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CLINICAL TRIAL REPORT

Pharmacokinetics and Bioequivalence of Apremilast Tablets in Chinese Healthy Subjects Under Fasting and Postprandial States

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Objective: This study compared the pharmacokinetics, safety and bioequivalence (BE) of generic and original apremilast tablets in healthy Chinese subjects under fasting and postprandial conditions, providing sufficient evidence for abbreviated new drug application.

Methods: A randomized, open-label, two-formulation, single-dose, two-period crossover pharmacokinetic study was performed. Thirty-two eligible healthy Chinese subjects were enrolled in fasting and postprandial studies, respectively. In each trial, subjects received a single 30-mg dose of the test or reference apremilast tablet, followed by a 7-day washout interval between periods. Serial blood samples were obtained for up to 48 h post-intake in each period, and the plasma concentrations of apremilast were determined by a validated method. The primary pharmacokinetic (PK) parameters, including the maximum plasma concentration (C_{max}), the areas under the plasma concentration–time curve (AUC_{0-t}, $AUC_{0-\infty}$), were calculated using the non-compartmental method. The geometric mean ratios of the two formulations and the corresponding 90% confidence intervals (CIs) were acquired for bioequivalence analysis. The safety of both formulations was also evaluated.

Results: Under fasting and postprandial states, the PK parameters of the test drug were similar to those of the reference drug. The 90% CIs of the geometric mean ratios of the test to reference formulations were 94.09–103.44% for C_{max}, 94.05–103.51% for AUC_{0-t}, and 94.56–103.86% for $AUC_{0-\infty}$ under fasting conditions, and 99.18–112.48% for C_{max}, 98.79–106.02% for AUC_{0-t}, and 98.95–105.89% for $AUC_{0-\infty}$ under postprandial conditions, all of which were within the bioequivalence range of 80.00–125.00%. Both formulations were well tolerated, and no serious adverse events occurred during the study.

Conclusion: The trial confirmed that the PK parameters of the generic and original apremilast tablets were bioequivalent in healthy Chinese subjects under fasting and postprandial states, which met the predetermined regulatory standards. Both formulations were safe and well tolerated.

Clinical Trial Registration: chinaDrugtrials.org.cn, identifier CTR20191056 (July 30, 2019); chictr.org.cn, identifier ChiCTR2300076806 (October 19, 2023).

Keywords: apremilast, psoriasis, pharmacokinetics, bioequivalence, safety

Introduction

Psoriasis is a chronic immune-mediated skin disease that affects more than 125 million people worldwide.[1,2] There are a variety of phenotypes of psoriasis, but the plaque or psoriasis vulgaris is the most frequent and most easily recognized.[3] It is characterized by well demarcated, salmon-pink plaques covered in silvery scales in white skin and of grey plaques in black skin.[3] Symptoms include itching, burning and soreness. Psoriasis can manifest at any age, and in men and women, it occurs equally. It can present earlier in women, with a bimodal onset at the age of 16–22 years and 55–60 years.[3,4] Patients with psoriasis experience substantial comorbidities, including psoriatic arthritis, cardiometabolic diseases, psychiatric disorders, and negative effects on quality of life.[1]

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The pathogenesis of psoriasis is associated with an increased release of pro-inflammatory cytokines from immune-related cells and chronic activation of the innate and adaptive immune systems.[2,3] Therefore, systemic treatments with non-biological and biological agents that target both immune systems and skin are the most appropriate therapies for psoriasis. Non-biological agents such as methotrexate, acitretin, cyclosporine, and fumaric acid ester derivatives are conventionally prescribed in case of moderate or severe psoriasis.[2,5,6] However, non-selectivity based on these drugs blockade of the inflammatory cascade and long-term continuous use of non-biologics is not recommended because of their organ toxicity and adverse effects, which often lead to treatment interruption or the need for clinical and laboratory monitoring during treatment.[5,6] Biological agents targeting TNF-α, IL-12/23, IL-17 or their receptors represent one of the most important therapeutic advances in psoriasis,[1] which have been shown to be highly effective, have a favorable safety profile and allow for long-term use.[7] Nevertheless, there are several limitations associated with biologic therapy, such as primary and secondary failure, parenteral administration, high cost and specialist management.[3] Therefore, despite the advantages of biologic therapies for psoriasis, there is still an unmet need that can be partially met through new, oral, safer and more cost-effective treatments.

Apremilast, an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly by binding to the catalytic site of the PDE4 enzyme thereby blocking the degradation of cAMP, which in turn down-regulating the pro-inflammatory markers (TNF-α, IL-23, IL-17 and other inflammatory cytokines) and increasing the levels of anti-inflammatory cytokines such as IL-10.[5,6] In 2014, the US Food and Drug Administration (FDA) first approved apremilast for the treatment of moderate-to-severe plaque psoriasis and active psoriatic arthritis, followed by the European Medicines Agency in 2015 for this indication.[2,8] The PK profile of apremilast tablet (OTEZLA®), originally developed by Celgene Corporation, exhibits an absolute bioavailability of 70%, time to C_{max} (T_{max}) of 2.5 h, terminal elimination half-life ($T_{1/2}$) of 5 ~ 7 h, and no food effect.[9] Apremilast is extensively metabolized by both CYP and non-CYP mediated pathways,[8,9] and dose adjustment is not required in patients with mild or moderate renal impairment or severe hepatic impairment.[9] Limited studies have shown that the PK characteristics of apremilast were similar irrespective of ethnicity.[9] The clinical PKs, safety, and tolerability of apremilast have been investigated in the United States' and Europe's populations.[8,9] However, data from PK studies of the Chinese population are limited. Furthermore, considering the access limitations or incapacity to afford the brand-name drugs, the development and application of generic drugs as substitutes is a clear and economical choice.

