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# Method for evaluating the human bioequivalence of acarbose based on pharmacodynamic parameters

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## Abstract

**Objective:** To explore a method for evaluating the bioequivalence of acarbose based on pharmacodynamic parameters using a single-dose, randomized-sequence, three-way crossover study of acarbose test (T) and reference (R) formulations.

**Methods:** Baseline-adjusted, pre-dose value deduction, and direct comparison methods were used to evaluate the geometric T/R ratios and 90% confidence intervals (CIs) of the ln-transformed pharmacodynamic parameters to identify the most suitable evaluation system. Twelve participants were randomly divided into three groups to receive treatment in the following sequences: TRR, RTR, and RRT, each including a 7-day washout period between treatment periods. The serum glucose concentration (baseline) was determined. Pharmacodynamic parameters, including the maximum reduction in serum glucose concentrations ($\Delta C_{SG,max}$) and difference of the AUC of glucose between before and after acarbose exposure ($\Delta$AUEC), were tested.

**Results:** Using the direct comparison method, the geometric mean ratios of $C_{SG,max}$, $AUEC_{(0\text{-}2h)}$, and $AUEC_{(0\text{-}4h)}$ were 94.13%, 97.82% and 99.76%, respectively. The 90% CIs of the geometric T/R ratios for $C_{SG,max}$, $AUEC_{(0\text{-}2h)}$, and $AUEC_{(0\text{-}4h)}$ all fell between 80% and 125%. Conversely, $\Delta C_{SG,max}$ and $\Delta AUEC_{(0\text{-}4h)}$ were less reliable measures of acarbose bioequivalence.

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**Conclusions:** Pre-dose value deduction and direct comparison methods can be initially considered suitable for assessing acarbose bioequivalence.

**Keywords**
Acarbose, pharmacodynamics, bioequivalence, variability, evaluation method, pharmacokinetics, crossover study

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## Introduction

Acarbose is an α-glucosidase inhibitor used to reduce glucose absorption from the small intestine and postprandial blood glucose levels in patients with type 2 diabetes.[1–3] It decreases the production of monosaccharides and their absorption from the gastrointestinal tract by inhibiting α-glucosidase in the brush border of the small intestine.[4] These changes result in reduced post-meal glucose levels and insulin-sparing effects.[5–7] A 200-mg dose of acarbose can reduce starch absorption by approximately 80%, and similar hypoglycemic effects were noted for acarbose over a dose range of 25 to 200 mg.[8,9] The US Food and Drug Administration (FDA) approved 25-, 50-, and 100-mg oral formulations of acarbose. Oral administration results in minimal systemic absorption of acarbose (<2% of the dose). Because of its low bioavailability, acarbose acts locally in the gastrointestinal tract, which is a requirement for therapeutic efficacy.[10]

In general, pharmacokinetic (PK) bioequivalence (BE) represents a substitute for therapeutic equivalence between original and common formulations. However, PK BE is not applicable for drugs with low systemic bioavailability. Although regulatory standards for the BE of drugs that are not systemically absorbed are not well established, many studies used pharmacodynamic (PD) endpoints rather than PK parameters.[11,12]

In 2009, the FDA released draft guidelines for acarbose BE evaluation based on PD parameters. The recommended evaluation parameters were as follows: (1) $\Delta C_{SG,max}$, the maximum reduction in serum glucose concentrations; and (2) $AUEC_{(0\text{-}4h)}$, the difference in $AUC_{(0\text{-}4h)}$ between baseline and 4 hours after the co-administration of acarbose and sucrose. At present, few BE studies on acarbose tablets in Asian populations have been published, and the evaluation results according to FDA guidelines are not equivalent.[13] Simultaneously, considering the possible *in vivo* biotransformation of acarbose tablets, there may be racial differences, and thus, we speculated that the FDA guidelines for acarbose tablet BE may not be fully applicable to Asian populations.

