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ARTICLE

Evaluating the bioequivalence of two pitavastatin calcium formulations based on IVIVC modeling and clinical study

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Abstract

In vitro-in vivo correlation (IVIVC) allows prediction of the in vivo performance of a pharmaceutical product based on its in vitro drug release profiles and can be used to reduce the number of bioequivalence (BE) studies during product development, and facilitate certain regulatory decisions. Here, we developed an IVIVC model for pitavastatin calcium, a basic Biopharmaceutics Classification System (BCS) II lipid-lowering drug, which was then used to predict the BE outcome of formulations manufactured at two manufacturers. In addition, virtual trials using the IVIVC model using pH 4.0 acetate buffer dissolution showed similarity in areas under the curves and maximum plasma concentration (C_{max}) for test and reference tablets under fasting condition. These predicted results were verified in definitive BE study. In conclusion, we demonstrated that for certain BCS II molecules, IVIVC modeling could be used as a priori to predict the BE outcome.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Biopharmaceutics Classification System (BSC) I, BCS III compounds, and in vitro-in vivo correlation (IVIVC) modeling predicted in vivo performance from in vitro dissolution data can be used to waive bioequivalence (BE) studies.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study explored the BE of pitavastatin calcium dispersible tablets and Livalo under fasting state, the BCS II compound, based on an IVIVC model and clinical study.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Virtual trials using IVIVC models predicted that two pitavastatin calcium formulations, the BCS II compound, were bioequivalent under fasting state, and confirmed by clinical study.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These results supported that IVIVC modeling could be used as a priori predict the BE outcome for BCS II drugs.

INTRODUCTION

Generic drugs are less expensive and have a significant worldwide impact.[1] The rate and the degree of a generic medicine absorption must be equivalent to that of its innovator product in order to ensure quality and therapeutic equivalence.[2] In vivo bioequivalence (BE) studies are a crucial component of meeting these requirements, however, they can result in costly clinical investigations.[3] In recent years, a number of physiologically and clinically pertinent silico models have shown promise in their ability to forecast the efficacy and safety of pharmaceutical products in vivo, significantly expediting efforts to develop new products.

The Biopharmaceutics Classification System (BCS) is a frequently used method for evaluating the relationship between an immediate-release (IR) medication product's in vitro dissolution and in vivo bioavailability. Based on their solubility and permeability, the BCS divides pharmacological compounds into four classes.[4] With regard to IR products, the creation of BCS and the adoption by regulatory agencies allowed for the connection between in vitro dissolution data and in vivo absorption as well as the use of dissolution data as BE substitutes for BCS I (highly soluble and highly permeable) and BCS III (highly soluble and low permeable) substances. In addition, BCS II (low solubility and high permeability) and BCS IV (low solubility and low permeability) compounds under current guidelines are not eligible for biowaiver.[5] However, for IR drug products comprising BCS II drug compounds, conventional in vitro-in vivo correlation (IVIVC) that links in vitro drug release and in vivo plasma concentration could be applied.[6]

One of the rate-limiting processes for drug penetration from the gastrointestinal tract is thought to be the in vivo dissolution and release behavior.[7] IVIVC, a mathematical model that predicts the relationship between conventional dissolving techniques and in vivo bioavailability of IR medicinal products, has been developed over the past few decades. It effectively lowers the number of BE studies by assisting in the formulation optimization of the drug.[8] Four different categories of IVIVCs can be identified from a regulatory perspective, but only a level A IVIVC can substitute human BE studies. In order to determine a level A IVIVC, a two-step process is typically used: first, an appropriate deconvolution technique (e.g., Wagner-Nelson, Loo-Riegelman, and numerical deconvolution) is used to estimate in vivo absorption, and then the amount of drug absorbed is compared to the amount of drug dissolved. The deconvolution approach is only compatible with linear pharmacokinetic (PK) regimens, despite the fact that it is frequently used for regulatory submission.[9] Through a validated level A IVIVC, active pharmaceutical components from the BCS II can get a dissolution-based biowaiver.[10]

Pitavastatin calcium, a BCS II drug, is one of the most widely used lipid-lowering drug.[11,12] Clinical trials are required to establish BE study comparing the innovator and generic drug that include the BCS II drug, as per regulatory requirements. To reduce clinic failure during the drug development and ensure the safety and efficacy of synonym drugs based on the BCS-based biowaivers, it is necessary to develop an oral absorption model as the basis of a biowaiver argument for pitavastatin calcium formulation. However, an oral absorption model of pitavastatin calcium has not been reported. Here, we simulated oral absorption profile for pitavastatin calcium using biorelevant dissolution testing and IVIVC modeling. Additionally, we reported virtual trial simulations to anticipate the BE study outcome of two formulations, and the predicted results were contrasted with the findings of the actual BE study.