Recently, a generic apremilast tablet, produced by the CSPC Ouyi Pharmaceutical Co., Ltd. (Hebei, China), is the first generic drug of its type in China. According to the National Medical Products Administration (NMPA) guidelines, this study compared the PK parameters of the new test, apremilast tablet, with those of the reference product (OTEZLA®). To support the marketing approval of the newly developed generic formulation in China, a pharmacokinetics and bioequivalence study was performed in healthy Chinese subjects under fasting and postprandial states.

Materials and Methods

Study Drugs

The test formulation was an apremilast tablet, which was produced and provided by CSPC Ouyi Pharmaceutical Co., Ltd., Hebei, China (30 mg/tablet, batch number: A82190601; expiry date: June 12, 2021). The reference formulation (30 mg/tablet, batch number F2367A; expiry date: February 2020), which is marketed under the brand name OTEZLA® and produced by Celgene Corporation, was also provided by CSPC Ouyi Pharmaceutical Co., Ltd.

Ethics Approval and Study Population

This study was conducted in compliance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines, and the Guidelines for Good Clinical Practice recommended by NMPA. The study was registered on the Drug Clinical Trial Registration and Information Publicity Platform (chinadrugtrials.org.cn) as CTR20191056 and was retrospectively registered in the Chinese Clinical Trial Registry (chictr.org.cn) as ChiCTR2300076806. The protocol and informed consent forms (ICFs) were approved by the independent ethics committee of Hebei General Hospital [Ethics Number: (2019) (08–01)]. This study was performed

at the Phase I Clinical Research Center of Hebei General Hospital, Shijiazhuang, Hebei, China. All participants signed ICFs after a full understanding of the study's objectives, content, procedures, and possible risks. A withdrawal option was available to participant at any time.

Healthy men and women aged over 18 years old with body mass index (BMI) between 19.0 and 26.0 kg/m^2 (with weights ≥50 kg for males and ≥45 kg for females) were eligible for the study. All subjects were judged to be healthy as determined by medical history, clinical examinations, vital signs, 12-lead electrocardiography (ECG), chest radiography, laboratory tests (routine analyses of the haematology, blood biochemistry, coagulation function, routine urinalysis, renal function, liver function, virological screening, alcohol breath test, drug abuse screening). Subjects were not eligible if they had any evidence of the following: clinically relevant acute or chronic diseases; smoking status or nicotine abuse; allergic constitution, especially allergy to any ingredient in apremilast tablet; history of blood donation (more than 400 mL) or receiving blood transfusion within 3 months; or those taking any medications (including Chinese herbal medicine and/or vitamin products) or supplements within 14 days prior to screening; or those taking part in other clinical trials within 3 months prior to screening. Meanwhile, female subjects who were lactating or have a positive pregnancy test before enrollment were not allowed to participate in the study. All subjects and their partners could not be undergoing fertility planning and had to be willing to take effective contraception before dosing to six months after the end of the study.

Study Design

A single-center, randomized, open-label, two-formulation, single-dose, two-sequence, two-period crossover bioequivalence study was designed to be conducted in healthy Chinese subjects. The study was comprised of two independent trials: the fasting bioequivalence trial and the postprandial bioequivalence trial. Based on a random number table generated by SAS statistical software (v9. 4), all subjects in each trial were randomly assigned to either the T-R or R-T group (where T refers to the test formulation and R refers to the reference formulation) at a 1:1 ratio. A 7-day washout period was used between the two treatment periods. After fasting for at least 10 h overnight, each subject in the fasting trial received a single 30 mg of the T or R formulation and administered orally with 240 mL of warm water. In the postprandial trial, the subjects received a standard high-calorie and high-fat (total energy 800–1000 kcal: approximately 500–600 kcal of fat, 150 kcal of protein, 250 kcal of carbohydrate) breakfast 30 min before drug administration. The subsequent procedure of drug administration for postprandial subjects was consistent with that for fasting subjects. Water intake was restricted for 1 h before and after administration. Standardized lunches and dinners were provided at 4 and 10 hours after drug administration.

As intra-individual variation in the pharmacokinetic parameters of apremilast is not fully understood, we conducted a comprehensive estimation of the sample size of the fasting and postprandial study. According to the clinical pharmacology and biopharmaceutical reviews of apremilast by FDA,[9] apremilast is not the drug with high intra-subject variability. Considering racial differences, the coefficient of intra-individual variation of apremilast in the fasting and fed groups was estimated as 22.5%. Assuming a one-sided test with $\alpha = 0.05$ and power of 0.8 ($\beta = 0.2$), the geometric mean ratios were expected to be 0.95–1.05, and 90% CI of 80.00%–125.00% for bioequivalence, 24 samples were required for the fasting and postprandial study. After considering the dropout rate, 32 participants were enrolled for each study.

Blood Sampling and Bioanalytical Assay

Serial blood samples for pharmacokinetic analysis of apremilast were collected within 1 hour pre-dose (baseline) and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 36.0, and 48.0 h post-dose in the study under both fasting and fed conditions. The blood samples were centrifuged at 1700 × *g* at 4 °C for 10 min within 1 h of collection, and plasma was obtained from the supernatants and stored at −60 °C within 2 h of collection until their use for analysis. Plasma samples were determined at Suzhou Haike Pharmaceutical Technology Co. Ltd., and the plasma concentration of apremilast was detected by a validated method according to the Chinese NMPA and FDA guidelines.

