evaluation, and their inter and intra-subject variability.

The final oral population PK model was evaluated using the following two criteria:

1. TMZ parameter estimates were compared to those previously obtained.
   In the previous population PK analysis, BSA and gender were found to statistically significantly correlate with clearance values of TMZ. The BSA adjusted clearance obtained in the previous population PK analysis were 5.30 L/m$^2$ for females and 5.58 L/m$^2$ for males). In the current analysis, the BSA adjusted CL value was:
   $CL = k_T \times V = 0.358 \times 14.5$ L/m$^2$ = 5.2 L/m$^2$

   In addition, half life (1.94 hr) obtained in the current analysis agrees with the results from the noncompartmental analysis reported in study I95-018 and I95-007.

2. The PO model was used to simulate a clinical study identical in design to study I95-007.
   The Monte Carlo simulations were performed using (b) (4) ( b and were repeated 100 times. The descriptive statistics were compared to those from study I95-007 in Table 3.

**Table 3** Simulated Versus Actual Cmax and AUC(I) of TMZ and MTIC

| | | Actual: Study I95-007 | | Simulated (100 replicates) | |
|---|---|---|---|---|---|
| | | Cmax | AUC(I) | Cmax | AUC(I) |
| TMZ | Mean | 8.22 | 24.1 | 8.84 | 27.1 |
| | CV% | 37 | 22 | 21 | 15 |
| MTIC | Mean | 211 | 585 | 260 | 739 |
| | CV% | 48 | 20 | 49 | 43 |

Mean and CV% simulated values of TMZ Cmax and AUC agree with the actual values reported in study I95-007 (% difference < 10%).

Mean and CV% of MTIC simulated values slightly over-predicted those reported in study I95-007 (% difference ≤ 25%).

Based on these results, the model reasonably described the Cmax and AUC(I) values of TMZ and MTIC when compared to an external dataset. Thus, the model predicted TMZ and MTIC pharmacokinetics well and can be used for IV model development and clinical trial simulations.

### 4.4 Monte Carlo Simulations: TMZ IV/PO BE Study

A summary of the results of the IV/PO bioequivalence simulations are presented in Table 4. The description of the Trial Simulation model used in TS can be found in Figure 6.

**Table 4** Probability of Bioequivalence Success (Power of Study): Simulation of Different Study Designs

| Number of Subjects | Overall Study Power: Meeting all 4 Criteria | | | |
|---|---|---|---|---|
| | 1 hr Infusion | | 1.5 hr Infusion | |
| | F = 0.9 | F = 1.0 | F = 0.9 | F = 1.0 |
| 20 | (b) (4) | | | |
| 24 | | | | |
| 28 | | | | |
| 32 | | | | |
| 36 | | | | |
| 40 | | | | |
| 50 | | | | |

The 1.5 hr IV infusion offers a higher probability of success compared to the 1 hr IV infusion. The probability of success is higher if the bioavailability of TMZ is closer to 100%.