METHODS

Formulations

The test (T) formulation was a branded generic product, pitavastatin calcium dispersible tablets (2.0 mg; batch: B1901142) manufactured by Zhejiang Jingxin Pharmaceutical Co., Ltd. The reference (R) formulation was a branded innovator product, pitavastatin calcium tablets (Livalo; 2.0 mg; batch: BS7H) manufactured by Japan Kowa Company Ltd.

Dissolution tests

Dissolution of 2.0 mg pitavastatin calcium dispersible tablets were conducted in pH 3.5 and pH 4.0 acetate buffer. The dissolution was carried out in a USP-2 apparatus using 500 ml of medium at 50 rpm, with a constant temperature of 37°C. Samples were drawn from the dissolution vessel at various timepoints of 2, 5, 7, 10, 15, 20, and 30 min. Pitavastatin calcium concentration was analyzed in high-performance liquid chromatography.

Development of an oral absorption model for pitavastatin calcium

All simulations were performed using the two-compartment model in GastroPlus version 9.8 (Simulations

Plus, Inc.), the relevant inputs in the model are listed below.

Pitavastatin calcium physicochemical properties

Pitavastatin calcium properties used in building the model are summarized in Table 1.

Dissolution data input

The dissolution data for the corresponding clinical batches shown in Table S1 were used to simulate the PK profiles and PK parameters shown in Figure 2 and Table 2. These dissolution data were primarily used for building and validating the pitavastatin calcium absorption model against historical data. Instead of directly include the dissolution curve in the simulation, GastroPlus™ fitted the in vitro dissolution data using the integrated Johnson dissolution model to produce a representative diffusion coefficient value. This allowed for a more mechanistic modeling of the dissolution process in the gastrointestinal tract.

TABLE 1 Input parameters of pitavastatin calcium for basic modeling

Parameters	Value
Molecular weight, g/mol[a]	421.47
Log P[a]	3.75
pKa[a]	4.86
Solubility, mg/ml[a]	0.0652 (pH 4.68) 0.00394 (water)
Permeability, Peff cm/s × 10^{-4}[b]	1.17
Mean precipitation time, s[c]	900
Particle size, μm[c]	25
Diffusion coefficient, $cm^2/s \times 10^{-5}$[b]	0.62
Drug particle density, g/ml[c]	1.2

[a]From website "drug bank."

[b]Calculated by GastroPlus.

[c]Default GastroPlus.

PK parameters

As no PK studies in which pitavastatin calcium was administered intravenously in humans were available, data of the reference product (2.0 mg tablet) from a previous study were used.[13] Plasma concentrations were extracted from the original figure using Web Plot Digitizer and used in the PKPlus module in GastroPlus to build a compartmental (1, 2, or 3 compartments) PK model. The PKPlus module calculated PK parameters under fasting conditions using the two-compartmental model and the generated mean PK parameters used in these simulations were clearance (CL) = 20.57 L/h ([percent coefficient of variation] %CV = 35.16%), volume of distribution (V_c) = 43.17 L (%CV = 94.09%), distribution constant from the central to the peripheral compartment (k_{12}) = 0.252 1/h (%CV = 148.88%), and distribution coefficient from the peripheral to central compartment determined (k_{21}) = 0.086 1/h (%CV = 144.08%).

Physiology

Gastrointestinal compartmental data (absorption scale factors [ASFs], pH, transit time, and fluid volumes) were used as default in the human fasting physiological model. We further adjusted the relevant parameters based on the previous study[8] to better fit the observed data, ASF of duodenum was changed to 3.794 from the default value of 2.794, ASF of jejunum changed to 3.900 from the default value of 2.900, and the stomach pH was set at 3.0.