Pharmacokinetic Analysis

The primary pharmacokinetic endpoints for apremilast were C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$. T_{max}, $T_{1/2}$, and elimination rate constant (λ_z) were the secondary endpoints. Based on the plasma concentration data, the pharmacokinetic

parameters of apremilast were calculated using a non-compartmental model using Phoenix WinNonlin software (Pharsight Corporation, Mountain View, CA, USA; version 8.1). C_{max} and T_{max} were determined directly from the observed plasma concentration–time profiles. AUC_{0-t} was calculated using the linear/log trapezoidal method. $AUC_{0-\infty}$ was determined by formula: $AUC_{0-\infty} = AUC_{0-t} + C_t / \lambda_z$, where C_t was the last measurable concentration. λ_z was estimated by linear regression of the logarithm of the concentration–time data in the terminal phase. $T_{1/2}$ was calculated as $0.693/\lambda_z$.

Bioequivalence and Statistical Analysis

After the transformation of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ to their natural logarithmic values, the data were subjected to multivariate analysis of variance by using a linear mixed-effect model, in which the subjects nested within the sequence were used as a random effect and the formulation, period and sequence were used as fixed effects, two-sided *t*-test were performed, and the level of significance was set at $p < 0.05$. To assess the bioequivalence between the test and reference formulations, 90% CIs of the geometric least-squares mean (GLSM) ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ between the two formulations were calculated. The acceptance criteria for bioequivalence were assumed if the 90% CIs were completely within the range of 80.00–125.00%.

The Wilcoxon signed-rank test was used to analyze the T_{max} between the two formulations. Descriptive statistics were used for the pharmacokinetic parameters, the count and grade data were expressed as frequencies and percentages, and the statistical analyses were performed by using the SAS software (SAS Institute Inc., Cary, NC, United States; version 9.4).

Safety Assessment

To assess the safety and tolerance of apremilast, adverse events (AEs), severe adverse events (SAEs), laboratory tests, vital sign measurements, physical examinations, and 12-lead ECG were monitored at predefined regular intervals throughout the study. Vital signs (body temperature, blood pressure, and heart rate) were monitored pre-dose (within 1 h), as well as at 2.0, 4.0, 8.0, 12.0, 24.0, and 48.0 h after each drug administration in each treatment period. Laboratory tests, physical examinations, and 12-lead ECG were performed at screening and during the follow-up period. All AEs were monitored throughout the study by the research doctors and spontaneously reported by the subjects, and these AEs were coded according to the preferred term and system organ class in the Medical Dictionary for Regulatory Activities (MedDRA®). The severity of AEs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0) from the National Cancer Institute of the United States.

Results

Study Population

This study was performed from August 1, 2019, to October 8, 2019. As shown in Figure 1A, a total of 109 potential Chinese adults were screened in the fasting study. Of these, 32 healthy subjects met the eligibility criteria for the protocol and were enrolled and randomized. All subjects completed the whole study as planned, and no subjects withdrew during the fasting trial. Under postprandial conditions, a total of 106 potential Chinese adults were screened, and 32 healthy subjects were enrolled and randomized (Figure 1B). One subject (C025) withdrew for suspected seizures before the first dosing (Figure 1B). One participant (C001) dropped out because of vomiting within 1 h after dosing in the second period. The remaining 30 subjects completed the whole postprandial trial (Figure 1B). The baseline demographic characteristics of each subject are presented in Table 1. The data showed that participants in the fasting and postprandial studies were similar in age, sex, weight, height, BMI, and ethnicity, and the ethnicity of the study population was almost Han Chinese.

Pharmacokinetics Results

Under fasting conditions, all 32 randomized subjects were enrolled in the pharmacokinetic concentration set (PKCS) and pharmacokinetic parameter set (PKPS) for PK parameter analysis of the test or the reference product. The major PK