Highly variable drugs are defined by an intra-participant variability (coefficient of variation [CV]) of 30% or higher in BE measurements. Zhang et al.[13] reported significant intra-participant variability in $\Delta C_{SG,max}$ (CV = 32.2%). To reduce the number of samples required for BE studies of highly variable drugs, the FDA and European Medicines Agency have recommended the reference-scaled average bioequivalence (RSABE) method, in which the BE acceptance limits are adjusted according to the variability of the reference product.[14,15] In the FDA-recommended RSABE method, the reference product is administered twice to determine its within-participant variability. Therefore,

bioequivalence studies can be designed using partial duplication (three-way crossover: RTR, RRT, or TRR) or complete duplication (tetragonal crossover: RTRT or TRTR).[15,16]

It is unclear whether the newly proposed method is suitable for assessing the BE of acarbose. Therefore, this study was designed to explore a BE evaluation method for acarbose based on PD parameters. This study used changes in serum glucose levels as indicators of acarbose BE.

## Methods

### Ethics

This study was conducted in accordance with the Declaration of Helsinki (International Conference on Harmonized Guidelines for Clinical Medical Practice),[17] and the local regulatory guidelines of the National Medical Products Administration of People's Republic of China. Prior to commencing the study, research protocols, protocol amendments, and informed consent were approved by the Independent Ethics and Research Committee of Xiangya Hospital, Central South University. Written consent was obtained from all participants.

### Participants

Eligible participants were selected from healthy volunteers aged 18 to 55 years with a body weight of $\geq$50 (for male participants) or $\geq$45 kg (for female participants) and BMI of 19 to 26 kg/m$^2$. Participants who met the inclusion and exclusion criteria described in the protocol were eligible for participation in the study. The inclusion criteria for the present study were as follows: negative findings in various physical examination and laboratory tests, including medication history, vital sign measurements, 12-lead electrocardiogram (ECG), blood biochemistry, routine blood testing, urinalysis, and serological tests for hepatitis C and hepatitis B surface antigen, anti-HIV antibody, and syphilis. In all participants, fasting blood glucose was $\leq$6.1 mmol/L. and the 2-hour post-prandial glucose concentration was $\leq$7.8 mmol/L. Participants with a family history of diabetes or abnormalities in a 75-g oral glucose challenge test were excluded.

Participants were required to avoid all drugs for 2 weeks before and throughout the study period and to abstain from the consumption of alcoholic beverages or coffee from 1 week before the study until the end of the study. Standard meals were supplied from the time participants were hospitalized 1 day before the study began. Diet and exercise were strictly controlled, and any excessive exertion or lying in a supine position for long periods was prohibited. Before each treatment, the participants fasted overnight for at least 10 hours.

### Study design

A single-dose, randomized-sequence, open-label, three-way crossover study was conducted in healthy adult human volunteers with a washout period of 7 days. The study was performed in the Phase I Clinical Research Unit of the Xiangya Hospital of Central South University (Changsha, China). Using SPSS 19.0 (IBM, Armonk, NY, USA), participants were assigned in a 1:1:1 ratio to receive sucrose alone or a single oral dose of either the test (50 mg, Hunan Qianjin Xiangjiang Pharmaceutical Co., Ltd., Hunan, China) or reference formulation of acarbose (specification: 50 mg, Bayer Pharma AG, Leverkusen, Germany) together with sucrose.

In the study, a baseline sucrose challenge was performed on the day prior to each drug treatment. For this challenge, participants received 75 g of sucrose dissolved in

150 mL of water. Blood samples were collected before treatment (0 hours) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, and 4 hours after treatment in each period. Participants were administered 50 mg of the test or reference formulation together with 75 g of sucrose dissolved in 150 mL of water at room temperature, and blood was then sampled as described for sucrose administration alone. Participants were not allowed to drink water for 1 hour after treatment, and they were given a standard lunch 4 hours after sucrose or sucrose/acarbose administration. Blood samples were drawn into BD Vacutainers® (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) with no anticoagulant and stored for 0.5 to 1 hour at room temperature. After clotting, all blood samples were centrifuged at 1300 $\times g$ at 4°C for 10 minutes to separate the serum.

The consumption of caffeinated or alcoholic beverages was not allowed until 72 hours after dosing. Participants were prohibited from smoking, using other medications, eating foods or beverages containing alcohol, caffeine, grapefruit juice, and xanthine. A physical examination, 12-lead ECG, hematology, blood biochemistry, and urinalysis were performed after sampling in all periods. The design of the study is summarized in Table 1.

The researchers who analyzed the samples were blinded to the randomization. The samples were analyzed for serum glucose concentrations using an AU680 Biochemistry Analyzer (Beckman Coulter, Brea, CA, USA).

