Cancer Chemotherapy and Pharmacology
https://doi.org/10.1007/s00280-020-04175-0

ORIGINAL ARTICLE

Bioequivalence study of 20-mg and 100-mg temozolomide capsules (TOZ309 and Temodal®) in glioma patients in China

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Received: 21 March 2020 / Accepted: 7 October 2020

Abstract

Background Temozolomide is an alkylating agent approved by the U.S. Food and Drug Administration in 1999 for the treatment of patients with primary brain tumors. The aim of this study was to confirm the bioequivalence and safety of two strengths (20–100 mg) of generic temozolomide in the form of TOZ039 and Temodal® capsules administered to brain tumor patients.

Study design An open-label, randomized, two-phase, two-period, crossover pharmacokinetic study was performed in a single institution. The reference and test drugs were prescribed at a dose of 150 mg/m^2 daily from days 1 to 5 of a 28-day cycle in the first phase; in the second phase, either a 150- or 200-mg/m^2 dose was prescribed, depending on patient tolerance. On days 1 and 2 of each phase, a fixed 200-mg dose was administered either as ten 20-mg capsules in the first cycle or two 100-mg capsules in the second cycle. Drug administration in the first two days was randomized, i.e., if TOZ309 was administered on day 1, Temodal® was administered on day 2, and vice versa. The rest of the prescribed dose was administered in the form of Temodal® and spread equally over days 3–5. Blood samples were obtained for pharmacokinetic evaluation on days 1 and 2. Bioequivalence was demonstrated if the geometric means ratio of the three main pharmacokinetic parameters (mean maximum plasma concentration (C_{max}), area under the concentration–time curve (AUC) 0-t, AUC $_{0-\infty}$) fell within the equivalence boundary of 80–125%.

Results Twenty-nine glioblastoma multiforme or anaplastic astrocytoma patients were enrolled and dosed with the test and reference formulations under fasting conditions. The 90% confidence interval of the geometric means ratio for C_{max} (91.08%, 106.18%), AUC_{0-t} (98.62%,102.18%), and $AUC_{0-\infty}$ (98.65%, 102.21%) was well within the 80%–125% range for the 20-mg capsule, as was the C_{max} (90.49%, 113.32%), AUC_{0-t} (99.89%, 104.63%) and $AUC_{0-\infty}$ (99.99%, 104.67%) for the 100-mg capsule drug product. Additionally, all the secondary pharmacokinetic parameters were not significantly different. After two cycles of treatment, there was no mortality among the 29 patients, treatment-related severe adverse events, or events that would require study discontinuation; however, one significant adverse effect (life-threatening seizures) occurred and was related to disease progression. Adverse events were reported in 82.8% (24/29) patients, and treatment emergent adverse events were reported in 72.4% (21/29) patients.

Conclusion It can be concluded that 20-mg and 100-mg capsules of TOZ309 are bioequivalent to Temodal® capsules of the same strength under fasting conditions.

Trial registration https://www.chinadrugtrials.org.cn/index.html, CTR2017 0122.

Keywords Temozolomide capsule · Gliomas · Pharmacokinetics · Bioequivalence

Introduction

Temozolomide is an effective chemotherapy drug in the treatment of glioblastoma multiforme and refractory anaplastic astrocytoma [1–3]. The anti-tumor cytotoxicity of temozolomide is through the active cytotoxic metabolite 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00280-020-04175-0) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Published online: 21 October 2020

(MTIC), which methylates tumor DNA, resulting in DNA damage and cell death [4, 5].Temozolomide is spontaneously hydrolyzed at physiologic pH to MTIC, which is further hydrolyzed to 5-aminoimidazole-4-carboxamide (AIC) and methyl-hydrazine. AIC is an intermediate in purine and nucleic acid biosynthesis and methyl-hydrazine is an active alkylating species [3, 5].

After oral administration, temozolomide is absorbed rapidly and completely, with an average time to peak concentration of 1–2 h under fasting conditions. The bioavailability of temozolomide is 100%, and the CSF to plasma ratio is 0.3:1 [6–9].The mean elimination half-life would be 1.8 h in glioma patients [6–9]. It has been shown that under fed conditions, the mean maximum plasma concentration (C_{max}) and area under the concentration–time curve (AUC) decreased by 32% and 9%, respectively, and the median T_{max} increased approximately twofold [9, 10].The branded temozolomide capsules were approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 1999, but only began to be marketed in China in 2008. Although two generic products have already been approved by the Chinese National Medicinal Product Administration (NMPA), the cost of this drug is still high and constitutes a financial burden for most patients. It is with this in mind that TOT BIOPHARM developed the generic TOZ309 temozolomide capsules. The purpose of this study was to assess the pharmacokinetics and bioequivalence (BE) of the generic test products (20-mg and 100-mg TOZ309 capsules) to Temodal® capsules of the same strength after administration of a single dose of 200 mg under fasting condition in glioma patients.

This study is essential to provide evidence of bioequivalence in support of marketing authorization in China. In addition, this was the first study reported to evaluate the bioequivalence of two oral specifications of temozolomide capsules simultaneously in glioma patients in China.