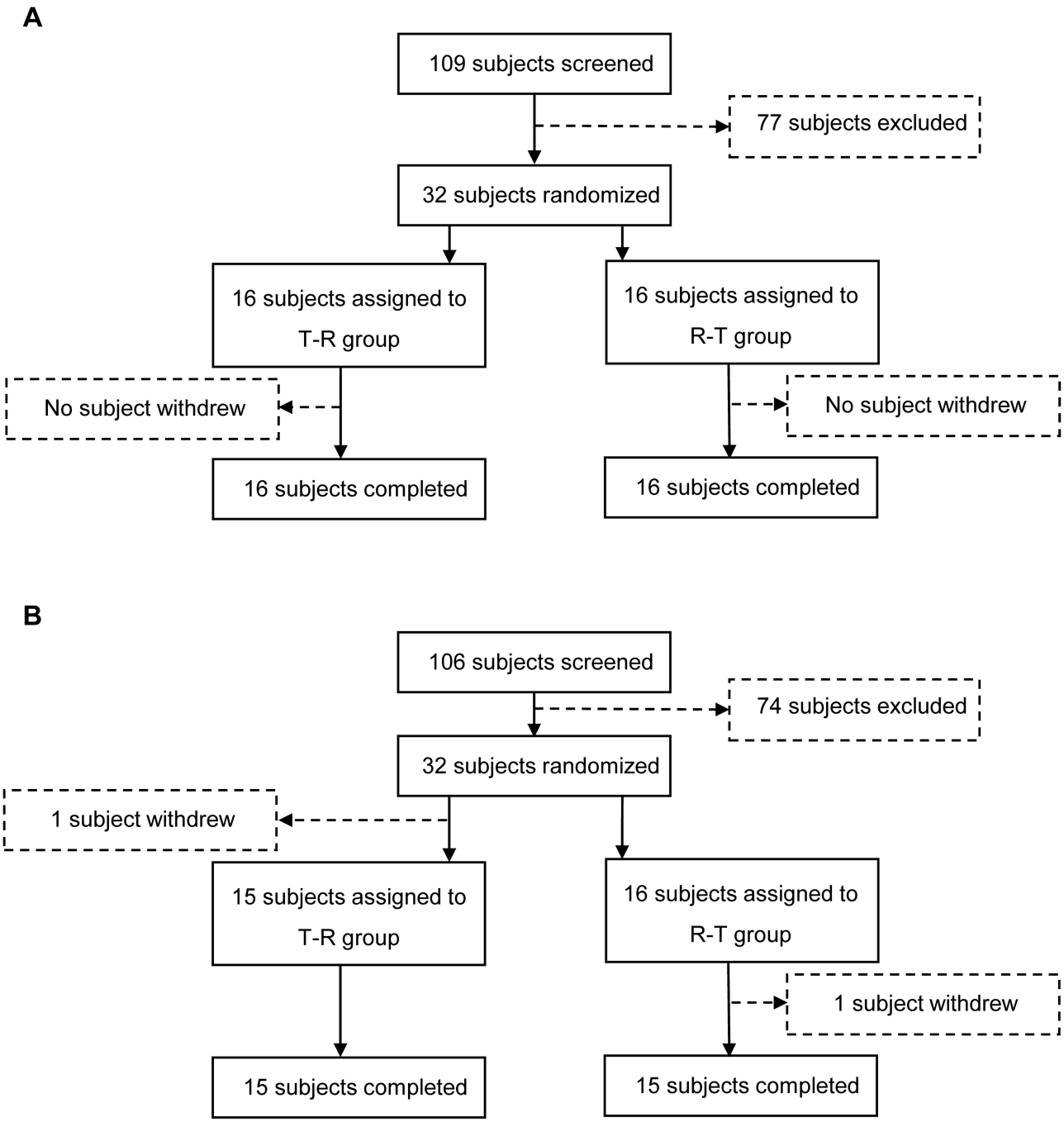

Figure 1 Study design and disposition flow diagram. Flow chart of the subjects in the fasting state (**A**). Flow chart of the subjects in the postprandial state (**B**).

parameters of apremilast were calculated using a non-compartmental model and are summarized in Table 2. The results showed that a C_{max} value of 362.19 ± 93.20 ng/mL of apremilast was achieved within 0.49–4.99 hours after oral administration of the test apremilast tablet; the mean AUC_{0-t} and $AUC_{0-\infty}$ value was 3065.11 ± 1084.86 h·ng/mL and 3129.16 ± 1122.37 h·ng/mL, respectively. Apremilast was eliminated slowly with an elimination $T_{1/2}$ of 7.43 ± 3.64 hours. The relative bioavailability (F) of the test apremilast tablets was 100.27 ± 18.61%. After oral administration of the reference apremilast tablet under fasting conditions, a C_{max} value of 370.34 ± 104.88 ng/mL of apremilast was achieved within 0.99–4.99 hours; the mean AUC_{0-t} and $AUC_{0-\infty}$ value was 3147.83 ± 1195.30 h·ng/mL and 3194.26 ± 1213.07 h·ng/mL, respectively. Apremilast was eliminated slowly with an elimination $T_{1/2}$ of 6.75 ± 1.77 hours. These results

Table 1 Demographic Characteristics of the Healthy Subjects

Parameters	Fasting	Postprandial
N	32	31
Age, years		
Mean ± SD	29.50 ± 8.29	35.50 ± 7.91
Min ~ Max	18 ~ 49	20 ~ 49
Gender, n (%)		
Male	28 (87.50)	20 (64.50)
Female	4 (12.50)	11 (35.50)
Weight, kg		
Mean ± SD	66.72 ± 9.58	61.80 ± 7.96
Min ~ Max	52.80 ~ 90.70	48.40 ~ 84.10
Height, cm		
Mean ± SD	170.44 ± 7.50	165.24 ± 9.75
Min - Max	153.50–187.00	148.50–186.00
BMI, kg/m^2		
Mean ± SD	22.90 ± 2.27	22.57 ± 1.44
Min - Max	19.00–25.90	19.50–25.70
Ethnicity, n (%)		
Ethnic Han	32 (100.00)	30 (96.80)
Others	0 (0)	1 (3.20)

Abbreviations: BMI, body mass index; SD, standard deviation.

Table 2 Pharmacokinetic Parameters Under Fasting Conditions

Parameter	Test (n = 32)		Reference (n = 32)	
	Mean ± SD	%CV	Mean ± SD	%CV
C_{max} (ng/mL)	362.19 ± 93.20	25.70	370.34 ± 104.88	28.30
T_{max} (h)	2.49 (0.49, 4.99)	–	2.76 (0.99, 4.99)	–
AUC_{0-t} (h·ng/mL)	3065.11 ± 1084.86	35.40	3147.83 ± 1195.30	38.00
$AUC_{0-\infty}$ (h·ng/mL)	3129.16 ± 1122.37	35.90	3194.26 ± 1213.07	38.00
$t_{1/2}$ (h)	7.43 ± 3.64	48.90	6.75 ± 1.77	26.10
λz (1/h)	0.11 ± 0.03	32.60	0.11 ± 0.04	32.20
F (%)	100.27 ± 18.61	0.19	-	-

Note: Values are expressed as Mean ± SD, except $T_{max,}$ which is the median (min, max).
Abbreviations: C_{max} indicates maximum plasma concentration; T_{max} indicates time to C_{max}, which was represented as the median (min, max); AUC_{0-t}, area under the concentration curve from 0 time to t; $AUC_{0-\infty}$, area under the concentration curve from 0 time to infinity; $t_{1/2}$, terminal elimination half-life; λz, the elimination rate constant; F, relative bioavailability; SD, standard deviation; CV, coefficient of variation.

indicate that the PK properties were similar between the test formulation and the reference formulation under fasting conditions. As shown in Figure 2A and B, the mean plasma concentration–time curves of the test and reference products under the fasting conditions were completely consistent. These results suggest that the in vivo disposal process of the test product was similar to that of the reference product under the fasting conditions.