**Table 1.** Study design for the bioequivalence evaluation of test and reference acarbose formulations.

| Period | Group A (TRR) | Group B (RTR) | Group C (RRT) |
|---|---|---|---|
| First | | | |
| Day 1 | Sucrose | Sucrose | Sucrose |
| Day 2 | T + Sucrose | R + Sucrose | R + Sucrose |
| Seven-day washout period | | | |
| Second | | | |
| Day 8 | Sucrose | Sucrose | Sucrose |
| Day 9 | R + Sucrose | T + Sucrose | R + Sucrose |
| Seven-day washout period | | | |
| Third | | | |
| Day 15 | Sucrose | Sucrose | Sucrose |
| Day 16 | R + Sucrose | R + Sucrose | T + Sucrose |

In total, 75 g of sucrose was dissolved in 150 mL of water. T, 50-mg acarbose test formulation; R, 50-mg acarbose reference formulation.

## *Safety assessment*

Tolerability was determined using 12-lead ECGs, clinical laboratory tests (blood biochemistry, hematology, and urinalysis), vital signs (heart rate, sitting blood pressure, oral body temperature, and breathing rate), and physical examinations. The laboratory tests were performed at the Department of Diagnostic Laboratory Medicine of Xiangya Hospital, Central South University (Changsha, Hunan, China). National Cancer Institute Common Toxicity Criteria for Adverse Events version 5.0 were used to described and grade all toxicities and adverse events. Clinical investigators assessed adverse reactions based on their severity and their relationship to the administered drug.

## *Pharmacodynamic analysis*

Individual PD parameters were calculated using serum glucose levels via a non-compartmental method with WinNonlin® professional software version 8.0 (Certara, Princeton, NJ, USA). The statistical parameters for BE evaluation as recommended by the FDA are $\Delta C_{SG,max}$ and $AUEC_{(0\text{-}4h)}$. In addition to the recommended parameters, we used the following parameters: $C_{SG,max\text{-}0h}$, $AUEC_{(0\text{-}2h)-0h}$, $AUEC_{(0\text{-}2h)}$, $AUEC_{(0\text{-}4h)}$, glucose excursion (GE), GE without the effect of the homeostatic

glucose control (GE′), (the plateau glucose concentration ($C_{ss}$), and the degree of fluctuation of serum glucose based on AUC (fAUC). GE was calculated as the difference between the peak ($C_{max}$) and trough ($C_{min}$) serum glucose concentrations in the 4-hour study period. GE′ was calculated as follows: $GE' = C_{max} - C'_{min}$, where $C'_{min}$ is the minimum glucose concentration in the time interval 0–$t_{max}$. fAUC was calculated as follows: $fAUC = AUC\ (C \geq C_{ss}) + AUC\ (C \leq C_{ss})$, where AUC ($C \geq C_{ss}$) is the AUC for concentrations $\geq C_{ss}$ and AUC ($C \leq C_{ss}$) is the AUC for concentrations $\leq C_{ss}$.

The maximum glucose concentration was obtained by directly examining each individual's serum glucose concentration–time curve. The area under the serum glucose concentration–time curve was calculated using the trapezoidal method. The intra-individual variability of PD parameters was assessed using the coefficient of variation (CV).

### Statistical analysis

The analysis of variance (ANOVA) model included sequence, treatment, and period as fixed effects and participant nested within the sequence as the random effect, and the main effects were tested at a significance level of 5% (0.05). $P < 0.05$ indicated statistical significance. The ratios of ln-transformed PD parameters were calculated. Non-transformed $t_{max}$ data were analyzed using the non-parametric Mann–Whitney U test. Data processing and statistical analyses were performed using SPSS version 19.0.

The geometric mean ratios of the PD parameters and the corresponding 90% confidence intervals (CIs) of the test and reference formulations were calculated. The probability of exceeding the acceptance range limit (80%–125%) was obtained using one-sided *t*-tests. If the 90% CI of the test/reference ratio of the PD parameters of the two preparations was within the range specified by the ABE method, then the two preparations were considered bioequivalent.