Materials and methods

Ethics

This clinical trial was performed in accordance with the principles of the Declaration of Helsinki [11], as well as Good Clinical Practice (GCP) guidelines. The clinical study protocol, protocol amendments, and all applicable documents (including the informed consent form) were reviewed and approved by the hospital Ethics Committee (2016 No.025)at Xuanwu Hospital Capital Medical University. Written informed consent was obtained from all subjects before screening.

Drugs and Instruments

Temozolomide capsules as test products (T1:20 mg, T2:100 mg) were manufactured by TOTBIOPHARM, and Temodal® capsules manufactured by Merck Sharp & Dohme Limited were selected as reference products (R1:20 mg, R2:100 mg). Only two capsule strengths have been approved by the NMPA; the 250-mg capsule has not been approved in China. Both the test and reference products were provided by the sponsor.

Bioanalytical standard temozolomide, batch number 1451-053A1, with a chemical purity of 100%, was purchased from TRC (Canada). The internal standard was also purchased from TRC, batch number 3-PSB-129–1, with a chemical purity of 98%. Pharmacokinetic analyses were performed on an API 4000 QTrap HPLC tandem MS (Applied BioSystems, United States) and a Prominence LC-20AT HPLC system (Shimadzu, Japan).

Subjects

Confirmed glioblastoma multiforme or anaplastic astrocytoma patients with a life expectancy of over three months and requiring temozolomide for tumor management were eligible for the study. Inclusion criteria required patients to be between the ages of 18 and 70 years and to have a body mass index (BMI) between 16 and 30 kg/m^2 (inclusive). General evaluation was based on medical history (including allergies to temozolomide or blood donation or blood loss over 200 mL within the past month), physical examination, vital signs, electrocardiogram, clinical laboratory and serologic tests to fulfil the inclusion criteria. Patients were excluded if they were heavy smokers or if they had a history of clinically significant systemic illnesses, drug and alcohol abuse, prior chemotherapy (except temozolomide) or biological drugs within 4 weeks, mitomycin C or nitrosourea within 6 weeks, or if they had participated in an investigational product study within 3 months of signing the informed consent for the study.

Study design and drug administration

This study was a single-center, open-label, randomized, two-phase, two-period, crossover trial. The sample size calculation was mainly driven by the intra-subject coefficient of variation (CV, about 20%) of C_{max} of temozolomide. Twenty-five subjects will provide at least 80% power to have 90% confidence interval (CI) of estimated geometric least square mean ratio within the bioequivalence acceptance criteria of 80.00–125.00%. So, we planned to enroll 32 subjects for each phase. Temozolomide was prescribed at a dose

of 150 mg/m^2 to be taken over a 5-day period, and patients who tolerated treatment well were prescribed 200 mg/m^2 in the second phase as well as anti-emetic premedication to be taken at least 1 h before administration of the study drugs. In the first phase, patients were administered 200-mg temozolomide (10 pills of T1) or Temodal®(10 capsules of R1) on day 1 (period 1) on an empty stomach, after which each patient crossed over to the other drug on day 2 (period 2), followed by sufficient Temodal® capsules to complete a standard chemotherapy cycle on days 3–5. After completion of the 28 days of phase 1, patients entered into phase 2, and received two capsules of T2 or R2 following the same procedure as phase 1, as outlined in the flow chart (Fig. 1). The subjects had to refrain from drinking liquids for 1 h before and 2 h after dosing. Standardized Chinese low-fat meals were provided approximately 2, 6, and 10 h post dose.

Blood sampling and methodological evaluation

Blood samples were collected in pre-cooled vacuum tubes at times 0 (within 60 min pre-dose), 0.167, 0.333, 0.667, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, and 12 h post dosing. These samples were centrifuged at 4 °C within 30 min of obtaining the plasma, which was divided into two parts (one for testing, and one for backup), immediately mixed with an equal volume of 5% formic acid aqueous solution, and then stored in a − 80 °C refrigerator until subsequent analysis.

The plasma samples for quantification of temozolomide were analyzed using validated LS–MS/MS methods. Temozolomide-d3 was used as internal standard. The plasma standard curves ranged from 10.0 to 10,000 ng/mL. Excluded LLOQ, intra-batch accuracy bias and precision were 0.8–11.3% and ≤ 3.6%, while inter-batch accuracy bias and precision were 0.8–9.4% and ≤ 3.4%, respectively. For LLOQ, intra-batch accuracy bias and precision were 2.5–9.0% and ≤ 4.8%, while inter-batch accuracy bias and precision were 1.0–6.9%, respectively. The variability, accuracy, relative recovery, matrix effect, and stability of this trial met the requirements of a pharmacokinetic methodological study.

Evaluation for safety

Safety monitoring included documentation of mortality, serious adverse events (SAEs), treatment emergent AEs (TEAEs), AE resulting in drug termination or study discontinuation, through monitoring of vital signs, physical examinations, clinical laboratory tests, and 12- lead ECG at predetermined intervals, throughout the entire study. All AEs and/or SAEs were assessed by clinical investigators for severity grading and association using the National Cancer Institute Common Toxicity Criteria, version 5 [12].