In the postprandial study, the remaining 30 subjects were enrolled in PKCS and PKPS as the two subjects discontinued the study. As shown in Table 3, a C_{max} value of 412.13 ± 87.52 ng/mL of apremilast was achieved within 1.49–7.99 hours after oral administration of the test apremilast tablet; the mean AUC_{0-t} and $AUC_{0-\infty}$ value was 3617.25 ±

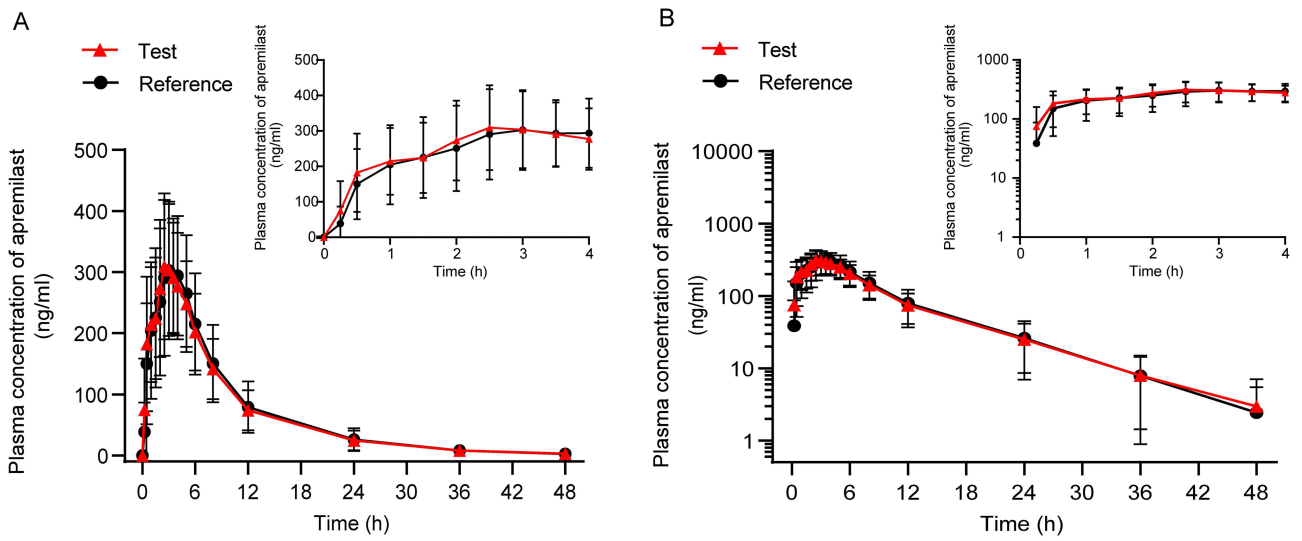

Figure 2 Pharmacokinetic analysis of apremilast formulations during fasting condition. Mean plasma concentration (±SD) time curve after oral test or reference formulation: arithmetic mean (**A**) and log transformation (**B**).

953.60 h·ng/mL and 3661.36 ± 959.69 h·ng/mL, respectively. Apremilast was eliminated slowly with an elimination $T_{1/2}$ of 5.89 ± 1.20 hours. The relative bioavailability (F) of the test apremilast tablets was 102.96 ± 11.71%. After oral administration of the reference apremilast tablet under fed conditions, a C_{max} value of 393.80 ± 99.01 ng/mL of apremilast was achieved within 1.49–7.99 hours; the mean AUC_{0-t} and $AUC_{0-\infty}$ value was 3534.52 ± 935.00 h·ng/mL and 3576.36 ± 937.91 h·ng/mL, respectively. Apremilast was eliminated with an elimination $T_{1/2}$ of 5.65 ± 1.00 hours. The mean plasma concentration–time curves of the test products were completely consistent with that of the reference products (Figures 3A and B). These results also provided the evidence for the similar disposal process in vivo under the fed conditions.

Bioequivalence Results

For PK bioequivalence evaluation, the subjects were enrolled in the bioequivalence analysis set (BES) as with PKPS under fasting and fed conditions. As shown in Tables 4 and 5, the coefficient of intra-subject variation (CV) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were all less than 30%. The average bioequivalence criterion was adopted to evaluate the bioequivalence of the fasting and postprandial PK parameters. The results of the fasting study are shown in Table 4,

Table 3 Pharmacokinetic Parameters Under Postprandial Conditions

Parameter	Test (n = 30)		Reference (n = 30)	
	Mean ± SD	%CV	Mean ± SD	%CV
C_{max} (ng/mL)	412.13 ± 87.52	21.20	393.80 ± 99.01	25.10
T_{max} (h)	2.50 (1.49, 7.99)	–	3.00 (1.49, 7.99)	–
AUC_{0-t} (h·ng/mL)	3617.25 ± 953.60	26.40	3534.52 ± 935.00	26.50
$AUC_{0-\infty}$ (h·ng/mL)	3661.36 ± 959.69	26.20	3576.36 ± 937.91	26.20
$t_{1/2}$ (h)	5.89 ± 1.20	20.30	5.65 ± 1.00	17.60
λz (1/h)	0.12 ± 0.02	20.10	0.13 ± 0.02	17.20
F (%)	102.96 ± 11.71	0.11	-	-

Note: Values are expressed as Mean ± SD, except T_{max}, which is the median (min, max).
Abbreviations: C_{max} indicates maximum plasma concentration; T_{max} indicates time to C_{max}, which was represented as the median (min, max); AUC_{0-t}, area under the concentration curve from 0 time to t; $AUC_{0-\infty}$, area under the concentration curve from 0 time to infinity; $t_{1/2}$, terminal elimination half-life; λz, the elimination rate constant; F, relative bioavailability; SD, standard deviation; CV, coefficient of variation.