## Results

### Participant characteristics

Twelve participants were enrolled in the study, all of whom completed the study. The characteristics of the participants were as follows: age, $22.70 \pm 3.12$ years (range, 18–45); weight, $58.50 \pm 6.90$ kg (range, 46.5–75.5); and BMI, $20.63 \pm 1.25\ kg/m^2$ (range, 19.20–25.65). Each participant received the test formulation once and the reference formulation twice.

### Safety

No protocol violations or serious adverse events were observed in the study. Both the test and reference formulations were well tolerated during the entire study. Four participants experienced a total of five mild adverse events (bloating, two events; nausea, two events; facial flushing, one event) that resolved spontaneously. Of these AEs, bloating and nausea were considered possibly related to the study drugs, whereas facial flushing was not associated with either treatment. No clinically relevant findings were found in the other safety assessments, including physical examinations, ECGs, or laboratory tests.

### PD parameters

The serum glucose concentration versus time curves (Figure 1) revealed a definite hypoglycemic effect after the administration of 50-mg acarbose tablets. The parameters recommended by the FDA for BE testing of acarbose formulations ($\Delta C_{SG,\ max}$ and $AUEC_{(0\text{-}4h)}$) and other related PD parameters are summarized in Table 2. $AUEC_{(0\text{-}4h)}$ could not be computed because

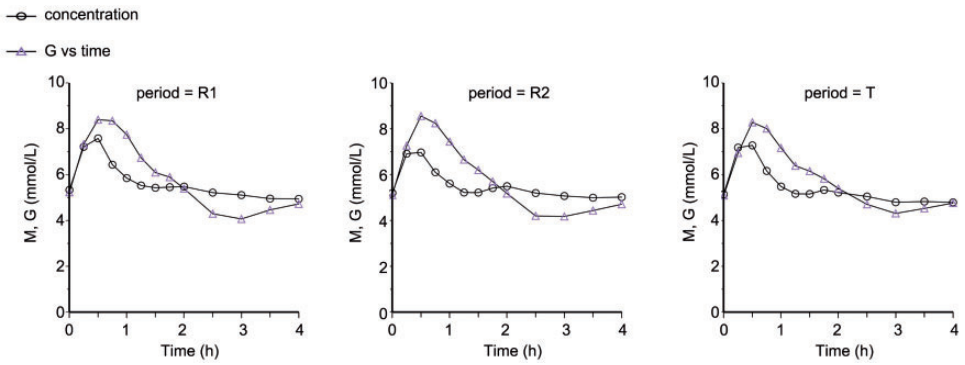


**Figure 1.** Average serum glucose concentration versus time curves for baseline and simultaneous acarbose/sucrose co-administration (reference or test formulation) in 12 participants (acarbose dose, 50 mg).

**Table 2.** Pharmacodynamic parameters following a single oral dose of 50 mg of acarbose (test or reference formulation) or placebo together with sucrose in healthy participants (n = 12).

| Parameter | T | R1 | R2 |
|---|---|---|---|
| $\Delta C_{SG,\ max}$ (mmol/L) | 2.28 ± 0.51 | 2.31 ± 0.87 | 2.39 ± 0.71 |
| $\Delta AUEC_{(0\text{-}2h)}$ (h*mmol/L) | 1.81 ± 0.88 | 1.74 ± 1.00 | 2.07 ± 1.05 |
| $\Delta AUEC_{(0\text{-}4h)}$ (h*mmol/L) | 0.85 ± 1.14 | 0.44 ± 0.96 | 1.11 ± 0.90 |
| $C_{SG,\ max,\ co\text{-}administered}$ (mmol/L) | 7.26 ± 0.88 | 7.83 ± 0.90 | 7.63 ± 1.24 |
| $AUEC_{(0\text{-}2h),\ co\text{-}administered}$ (h*mmol/L) | 11.70 ± 0.89 | 12.23 ± 1.04 | 11.73 ± 1.24 |
| $AUEC_{(0\text{-}4h),\ co\text{-}administered}$ (h*mmol/L) | 21.96 ± 1.34 | 22.47 ± 1.43 | 21.57 ± 1.39 |
| $C_{SG,\ max\text{-}0h}$ (mmol/L) | 2.06 ± 0.80 | 2.50 ± 0.91 | 2.50 ± 1.13 |
| $AUEC_{(0\text{-}2h)-0h}$ (h*mmol/L) | 1.41 ± 0.56 | 1.69 ± 0.84 | 1.62 ± 0.90 |
| $AUEC_{(0\text{-}4h)-0h}$ (h*mmol/L) | 1.60 ± 0.57 | 1.81 ± 0.89 | 1.71 ± 0.86 |
| GE (mmol/L) | 2.46 ± 0.94 | 3.04 ± 0.87 | 3.06 ± 1.32 |
| GE′ (mmol/L) | 2.06 ± 0.80 | 2.50 ± 0.91 | 2.50 ± 1.13 |
| $C_{ss}$ (mmol/L) | 5.49 ± 0.33 | 5.62 ± 0.36 | 5.39 ± 0.35 |
| fAUC (h*mmol/L) | 1.82 ± 0.83 | 2.36 ± 0.96 | 2.19 ± 1.40 |