Pharmacokinetics, bioequivalence, and statistical analyses

Pharmacokinetic parameters were evaluated with the validated computer program Phoenix® WinNonlin8.1 (Certara, L.P., Princeton, New Jersey, USA).Statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC, USA).

The primary endpoints to be derived from the pharmacokinetic data were the maximum serum concentration (C_{max}), the area under the concentration–time curve (using a non-compartmental approach) from time zero to the last measurable concentration ($AUC_{0\text{-}t}$), and the area under the concentration–time curve from time zero to infinity ($AUC_{0\text{-}\infty}$). Other parameters evaluated include the time to reach

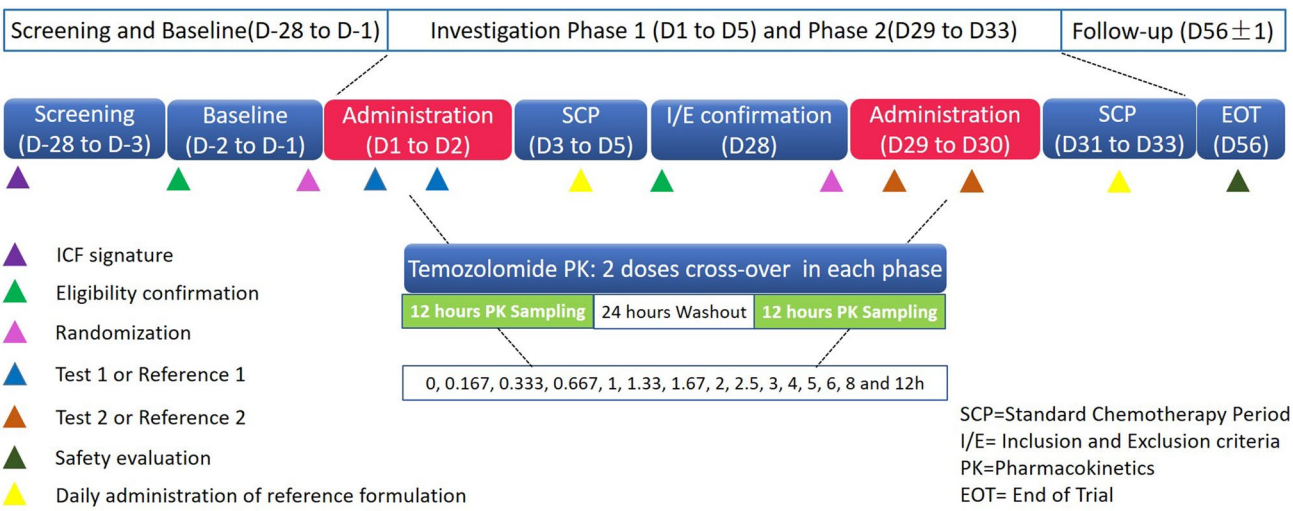

Fig. 1 Study flowchart

the maximum concentration (t_{max}) and the elimination half-life ($t_{1/2}$).The geometric least square mean ratios (test/reference) and the corresponding 90% confidence intervals of $AUC_{0-\infty}$, AUC_{0-t},and C_{max} were calculated.

Results

Subjects disposition and baseline characteristic

A total of 40 glioma patients were screened. (The patient disposition is documented in Fig. 2.) Twenty seven patients completed phase 1 and entered phase 2. One patient, after completing dosing in phase one, withdrew from the study due to progressive disease-related seizures and had to be replaced by the 29th patient in the second phase. Demographic data of all 29 patients, with relevant age, height, weight, BMI can be seen in Table 1. Two patients with out-of-range BMI were excluded from evaluation for bioequivalence in both phases. In the second phase, two more patients were excluded; a diluent other than 5% formic acid aqueous solution was added to the serum of one patient and the other patient was excluded due to a reversal of the randomization sequence. After exclusion of protocol deviations, 26 patients in the first phase and 24 in the second phase were included in the pharmacokinetic set and BE set. All patients