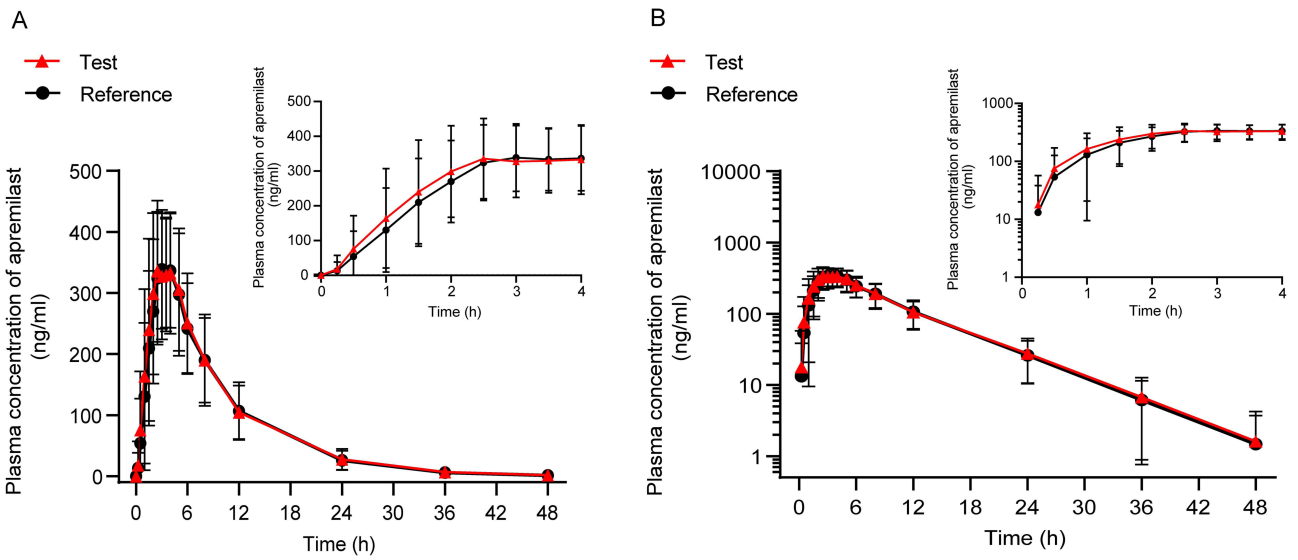

Figure 3 Pharmacokinetic analysis of apremilast formulations during postprandial condition. Mean plasma concentration (±SD) time curve after oral test or reference formulation: arithmetic mean (**A**) and log transformation (**B**).

the GLSM ratios of the test to reference products for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 98.65%, 98.67% and 99.10%, respectively (Table 4). The corresponding 90% CIs for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 94.09%–103.44%, 94.05%–103.51% and 94.56%–103.86% (Table 4), respectively, all within the accepted bioequivalence range of 80.00%–125.00%, indicating that the test and reference products of apremilast were bioequivalent under fasting conditions. The Wilcoxon signed-rank test ($p = 0.431$) also indicated that there was no significant difference in T_{max} between the two products. In the postprandial trial, the GLSM ratios of the test to reference products for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 105.62%, 102.34% and 102.36%, respectively (Table 5). The corresponding 90% CIs were 99.18%–112.48% for C_{max},

Table 4 Bioequivalence Assessment of the Primary Pharmacokinetic Parameters Under Fasting Conditions

PK Parameter	GLSM		Ratio (%)	Intra-Subject CV (%)	Power (%)	90% CI (%)
	Test (n=32)	Reference (n=32)				
C_{max} (ng/mL)	351.31	356.10	98.65	11.19	>99.99	94.09–103.44
AUC_{0-t} (h·ng/mL)	2904.04	2943.29	98.67	11.32	>99.99	94.05–103.51
$AUC_{0-\infty}$ (h·ng/mL)	2960.11	2987.03	99.10	11.09	>99.99	94.56–103.86

Abbreviations: C_{max}, maximum plasma concentration; AUC0-t, area under the concentration curve from 0 time to t; AUC0-∞, area under the concentration curve from 0 time to infinity; GLSM, geometric least-squares mean; CV, coefficient of variation; CI, confidence intervals.

Table 5 Bioequivalence Assessment of the Primary Pharmacokinetic Parameters Under Postprandial Conditions

PK Parameter	GLSM		Ratio (%)	Intra-Subject CV (%)	Power (%)	90% CI (%)
	Test (n=30)	Reference (n=30)				
C_{max} (ng/mL)	403.44	381.96	105.62	14.40	99.74	99.18–112.48
AUC_{0-t} (h·ng/mL)	3500.02	3420.05	102.34	8.05	>99.99	98.79–106.02
$AUC_{0-\infty}$ (h·ng/mL)	3544.66	3462.93	102.36	7.72	>99.99	98.95–105.89

Abbreviations: C_{max}, maximum plasma concentration; AUC0-t, area under the concentration curve from 0 time to t; AUC0-∞, area under the concentration curve from 0 time to infinity; GLSM, geometric least-squares mean; CV, coefficient of variation; CI, confidence intervals.