Data are expressed as the mean ± SD.

T, test formulation; R, reference formulation; $C_{SG,\ max}$, maximum reduction in the serum glucose concentration; ΔAUEC, difference of the AUC of glucose between before and after acarbose exposure; GE, glucose excursion; GE′, GE without the effect of the homeostatic glucose control; $C_{ss}$, the plateau glucose concentration; fAUC, the degree of fluctuation of serum glucose based on AUC.

Alone: sucrose administration alone; co-administered: Sucrose + test/reference.

of the presence of negative values. All PD parameters were characterized on the basis of the adequate study design. ANOVA indicated a lack of group, period, sequence, and treatment effects for both $\Delta C_{SG,max}$ and $\Delta C_{SG,max}$ (Table 3).

## *BE evaluation*

The 90% CIs of the ratios (T/R) for the ln-transformed PD parameters and the power of the test are presented in Table 4, using baseline-adjusted, pre-dose deduction, and direct comparison methods. The power of

**Table 3.** Analysis of variance of the primary pharmacodynamic parameters.

| | *P* | | |
|---|---|---|---|
| Dependent variable | $Ln\Delta C_{SG,max}$ | $Ln\Delta AUEC_{0\text{-}4h}$ | LnRatio $C_{SG,max}$ |
| Sequence | 0.033 | 0.735 | 0.250 |
| Period | 0.270 | 0.323 | 0.336 |
| Treatment | 0.429 | 0.155 | 0.229 |

$C_{SG,max}$, maximum reduction in the serum glucose concentration; ΔAUEC, difference of the AUC of glucose between before and after acarbose exposure.

**Table 4.** Comparison of the geometric mean ratios (90% confidence intervals) of parameters for the test or reference formulation of acarbose in healthy participants (n = 12).

| Parameter | Ratio | 90% CI | Power |
|---|---|---|---|
| Baseline adjusted | | | |
| $\Delta C_{SG,max}$ (mmol/L) | 100.72 | 85.32 to 118.90 | 0.45 |
| $\Delta AUEC_{(0\text{-}2h)}$ (h*mmol/L) | 100.70 | 71.20–148.13 | 0.00 |
| $\Delta AUEC_{(0\text{-}4h)}$ (h*mmol/L) | 48.29 | 22.64–102.98 | 0.00 |
| Pre-dose value deduction | | | |
| $C_{SG,max\text{-}0h}$ (mmol/L) | 82.74 | 69.36–98.70 | 0.67 |
| $AUEC_{(0\text{-}2h)-0h}$ (h*mmol/L) | 85.69 | 66.96–109.67 | 0.00 |
| $AUEC_{(0\text{-}4h)-0h}$ (h*mmol/L) | 94.06 | 75.31–114.43 | 7.10 |
| Direct comparison | | | |
| $C_{SG,max,\ co\text{-}administered}$ (mmol/L) | 94.13 | 89.20–99.34 | 1.000 |
| $AUEC_{(0\text{-}2h),\ co\text{-}administered}$ (h*mmol/L) | 97.82 | 94.88–100.85 | 1.000 |
| $AUEC_{(0\text{-}4h),\ co\text{-}administered}$ (h*mmol/L) | 99.76 | 97.94–101.62 | 1.000 |

CI, confidence interval; $C_{SG,max}$, maximum reduction in the serum glucose concentration; ΔAUEC, difference of the AUC of glucose between before and after acarbose exposure.