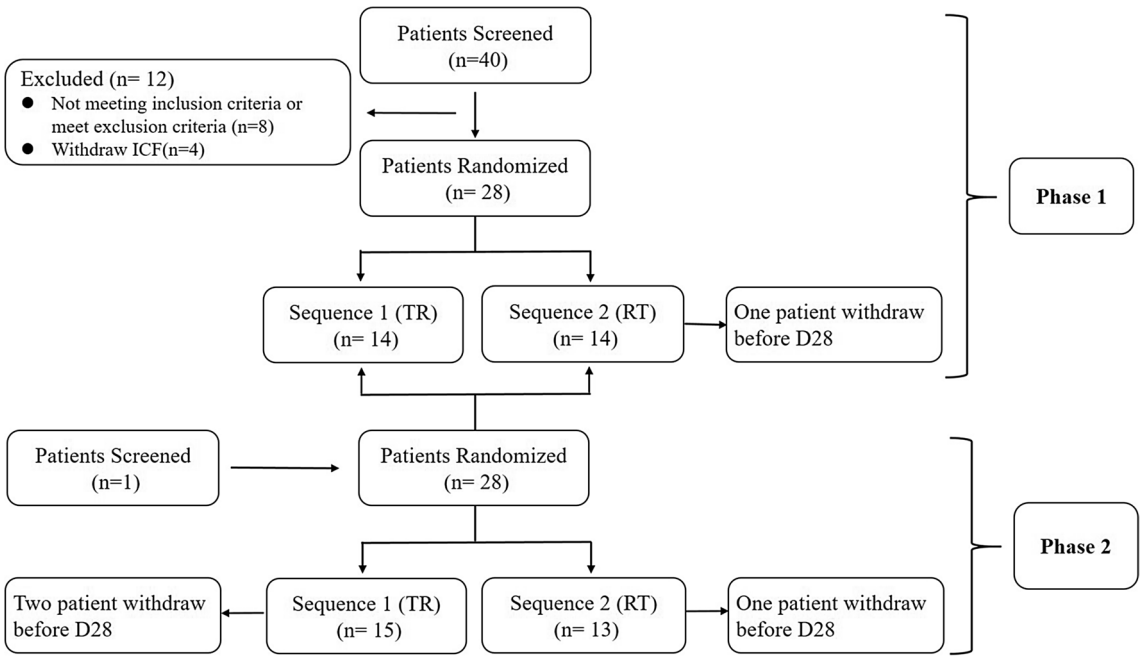

Fig. 2 Patients disposition

Table 1 Demographic characteristics (safety analysis set)

Parameters (Units)	Phase 1 (20 mg)			Phase 2 (100 mg)		
	TR ($N=14$)	RT ($N=14$)	Total ($N=28$)	TR ($N=15$)	RT ($N=13$)	Total ($N=28$)
Age (years)	37.0 ± 9.98 (21, 57)	45.7 ± 11.57 (20, 63)	41.4 ± 11.49 (20, 63)	41.9 ± 12.59 (21, 63)	39.3 ± 9.71 (20, 55)	40.7 ± 11.22 (20, 63)
Height (cm)	165.5 ± 7.86 (152.0, 177.0)	168.9 ± 7.96 (149.5, 184.0)	167.2 ± 7.95 (149.5, 184.0)	168.8 ± 8.40 (152.0, 176.0)	165.3 ± 7.24 (149.5, 184.0)	167.1 ± 7.94 (149.5, 184.0)
Weight (kg)	68.1 ± 11.29 (54, 89)	71.1 ± 9.90 (51, 86)	69.6 ± 10.53 (51, 89)	70.5 ± 10.36 (51, 89)	68.8 ± 11.20 (54, 86)	69.7 ± 10.59 (51, 89)
BMI	24.95 ± 4.48 (19.0, 35.5)	24.87 ± 2.83 (20.9, 32.2)	24.91 ± 3.68 (19.0, 35.5)	24.71 ± 2.87 (19.0, 28.9)	25.28 ± 4.57 (20.1, 35.5)	24.98 ± 3.70 (19.0, 35.5)

All results were reported as mean ± standard deviation (minimum, maximum)

N patient number, *BMI* body mass index

who received at least one full dose were included in the safety analysis. Sensitivity analyses to include the data of the two patients with out-of-range BMI in both phases and inclusion of the patient dosed in the incorrect randomization sequence demonstrated bioequivalent pharmacokinetic parameters (results not shown).

The patients, who were all of Chinese ethnicity, consisted of 17 males and 12 females, with an average age of about 41 years (20–63), average height approximately 167 cm (149.5–184.0), mean weight 70 kg (51–89), and average BMI of around 25 kg/m^2 (19.0–35.5). The average dose per day administered in phase 1 was 263 mg (212–309), which increased slightly in phase 2 to 279 mg (212–370). Because the dose in the first 2 days was fixed at 200 mg/day, the dose administered per day to make up the total prescription was increased daily for days 3–5. Thus, the average dose in phase 1 was 306 mg (267–340), increasing to 331 mg (220–480) in phase 2.

Safety and tolerability

Temozolomide was generally well tolerated at doses of 150–200 mg/m^2. There was no treatment-related mortality, nor SAEs; however, one patient suffered a severe, life-threatening seizure a week after completing phase 1 therapy. She was found to have progressive disease with increased intracranial pressure and underwent surgery to relieve the pressure. Of the 29 subjects, 24 experienced 108 AEs, and 55 AEs of 21 patients were judged to be related to temozolomide. One patient had grade 3 drug-related neutropenia during the drug withdrawal period of phase 1. All other reported AEs were mild or moderate; the most common AEs were leucopenia (25%), constipation (22%), neutropenia (14%), spike in ALT levels, nausea and vomiting in 8.33% patients each. Abdominal distension, proteinuria, increased eosinophil count, and thrombocytopenia were reported in one patient each (Table 2) [12].The type and frequency of AEs were similar to those already described for temozolomide administration [6–10, 13].