The following is the Report from **(b) (4)**

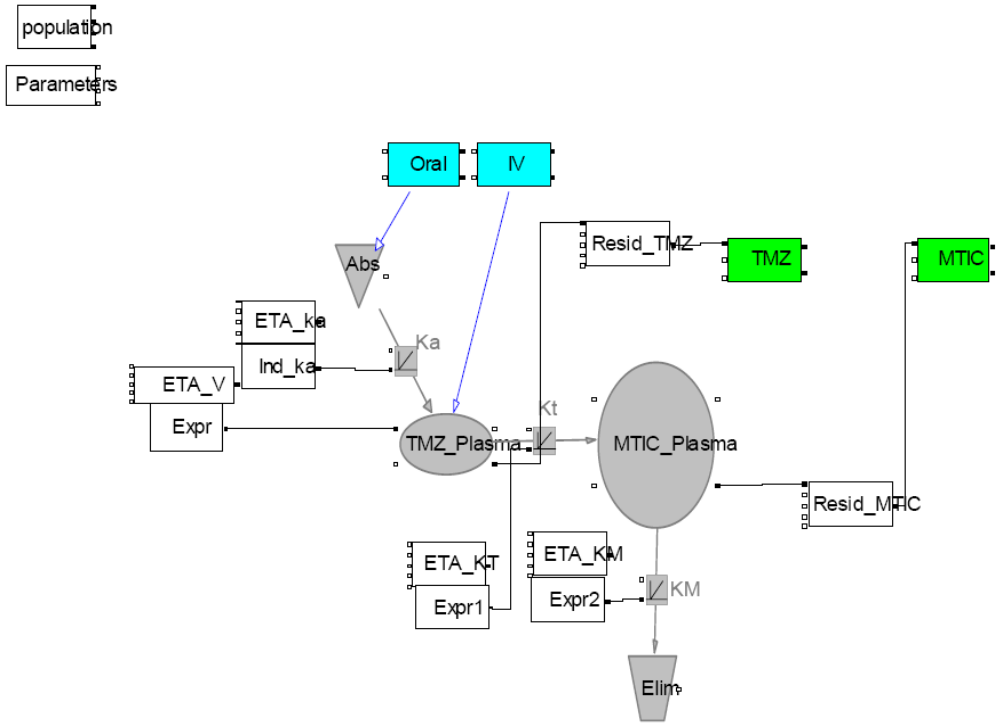


**Figure 6** Monte Carlo Simulation Model for the IV/PO BE Study

## 5. PHARMACOMETRICS REVIEW CONCLUSIONS

The overall conclusions for the pharmacometrics review are:

• A one-compartment model with first-order absorption (ka) and elimination ($k_T$ for TMZ and $k_M$ for MTIC) adequately described the time-course of the plasma concentrations of TMZ and MTIC.

• Volume of distribution of TMZ was found to be influenced by body surface area (BSA).

• Based on the oral model, an IV population PK model was developed and Monte Carlo simulations were performed to virtually conduct cross-over bioequivalence clinical trials comparing the oral and IV TMZ and MTIC PK profiles.

• The study with the most optimal design was chosen. A bioequivalence study comparing oral TMZ administration to a 1.5 hr IV infusion with 20 patient's data is expected to have 90% probability of success to show bioequivalence if the bioavailability of TMZ is 100%.

## 4.3 OCP Filing/Review Form

| Office of Clinical Pharmacology<br>***New Drug Application Filing and Review Form*** | | | | |
|---|---|---|---|---|
| **GENERAL INFORMATION ABOUT THE SUBMISSION** | | | | |
| | **Information** | | **Information** | |
| **NDA Number** | 22-277 | **Brand Name** | Temodar | |
| **OCP Division** | DCP 5 | **Generic Name** | Temozolomide | |
| **Medical Division** | DDOP | **Drug Class** | imidazotetrazinones | |
| **OCPB Reviewer** | Sophia Abraham, Ph.D. | **Indication(s)** | glioblastoma multiforme & anaplastic astrocytoma | |
| **OCP Team Leader** | Brian Booth, Ph.D. | **Dosage Form** | 100 mg Powder for Injection | |
| | | **Dosing Regimen** | 150 mg/m$^2$ once a day for 5 days of a 28-day cycle | |
| **Date of Submission** | 23-Jan-2008 | **Route of Administration** | 90-min Intravenous infusion | |
| **Estimated Due Date of OCP Review** | 15-Jun-2008 | **Sponsor** | Schering-Plough | |
| **PDUFA Due Date** | 24-Nov-2008 | **Priority Classification** | P | |
| **Division Due Date** | 24-Aug-2008 | | | |
| *Clin. Pharm. and Biopharm. Information* | | | | |
| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Critical Comments If any** |
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | | | | |
| **Tabular Listing of All Human Studies** | | | | |
| **HPK Summary** | | | | |
| **Labeling** | | | | |
| **Reference Bioanalytical and Analytical Methods** | **x** | **2** | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |

| | | | | |
|---|---|---|---|---|
| **Pharmacokinetics (e.g., Phase I)** | | | | |
| ***Healthy Volunteers-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| **In-vitro:** | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |

| | | | | |
|---|---|---|---|---|
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | **x** | **1** | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | **x** | **1** | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CP Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | | | |
| | | | | |

| **FILABILITY AND QBR COMMENTS** | | |
|---|---|---|
| | **"X" if yes** | **COMMENTS** |
| **Application filable?** | **x** | |
| **Comments sent to firm?** | | |
| **QBR questions (key issues to be considered)** | | |
| **Other comments or information not included above** | | |
| **Primary reviewer Signature and Date** | **Sophia Abraham** | |
| **Secondary reviewer Signature and Date** | **Julie Bullock** | |

**CC: NDA 22-277, DDOP (Electronic Entry), DDOP (Kim Roberton), OCP-DCP (Rahman, Booth, Abraham, Bullock), CDR (Biopharm)**

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/s/
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