$\Delta C_{SG,max}$ was 0.45. Using the direct comparison method, the geometric mean ratios (90% CIs) of the log-transformed parameters for co-administration were 94.13 (89.20–99.34) for $C_{SG,max}$, 97.82 (94.88–100.85) for $AUEC_{(0\text{-}2h)}$, and 99.76 (97.94–101.62) for $AUEC_{(0\text{-}4h)}$, all of which were within the predefined equivalence limit. There was no carryover effect among the periods.

## Discussion

At present, there is a lack of research on the BE of acarbose tablets. The greatest controversy concerning the BE of acarbose tablets is identification of the optimal parameters as evaluation indicators. Following the FDA guidance, Zhang et al.[13] found that although the recommended parameter $\Delta C_{SG,max}$ is valuable for acarbose BE evaluation, the combination of $C_{ss}$, GE, GE′, and fAUC is more preferable than $AUEC_{(0\text{-}4h)}$, in line with our findings. However, the results for the FDA-recommended were not equivalent in this study. Bae et al.[18] applied this PD-based BE method to acarbose tablets in a placebo-controlled crossover ($3 \times 3$) study of healthy volunteers. However, statistical results for BE were not presented in their paper, nor was a clear conclusion drawn

concerning whether the two formulations were bioequivalent. Lee et al.[19] reported that the baseline-adjusted serum glucose $C_{SG,\ max}$ and AUC (from 0–1 hour post-dose) were close to 1. However, the 90% CI of the geometric mean ratio did not fully fall within the current acceptance range of 80% to 125%, and the within-participant variability has not been determined. In fact, the sponsor conducted a pilot BE study of acarbose according to the FDA guidance, finding that 50 mg is the most suitable dosage.

After sucrose administration (baseline), serum glucose levels increased rapidly and then rapidly decreased to 4 to 6 mmol/L (normal range) after 0.75 hours. During acarbose/sucrose co-administration, glucose levels rose slightly outside the normal range and then rapidly returned to the normal range. Because of the steady-state control of the glucose concentration, $AUEC_{(0\text{-}4h)}$ could not be computed because of the presence of negative values, meaning that ln-transformation was not possible in these participants. In clinical practice, the glucose level of patients with diabetes should be maintained within a normal, safe, and acceptable range. Therefore, fluctuations in blood glucose levels are important indicators of glycemic control.[20] Therefore, $C_{ss}$, GE, GE′, and fAUC were calculated in this study.

In the present study, we simultaneously used three methods, namely baseline-adjusted, pre-dose value deduction, and direct comparison methods, to assess the BE of two acarbose formulations in healthy participants for the first time. Following co-administration, the geometric mean ratios (90% CIs) of the log-transformed parameters values were 94.13 (89.20–99.34) for $C_{SG,max}$, 97.82 (94.88–100.85) for $AUEC_{(0\text{-}2h)}$, and 99.76 (97.94–101.62) for $AUEC_{(0\text{-}4h)}$, all of which were within the predefined equivalence limit for the direct comparison method. Kim et al. proposed the use of the ratio of $C_{SG,\ max}$ and AUEC instead of the difference for analysis, which is reasonable. Further research using simulation methods will be helpful for assessing the suitability of these newly proposed methods for PD BE testing.[21]

In our study, large differences in PD behavior between participants were observed. The FDA has recommended the RSABE approach to evaluate the BE of highly variable drugs. However, the suitability of the adjusted acceptance interval method for PD-based BE testing remains an open question because highly variable drugs are often defined by the intra-participant variability of their PK parameters. In PD-based BE testing, adjusting the acceptance interval based on the participant's internal variability in PD parameters may also be helpful. In addition, it should be noted that an appropriate study design should also be used to estimate intra-participant variability in PD responses.

As with any clinical trials, the present study had several limitations. Because the PD data of this study were obtained from healthy Chinese adults who received a single dose of treatment, the PD characteristics of serum glucose may vary in other target populations or after other dosing regimens. Moreover, this was an open-label study, and the assessment of AEs was not blinded. Therefore, the safety of the test and reference formulations may not have been addressed objectively. The small sample size was a major limitation of the present study, and the possibility of false-positive or false-negative findings cannot be excluded.

## Conclusion

Our test acarbose tablets were demonstrated to be bioequivalent to marketed acarbose tablets using the direct comparison method. Both drugs were well tolerated,

and no serious adverse events occurred during the entire study period.

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## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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