Pharmacokinetics and bioequivalence

After the administration of 200 mg of the test or reference products, the mean plasma concentrations versus time profiles for the 20–100 mg comparative studies under fasting condition were recorded (Figs. 3, 4) For the 20-mg test versus reference product, the C_{max} was 7290 ± 2020 and 7470 ± 2300 ng/mL; AUC_{0-t} 20,700 ± 3190 and 20,600 ± 3250 h ng/mL, and $AUC_{0-\infty}$ 20,900 ± 3220 and 20,800 ± 3280 h ng/mL, respectively. For the 100-mg strength group, the C_{max} was 6780 ± 2020 and 6550 ± 2070 ng/mL, AUC_{0-t} 20,900 ± 3860 and 20,400 ± 3990 h ng/mL, and $AUC_{0-\infty}$ of 21,200 ± 3,940 and 20,700 ± 4050 h ng/mL, respectively. The pharmacokinetic parameters of each product are summarized in Table 3.

Table 2 Treatment-related adverse events reported in this BE study

Adverse events	*N*	Percent (%)	Intensity
WBC count decreased	9	25	Mild/moderate
Constipation	8	22.22	Mild
Neutropenia	5	13.89	Severe/mild
ALT increased	3	8.33	Mild
Nausea	3	8.33	Mild
Vomiting	3	8.33	Mild
Abdominal distension	1	2.78	Moderate
Proteinuria	1	2.78	Mld
Eosinophils count increased	1	2.78	Moderate
Thrombocytopenia	1	2.78	Mild
	1	2.78	Moderate
Total	36	100	/

N TEAE number

Temozolomide was rapidly absorbed, with a median t_{max} of 40 min ($p = 0.2173$) and 1 h ($p = 0.5847$) after a single dose of T1/R1 and T2/R2, respectively. There was no statistical difference in this parameter for either the 20-mg or 100-mg capsules. The geometric means ratio of the three main pharmacokinetic parameters of C_{max} (0.98, 90% CI 91.08–106.18), AUC_{0-t} (1, 90% CI 98.62–102.18), and $AUC_{0-\infty}$ (1, 90% CI 98.65–102.21) all fell within the equivalence boundary of 80–125%, with > 80% power (Table 4). There was no significant difference in any of the secondary pharmacokinetic parameters: λz (elimination rate constants), Vz/F (volume of distribution), Cl/F (clearance rate),and t½(half-life).We found that the mean $t_{1/2}$ was also similar at approximately 1.8 h, which is in agreement with the previous studies [6–9]. Overall, the mean pharmacokinetic profiles of temozolomide overlapped between T1 and R1, as well as between T2 and R2, under fasting conditions. Variance analysis showed that there was no significant difference between period and sequence.

Discussion

Temozolomide exhibits linear pharmacokinetics over the therapeutic dose range, and its pharmacokinetic profile is independent of the route of administration, i.e., oral, intravenous, or hepatic intra-arterial [6, 7]. Temozolomide total body clearance is linear and independent of dose and its half-life is approximately 1.8 h; thus, a 24-h period encompasses 13.3 half-lives, enabling bioequivalence studies, with more than sufficient time for clearance in the same patient if test and reference products are prescribed 24 h apart on any 2 of the 5 days of dosing in a 28-day cycle.