Virtual BE trials

To assess the bioperformance of two formulations, virtual trials were carried out through crossover designs in 24 and 36 healthy Chinese subjects, randomly chosen by GastroPlus. The default population in GastroPlus was used in these simulations. The mean values and %CV for pitavastatin calcium-specific characteristics including dosage, solubility, permeability, PK parameters, drug

TABLE 2 Observed and predicted AUC_{0-t} and C_{max} for reference formulation at 2.0 mg under pH 3.5 and pH 4.0

	AUC_{0-t}, μg × h/ml			C_{max}, μg/ml		
pH	Observed	Predicted	%PE	Observed	Predicted	%PE
3.5	89.147	86.19	−3.3	20.193	7.1734	−64.5
4.0		102.16	14.6		18.063	−10.5

Note: The percentage prediction errors (%PE) for these simulations were calculated as ([predicted–observed]/observed) × 100, and the criteria of %PE was no more than 15%.

Abbreviations: AUC_{0-t}, area under the drug plasma concentration–time curve from time 0 to the last measurable point; C_{max}, maximum plasma concentration.

particle size, and fraction unbound in plasma were modified to the measured values, as mentioned in the previous section. These simulations made it possible to evaluate the combined impacts of population physiology and formulation factors, allowing evaluation of the BE result.

Definitive BE study

Subjects

Subjects should be aged 18–45 years with a body mass index of 19–26 kg/m^2. Men and women weighed more than 50 or 45 kg, respectively. History and physical examination, as well as laboratory and electrocardiogram (ECG) were used to evaluate health condition. Subject exclusion criteria were as follows: history of any disease; taking medication within 2 weeks; abnormal ECG, physical examination, or laboratory tests; smoking, drinking more than 14 units per week; blood donation within 1 month before administration (≥200 ml); allergic predisposition or hypersensitivity to any component of the tablet; and expected lack of compliance during the study period. The demographic characteristics of the subjects are summarized in Table S2.

The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki at the Center of Clinical Pharmacology, at the Second Affiliated Hospital, School of Medicine, Zhejiang University. The protocol was reviewed and registered at the Center for Drug Evaluation, National Medical Products Administration (CTR20190940 and CTR20191166) and approved by the Ethics Committee of the Second Affiliated Hospital of the Zhejiang University School of Medicine (No. Drug 2018-535 and No. Drug 2019-338). All subjects provided written informed consent before dosing.

Study design

This single-dose, randomized, open-label, two-period, and two-treatment self-crossover study was executed under fasting condition. In general, the subjects were randomly assigned by DAS 3.2.8 to receive 2.0 mg T or R product in a 1:1 ratio, and then received the alternative products, following a 1-week washout period. At the end of the crossover, each subject had received two formulations. The blood samples were collected in EDTA-K_2 tubes before drug administration (0 h) and 0.17, 0.33, 0.5, 0.67, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 h after administration. Following blood collection, the samples were slowly tilted backward and forward immediately. The plasma was obtained via centrifugation (1700 *g*, 10 min, 4°C) within 60 min of blood collection and stored at −70°C for analysis.

Statistical analysis

Analysis of variance (ANOVA) was performed on the logarithmically transformed maximum plasma concentration (C_{max}), area under the curve (AUC) to assess the effects from sequence, period, and formulation. Statistical data were presented as mean ± SD. The probability value <0.05 is considered statistically significant. The ratio of geometric means (GMRs) of the primary PK parameters and their 90% confidence intervals (CIs) were calculated. If it is within the equivalent range (80%–125%), it is judged as BE, and the results of double unilateral *t*-test are listed. Time to maximum concentration (T_{max}) was analyzed by nonparametric statistical test. Statistical analyses were performed by SAS 9.4 (SAS Institute).

RESULTS

In vitro dissolution

Different pH is supposed to affect the dissolution rate because the solubility of the pitavastatin calcium is pH-dependent (pKa of 4.86). The dissolution profiles for the R and T formulations in different pH media were shown in Figure 1, and results showed that two formulations were nearly completely dissolved within 7 min in both pH 3.5 and pH 4.0 (>85%). We calculated dissolution similarity factor f_2 to justify the similarity between the R and T drugs. However, two formulations were considered similar only in pH 4.0 media ($f_2 > 50$), not in pH 3.5 media ($f_2 = 46$).