98.79%–106.02% for AUC_{0-t}, and 98.95%–105.89% for $AUC_{0-\infty}$ (Table 5), and all 90% CIs were within the predefined equivalence margin of 80.00% to 125.00%. T_{max} also did not differ significantly ($p = 0.078$) between the two products. These data indicated that the test and reference products of apremilast were also considered bioequivalent under the fed conditions.

To assess whether period, sequence, and formulation factors had an impact on the current study, a multivariate analysis of variance was performed using a linear mixed-effects model for the natural logarithmic of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ in the fasting or postprandial studies, respectively. The results are shown in Table 6. In addition to the significant differences in the effects of different periods on LnC_{max}, Ln AUC_{0-t}, Ln $AUC_{0-\infty}$ under fasting conditions and LnC_{max} under postprandial conditions, there was no significant difference in the effects of different sequences and formulations on the main parameters under the two conditions. However, the establishment of bioequivalence was not affected.

Safety Assessment

The safety and tolerability of apremilast were assessed based on the safety analysis set (SS). Under the fasting study, 32 subjects received at least one dose of the study drug and were included in SS. Forty-nine AEs for 24 subjects were reported, and the incidence of AEs was 75.00% (24/32) (Table 7). Of these, 24 AEs were reported for 17 subjects in the test product; the incidence of AEs was 53.12% (17/32) (Table 7), whereas 25 AEs were reported for 16 subjects and an incidence of 50.00% (16/32) in the reference product (Table 7). Among the AEs related to the test product, two subjects experienced upper respiratory infection and abdominal pain, respectively, which were defined as adverse drug reactions (ADRs). All AEs were reported as grade 1 and spontaneously resolved without any specific treatment. No SAEs occurred during the fasting period. Similarly, 31 subjects were included in the SS group in the postprandial study, 27 AEs were reported in 17 subjects, and the incidence of AEs was 54.84% (17/31) (Table 7). The incidence rates of AEs in the test and reference products were 26.67% (8/30) and 38.71% (12/31), respectively (Table 7). Of these AEs, one subject related to the test product experienced nausea, abdominal distension, and increased frequency of bowel movements, which were defined as ADRs. Three AEs for 3 subjects related to the reference product were defined as ADRs, including nausea, vomiting, and upper respiratory infection, respectively. All AEs were mild and reported as grade 1, except for the vomiting cases reported as grade 2, the subject (C001) vomited within 1 h of administrated of the reference product and dropped out of the study. No SAEs occurred during the fed period. All AEs or ADRs were spontaneously resolved without any specific treatment. The results indicated that apremilast had good safety and was well tolerated in healthy subjects under fasting and postprandial conditions.

Discussion

The present study first provided evidence for the bioequivalence of the generic and original apremilast tablets in healthy Chinese subjects under fasting and postprandial states. Both formulations met the acceptance criteria of the pharmacokinetics bioequivalence and were well tolerated in healthy Chinese subjects. The present study provided sufficient evidence for the better understanding the pharmacokinetic characteristics of apremilast tablets in vivo and approval for abbreviated new drug application in China.

Table 6 The Analysis of Variance Test of the Primary Pharmacokinetic Parameters

PK Parameter	*P* (Fasting)			*P* (Postprandial)		
	LnC_{max}	$LnAUC_{0-t}$	$LnAUC_{0-\infty}$	LnC_{max}	$LnAUC_{0-t}$	$LnAUC_{0-\infty}$
Period	0.001	0.003	0.002	0.015	0.849	0.877
Sequence	0.400	0.590	0.549	0.811	0.793	0.767
Formulation	0.630	0.638	0.746	0.150	0.275	0.251

Abbreviations: C_{max}, maximum plasma concentration; AUC0-t, area under the concentration curve from 0 time to t; AUC0-∞, area under the concentration curve from 0 time to infinity; $p < 0.05$ was considered to be statistically significant.