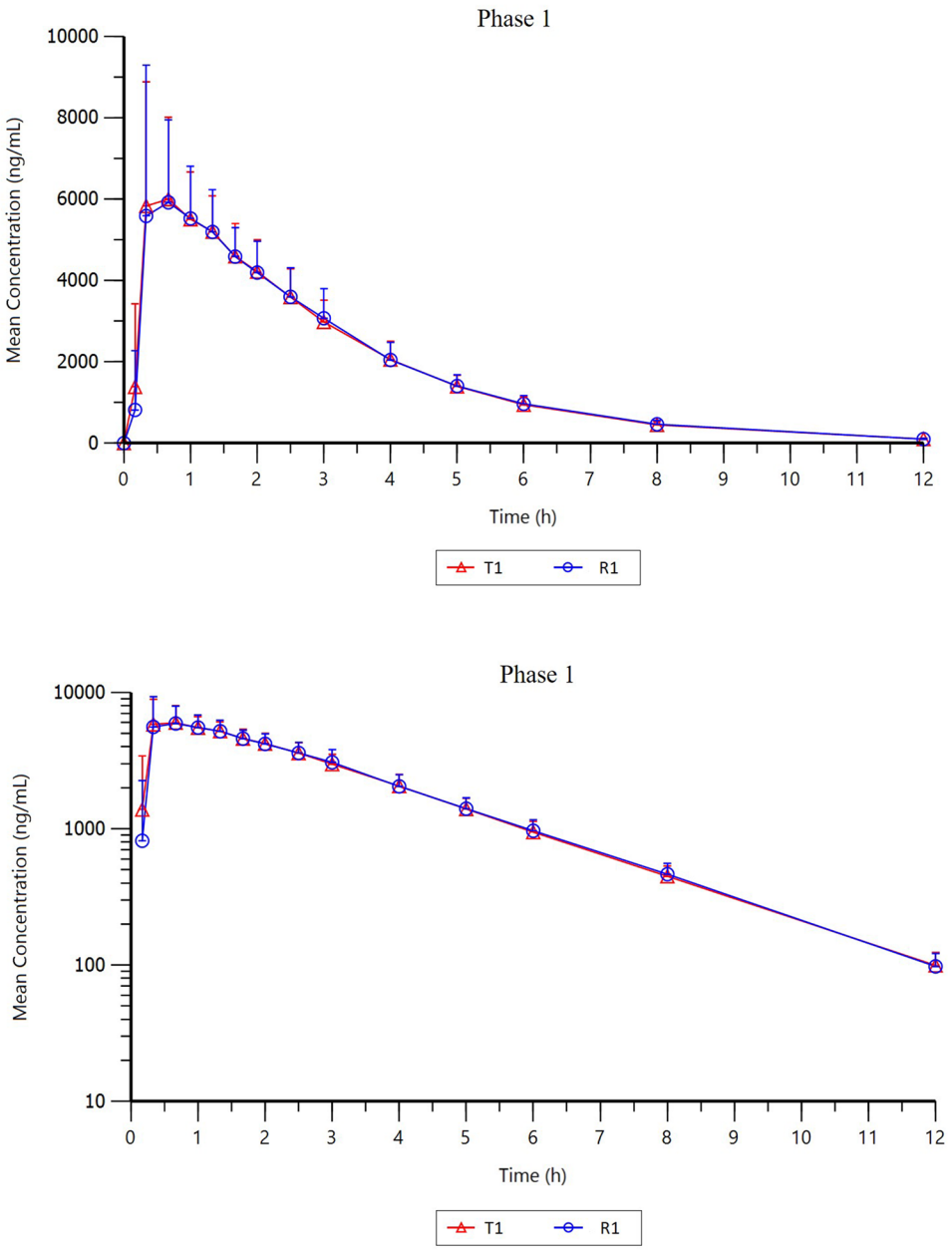

Fig. 3 Mean plasma concentration–time profiles of temozolomide in glioma patients following single oral dose administration of the test (T1) and reference (R1) products (20 mg Tempdal®). Upper: Linear scale. Lower: Semi-log scale

The 2009 FDA guidance on establishing bioequivalence of a generic temozolomide allows for 250-mg capsules to be administered on days 1 and 2 of 5 days of dosing in a 28-day treatment cycle; if the test drug is administered on day 1, then the reference drug would be administered on day 2 and vice versa. If bioequivalence is established, the guidelines allow for waiver of in vivo testing of the other capsule strengths (5, 20, 100, 140, and 180 mg) based on (1) acceptable bioequivalence study results from the 250-mg capsule, (2) proportional similarity of the formulations across all capsule strengths, and (3) acceptable in vitro dissolution testing of all capsule strengths for BE study [14]. In the present study, we adopted a very stringent standard for confirmation of the bioequivalence of the 20-mg and 100-mg capsules of the TOZ039 generic with those of Temodal® separately and over two cycles of treatment, and we successfully demonstrated that both capsules strengths are bioequivalent for all of the primary pharmacokinetic parameters and showed no significant difference in the secondary pharmacokinetic parameters. Our results are comparable to data reported in the literature [6–9]; however, alternate studies have been reported in which different capsule strengths are in corporate in one dosing, to make up the prescription dose of the test drug, and the exact same capsule formulation is repeated for the reference drug on the preceding or following day [6].