IVIVC modeling for prediction of reference formulation PKs

An IVIVC model was established based on the different in vitro dissolution data and validated using previous reported in vivo data of reference product (2.0 mg, tablet).[13] Table 1 shows the detailed input parameters of the IVIVC model. We compared the predicted and observed mean plasma concentration curves, AUC, and C_{max} after oral administration of 2.0 mg pitavastatin calcium tablets. The results showed that under pH 4.0 media simulation, the percentage prediction error (%PE) values of both AUC and C_{max} were below 15% (Figure 2a,b and Table 2). Although the absolute AUC_{0-t} %PE value of pH 3.5 was smaller than the pH 4.0, the deviation of parameters was out of the ranges under pH 3.5 simulation ($R^2 = 0.072$). In conclusion, using pH 4.0 dissolution data enables the IVIVC model to predict the in vivo behavior more accurately.

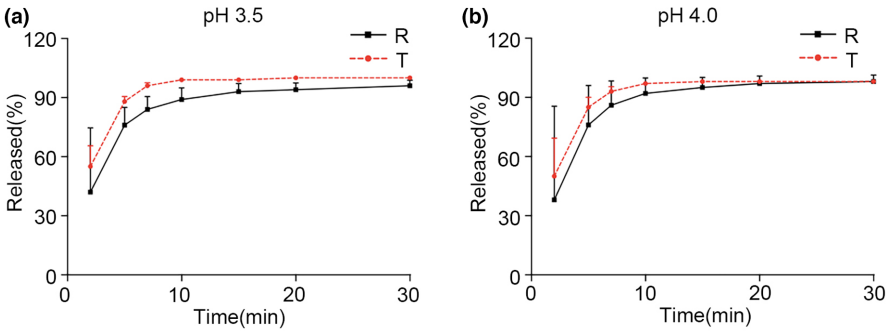

FIGURE 1 Dissolution profiles of the T and R formulations in pH 3.5 (a) and pH 4.0 (b) media (data are presented as mean ± SD, $n = 3$). R, reference; T, test

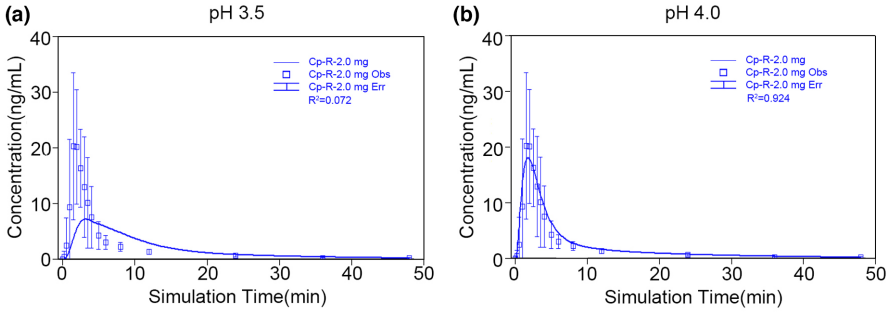

FIGURE 2 Predicted (line) and observed (squares) PK profiles of reference formulation (R) at a dose of 2.0 mg in pH 3.5 (a) and 4.0 (b) media. Obs, observed; PK, pharmacokinetic