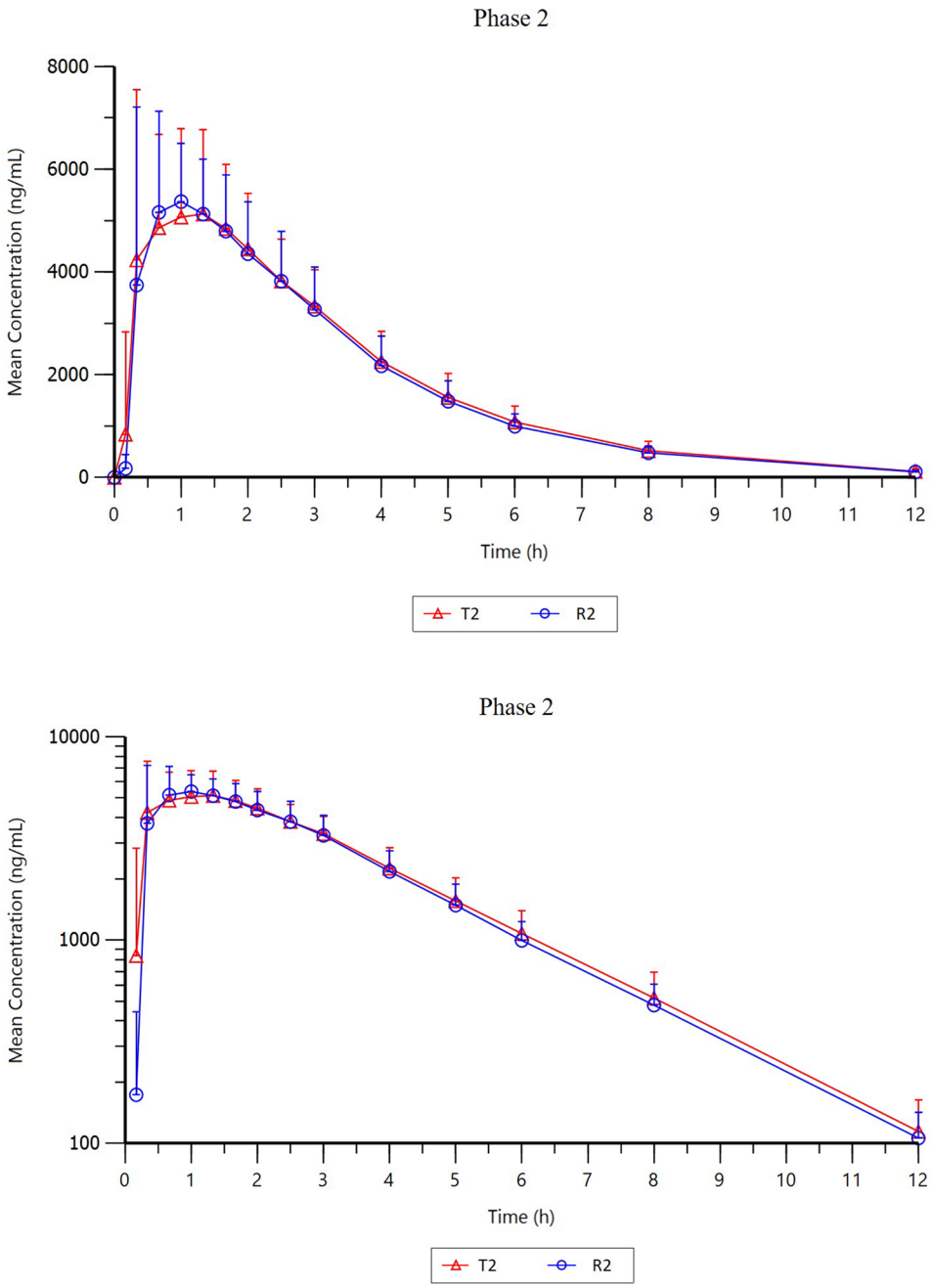

Fig. 4 Mean plasma concentration–time profiles of temozolomide in gliomas patients following single oral dose administration of the test (T2) and reference (R2) products (100-mg Tempdal®). Upper: Linear scale. Lower: Semi-log scale

Table 3 Pharmacokinetics parameters of temozolomide in glioma patients under fasting condition

PK Parameters	Phase 1 (20 mg, $n=26$)		Phase 2 (100 mg, $n=24$)	
	T1	R1	T2	R2
*T_{max} (h)	0.667 (0.167, 2.00)	0.667 (0.333, 3.00)	1.00 (0.333, 2.00)	1.00 (0.333, 2.50)
C_{max} (ng/mL)	7290 ± 2020	7470 ± 2300	6780 ± 2020	6550 ± 2070
$AUC_{0\text{-}t}$ (h*ng/mL)	20700 ± 3190	20600 ± 3250	20900 ± 3860	20400 ± 3990
$AUC_{0\text{-}\infty}$ (h*ng/mL)	20900 ± 3220	20800 ± 3280	21200 ± 3940	20700 ± 4050
$t_{1/2}$ (h)	1.84 ± 0.108	1.82 ± 0.121	1.83 ± 0.134	1.83 ± 0.127

Except T_{max}, all results were reported as arithmetic mean and standard deviation

n PK parameters number, *T* test, *R* reference

*Median (minimum, maximum)

Table 4 Bioequivalence evaluation of the test and reference formulations of oral temozolomide in fasting condition

Phase 1(20 mg) PK parameters	Geometric mean				90% CI	Power%
	n	T1	R1	T/R ratio		
C_{max} (ng/mL)	26	7041	7160	0.98	(91.08,106.18)	99.74
$AUC_{0\text{-}t}$ (h*ng/mL)	26	20422	20343	1.00	(98.62,102.18)	> 99.99
$AUC_{0\text{-}\infty}$(h*ng/mL)	26	20686	20601	1.00	(98.65,102.21)	> 99.99
Phase 2(100 mg) PK parameters	Geometric mean				90% CI	Power%
	n	T2	R2	T/R ratio		
C_{max} (ng/mL)	24	6446	6366	1.01	(90.49,113.32)	89.64
$AUC_{0\text{-}t}$ (h*ng/mL)	24	20654	20203	1.02	(99.89,104.63)	> 99.99
$AUC_{0\text{-}\infty}$ (h*ng/mL)	24	20955	20484	1.02	(99.99,104.67)	> 99.99

T test, *R* reference, *CI* confidence interval

Due to complicated medical history, medication history, and complications experienced by patients during this study, the tolerance of glioma patients was poor, such that most patients were prescribed 150 mg/m^2 in both treatment phases, with a proportionately lower C_{max} and AUC compared to results from other bioequivalence studies in which higher dosing (200 mg/m^2) was used. Temozolomide is cytotoxic drug, associated with a spectrum of known side effects. AEs observed in this study were consistent with previously known complications in glioma patients, and there was no unexpected SAEs. Common gastro-intestinal side effects of nausea and vomiting were most likely avoided by premedication prior to temozolomide dosing.