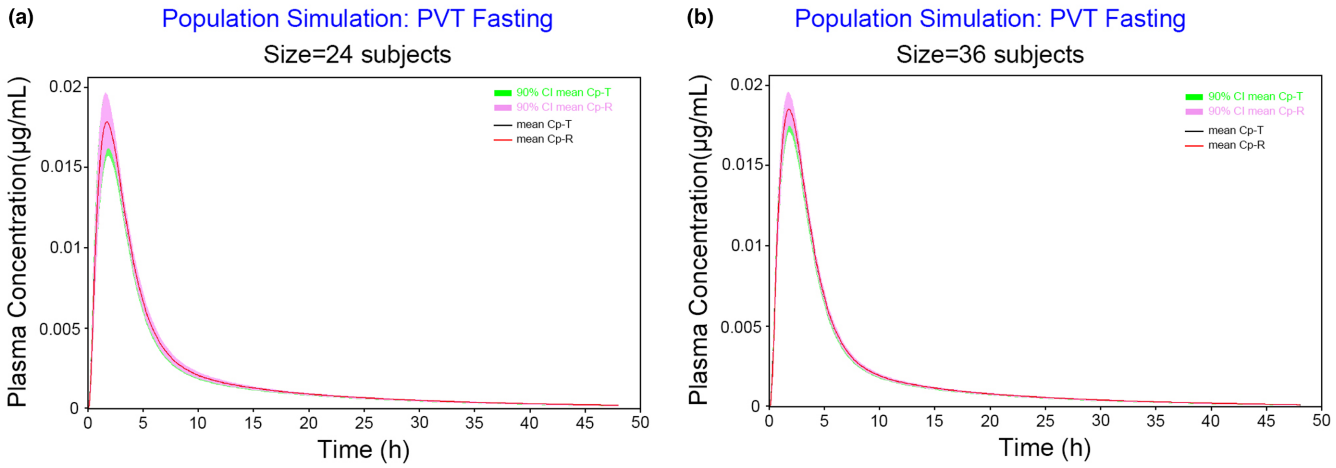

FIGURE 3 Virtual BE trials in (a) 24 and (b) 36 subjects in fasting state. BE, bioequivalence

Prediction of BE of pitavastatin calcium

The developed IVIVC model was used to predict the mean plasma concentration profiles and PK parameters of T and R formulations in fasting state. Subsequently, virtual trial simulations were performed at a dose of 2.0 mg in 24 and 36 subjects according to the BE study population size requirements.[8,13] Simulations predicted that T and R formulation to be bioequivalent only in 36 subjects, as the 90% CIs of the geometric mean T/R ratios for AUC and C_{max} were within the regulatory acceptance limit for BE (80%–125%) (Figure 3a,b and Table 3).

BE study outcome

In fact, we first conducted BE study in 24 subjects before virtual BE prediction, however, these two formulations were not equivalent as 90% CIs for the GMR of C_{max} ratios were 104.33%–126.36% (out of the range of 80.00%–125.00%; Table S3). Subsequently, we expanded subject size up to 36 according to the predicted results from the IVIVC model. The mean plasma concentration profiles of the T and R products are shown in Figure 4 and the mean PK parameters are summarized in Table S4. Results showed that the bioavailability of the test product was

TABLE 3 The 90% CIs of two virtual BE trials in fasting conditions

Population size	C_{max} ratio T/R	$AUC_{0-\infty}$ ratio T/R	AUC_{0-t} ratio T/R
24	98.385–125.649	95.083–99.811	95.059–99.841
36	92.451–103.770	96.791–98.879	96.676–99.017

Abbreviations: $AUC_{0-\infty}$, area under the drug plasma concentration–time curve from time 0 h to infinity; BE, bioequivalence; CI, confidence interval; C_{max}, maximum plasma concentration; T/R, test/reference.

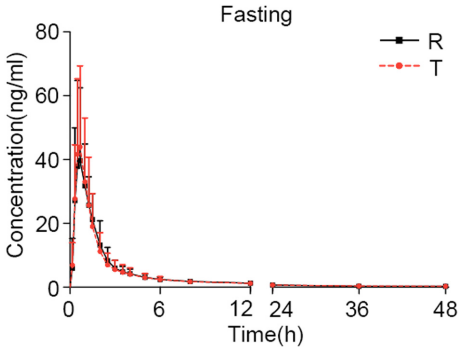

FIGURE 4 BE evaluation of the T and R formulations (2.0 mg) of pitavastatin calcium under fasting condition in 36 healthy subjects. Data are presented as mean ± SD. BE, bioequivalence; R, reference; T, test

similar to that of the reference product under fasting conditions (Figure 4, Table S4). The 90% CIs for the GMR of AUC_{0-t} ratios were 94.46%–101.19%, 90% CIs for the GMR of $AUC_{0-\infty}$ ratios were 94.77%–101.31%, and 90% CIs of the geometric mean of T/R C_{max} ratios were 96.28%–111.16%. In conclusion, these results indicated that these two formulations were bioequivalent.