As a result of the study design incorporating 200 mg (TOZ309 20 mg*10 or 100 mg*2) of the test drug into one day of the 5-day dosing period, it became impossible to extract and attribute different AEs to the test or reference drug product, such that there could be no separate statistics of AEs in each phase, sequence, and treatment; however, none of the recorded AEs were unusual.

Conclusion

In this study, TOZ309, administered as 20–100-mg temozolomide capsules, were shown to be safe and well tolerated in glioma patients under fasting condition and was statistically bioequivalent to the reference product with no new safety signals.

Acknowledgments All authors would like to thank the subjects for their participation in this study, as well as the clinical investigators, nurses, and study coordinators at Xuanwu Hospital for their contribution to this study.

Funding This study was supported by TOT BIOPHARM Ltd., National Science and Technology Major Project (No.2017ZX09101001-002-044), National Key Research and Development Program of China (2016YFC0103909), Capital Science and Technology Leading Talent Training Project (Z191100006119017), and Beijing Hospitals Authority Ascent Plan (DFL20190803).

Compliance with ethical standards

Conflict of interest All the academic authors declare that they have no conflict of interest or financial disclosures.

Ethical approval The study protocol, protocol amendments, and all applicable documents (including informed consent form) were reviewed and approved by the Ethics Committee of Xuanwu Hospital Capital Medical University (2016 No.025).

Informed consent Informed consent was obtained from all patients prior to screening.

References

1. Mutter N, Stupp R (2006) Temozolomide: a milestone in neuro-oncology and beyond? Expert Rev Anticancer Ther 6(8):1187–1204
2. Chua J, Nafziger E, Leung D (2019) Evidence-based practice: temozolomide beyond glioblastoma. Curr Oncol Rep 21(4):30
3. Strobel H, Baisch T, Fitzel R et al (2019) Temozolomide and other alkylating agents in glioblastoma therapy. Biomedicines 7(3):69
4. Friedman HS, Kerby T, Calvert H (2000) Temozolomide and treatment of malignant glioma. Clin Cancer Res 6(7):2585–2597
5. Denny BJ, Wheelhouse RT, Stevens MF et al (1994) NMR and molecular modeling investigation of the mechanism of activation of the antitumor drug temozolomide and its interaction with DNA. Biochemistry 33(31):9045–9051
6. Muggeri A, Vago M, Pérez S et al (2017) A randomized, open-label, two-way crossover, single-dose bioequivalence study of temozolomide 200 mg/m2 (Dralitem® vs. Temodal® capsules) in patients with primary tumors of the central nervous system under fasting conditions. Drugs in R D 17(3):427–434
7. Diez BD, Statkevich P, Zhu Y et al (2010) Evaluation of the exposure equivalence of oral versus intravenous temozolomide. Cancer Chemother Pharmacol 65(4):727–734
8. Dhodapkar M, Rubin J, Reid JM et al (1997) Phase I trial of temozolomide (NSC 362856) in patients with advanced cancer. Clin Cancer Res 3(7):1093–1100

9. Brada M, Judson I, Beale P et al (1999) Phase I dose-escalation and pharmacokinetic study of temozolomide (SCH 52365) for refractory or relapsing malignancies. Br J Cancer 81(6):1022–1030
10. U.S. food and drug administration. Tempdal® Label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021029s033lbl.pdf. Accessed 23 February 2020.
11. Declaration of Helsinki. World medical association declaration of hensinki, adopted by the 18th WMA general assembly, Helsinki, Finland, June 1964 and last amended by the 64th general assembly, Fortaleza, Brazil, October 2013. https://www.health.uct.ac.za/sites/default/files/image_tool/images/116/Helsinki%202013.pdf Accessed 23 Feb 2020
12. US Department of health and human services. National institutes of health. National cancer institute. Common terminology criteria for adverse events (CTCAE). Version 5.0. Published 27 November 2017. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. Accessed 19 Oct 2020
13. Baruchel S, Diezi M, Hargrave D et al (2006) Safety and pharmacokinetics of temozolomide using a dose-escalation, metronomic schedule in recurrent paediatric brain tumours. Eur J Cancer 42(14):2335–2342
14. U.S. food and drug administration. Draft guidance on temozolomide. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Temozolomide_cap_21029_RC12-08.pdf. Accessed 23 February 2020

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