Table S5 gives the ANOVA results on pitavastatin calcium formulation for the ln-transformed PK parameters of AUC and C_{max} concerning the fixed effects of sequence, formulation, and period between the T and R groups. In addition, there was no sequence, formulation, or period effect on $\ln AUC_{0-t}$, $\ln AUC_{0-\infty}$, and $\ln C_{max}$ ($p > 0.05$), indicating these factors did not affect the establishment of BE.

DISCUSSION

In this study, we built an IVIVC absorption model for pitavastatin calcium to predict the BE of T and R formulations in fasting state using virtual trials. The outcome of virtual simulations was confirmed by the definite BE study, all results demonstrated that 2.0 mg pitavastatin calcium tablets manufactured from two companies were bioequivalent.

Pitavastatin calcium, as a basic BCS II drug, have high solubility at lower pH, it is anticipated that the initial dissolution in the normal stomach environment (pH < 3) will determine the absorption and bioavailability. In our research, however, the simulation data showed that dissolution in pH 4.0 media could better assess the bioperformance of pitavastatin calcium formulations. Most weakly basic BCS II drugs have a higher solubility in the stomach with acidic pH and lower solubility in the small intestine near-neutral pH under fasting conditions. Although these drugs are rapidly dissolved and ionized in gastric pH, absorption is less, and most drugs are absorbed in the small intestine.[14] In order to better mimic gastric transfer and intestinal absorption, we will further develop gastric transit and biphasic dissolution models.

Because BCS principles exempt BCS I and BCS III drugs for BE studies, in vitro dissolution data may become a surrogate for BE studies for many drugs. In this paper, we developed an absorption model for pitavastatin calcium, a BCS II drug, was described to a priori predict the BE. We demonstrated here that, for some weakly basic low-solubility molecules, absorption modeling could be used to justify a BE study waiver. As expected, whereas $f_2 > 50$ at pH 4.0 under fasting conditions could suggest drug performance in vivo, f_2 failure at pH 3.5 dissolution could not establish a correlation. We speculated that pitavastatin calcium dissolved completely in the acidic environment of the stomach and was supersaturated in the small intestine.[15]

A virtual trial stochastically selects parameters from predefined distributions to predict BE study outcome. To evaluate the effect of population variability and size on the pitavastatin calcium plasma concentration distribution, two virtual simulations were conducted. Populations of 30-year-old Chinese men/women, including 24 and 36 subjects, respectively, were subjected to 2.0 mg T or R formulations. GastroPlus randomly generates subjects by varying the physiological factors, such as compound parameters, PK parameters, pHs, fluid volumes, and gastrointestinal transit times. Simulation results showed that T and R formulations were only bioequivalent among 36 subjects, but not 24 subjects. Our first BE study was failed in 24 subjects; however, it was confirmed that these two formulations were bioequivalent after using a 36-person population size according to simulation results. Indicating that IVIVC simulation could provide guidance for BE study of BCS II drug in population size.

Conventional IVIVC is a mathematical relationship between in vivo absorption and in vitro dissolution, limits its application in certain conditions, such as different species or physiological conditions, and using the physiologically based IVIVC currently is extensively utilized for biopharmaceutics modeling.[16] In further study, pitavastatin calcium uptaken transporter OATP1B1[17] and biliary excretion by breast cancer resistance protein[18] could be

considered in IVIVC. Moreover, for a BCS II drug BE study, the food effect needed to be explored as per the regulatory requirement.[6] Solution data of pitavastatin calcium in fed state simulated gastric fluid and fed state simulated intestinal fluid were needed to develop IVIVC model for the fed condition.

In conclusion, we developed an IVIVC model to predict the BE of two pitavastatin calcium formulations in fasting state. In addition, the clinical study confirmed the successful IVIVC model development and showed that T and R formulations were bioequivalent.

AUTHOR CONTRIBUTIONS

J.W., J.C., and L.W. wrote the manuscript. D.Y., R.S., H.L., Z.R., and B.J. designed the research. J.W., J.C., D.Y., R.S., H.L., Z.R., and B.J. performed the research. J.W., J.C., L.W., Z.R., and B.J. analyzed the data.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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