Table 7 Summary of Treatment-Emergent AEs

Parameter	Fasting Trial						Postprandial Trial					
	Test (n=32)		Reference (n=32)		Total (n=32)		Test (n=30)		Reference (n=31)		Total (n=31)	
	AE count	N (%)	AE count	N (%)	AE count	N (%)	AE count	N (%)	AE count	N (%)	AE count	N (%)
Sum	24	17 (53.12)	25	16 (50.00)	49	24 (75.00)	12	8 (26.67)	15	12 (38.71)	27	17 (54.84)
Grade 1	24	17 (53.12)	25	16 (50.00)	49	24 (75.00)	12	8 (26.67)	14	11 (35.49)	26	16 (51.62)
Grade 2	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (3.22)	1	1 (3.22)
≥ Grade 3	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Results of inspection	21	16 (50.00)	24	16 (50.00)	45	23 (71.88)	9	7 (23.33)	11	8 (25.81)	20	13 (41.94)
TG increased	4	4 (12.50)	4	4 (12.50)	8	8 (25.00)	1	1 (3.33)	0	0 (0)	1	1 (3.22)
Body temperature increased	3	3 (9.38)	3	3 (9.38)	6	6 (18.75)	3	3 (10.00)	1	1 (3.22)	4	3 (9.68)
Heart rate decreased	5	4 (12.50)	5	5 (15.62)	10	6 (18.75)	2	2 (6.67)	4	4 (12.90)	6	6 (19.35)
Heart rate increased	2	2 (6.25)	0	0 (0)	2	2 (6.25)	0	0 (0)	1	1 (3.22)	1	1 (3.22)
Blood pressure increased	3	1 (3.12)	1	1 (3.12)	4	1 (3.12)	1	1 (3.33)	2	2 (6.45)	3	2 (6.45)
Blood pressure decreased	3	3 (9.38)	2	2 (6.25)	5	5 (15.62)	0	0 (0)	1	1 (3.22)	1	1 (3.22)
ALT increased	0	0 (0)	2	2 (6.25)	2	2 (6.25)	1	1 (3.33)	0	0 (0)	1	1 (3.22)
AST increased	0	0 (0)	1	1 (3.12)	1	1 (3.12)						
Increased percentage of basophil leukocytes	0	0 (0)	1	1 (3.12)	1	1 (3.12)						
Increased count of basophil leukocytes	0	0 (0)	1	1 (3.12)	1	1 (3.12)						
ECG T-wave abnormalities	0	0 (0)	1	1 (3.12)	1	1 (3.12)						
ECG repolarization abnormalities	0	0 (0)	1	1 (3.12)	1	1 (3.12)						
Blood uric acid increased	0	0 (0)	1	1 (3.12)	1	1 (3.12)						
Lipoproteins increased	1	1 (3.12)	0	0 (0)	1	1 (3.12)						
Total bile acids increased	0	0 (0)	1	1 (3.12)	1	1 (3.12)						
Urine sediment							0	0 (0)	1	1 (3.22)	1	1 (3.22)
Blood phosphorus decreased							1	1 (3.33)	0	0 (0)	1	1 (3.22)
Neutrophil count increased							0	0 (0)	1	1 (3.22)	1	1 (3.22)
Infections and infestations	1	1 (3.12)	0	0 (0)	1	1 (3.12)	0	0 (0)	2	2 (6.45)	2	2 (6.45)
Urinary tract infection							0	0 (0)	1	1 (3.22)	1	1 (3.22)
Upper respiratory infection	1	1 (3.12)	0	0 (0)	1	1 (3.12)	0	0 (0)	1	1 (3.22)	1	1 (3.22)
Psychiatric disorders	1	1 (3.12)	0	0 (0)	1	1 (3.12)						
Inject fear	1	1 (3.12)	0	0 (0)	1	1 (3.12)						
Gastrointestinal disorders	1	1 (3.12)	0	0 (0)	1	1 (3.12)	3	1 (3.33)	2	2 (6.45)	5	3 (9.68)
Abdominal pain	1	1 (3.12)	0	0 (0)	1	1 (3.12)						
Nausea							1	1 (3.33)	1	1 (3.22)	2	2 (6.45)
Abdominal distension							1	1 (3.33)	0	0 (0)	1	1 (3.22)
Vomiting							0	0 (0)	1	1 (3.22)	1	1 (3.22)
Increased frequency of bowel movements							1	1 (3.33)	0	0 (0)	1	1 (3.22)
Cardiac disorders	0	0 (0)	1	1 (3.12)	1	1 (3.12)						
Sinus bradycardia	0	0 (0)	1	1 (3.12)	1	1 (3.12)						

Abbreviations: TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram.

Apremilast is classified as a biopharmaceutics classification system (BCS) class IV drug. Based on the low aqueous solubility and low intestinal permeability characteristics of apremilast,[9] a bioequivalence study is required for a generic Apremilast tablet to be marketed.[10] According to the bioequivalence guidelines of FDA[5,11] and EMA,[12] the present study used a standard experimental design of two-period, two-sequence, crossover study under the fasting and postprandial status, which is in line with FDA recommendations.[13] Considering the generic Apremilast tablet is intended for use in both sexes, this study recruited male and female subjects between the ages from 18 to 49 years. Previous studies reported that the metabolic half-life of oral apremilast was 5–7 h,[8] and the washout period was set at 7 days in the current study, which was 7 times more than the half-life and enough to avoid the influence of the previous administration induced residue. The sampling schedule is the key point in the pharmacokinetic study, and a sufficient number of samples should cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure which is achieved if $AUC_{0\text{-}t}$ covers at least 80% of $AUC_{0\text{-}\infty}$.[12] Therefore, the sampling protocol in previous pharmacokinetic study of apremilast was typically planned to be 72 h post-dose,[14] so far as to 168 h.[15] Our study provided the evidence that a sampling schedule of 48.0 h post-dose is sufficient for the pharmacokinetic study of apremilast, with $AUC_{0\text{–}48\ h}$ covering almost 98% of AUC0-∞. This has clear advantages in improving subject compliance and pharmacokinetic trial efficiency.

As shown in this study, apremilast was well absorbed by the gastrointestinal tract, with C_{max} occurring at a median time of approximately 2.7 h after a single 30 mg dose under fasting and postprandial condition, respectively. The pharmacokinetic characteristics of apremilast in Han Chinese population, as we showed in this study, were compared with those of previous studies. The results indicated that there were somewhat differences in C_{max} (370.34 ng/mL vs 273.00 ng/mL), $AUC_{0\text{-}t}$ (3147.83 h·ng/mL vs 2330.00 h·ng/mL) and $AUC_{0\text{-}\infty}$ (3194.26 h·ng/mL vs 2360.00 h·ng/mL) between Han Chinese and Korean subjects.[14] The findings did not support the lack of interethnic sensitivity in the PK of apremilast, although available FDA data suggest that apremilast systemic exposure is comparable across ethnicities.[9] This may be related to the multiple metabolic pathways of apremilast in vivo. Apremilast was extensively metabolized via CYP3A4, CYP1A2 and CYP2A6 mediated oxidative metabolism with subsequent glucuronidation, and non-CYP mediated hydrolysis and N-deacetylation metabolism.[8,15] Ethnic differences in any single metabolic pathway (such as CYP isoenzyme) may result in somewhat difference in PK parameters of apremilast in *vivo*. Furthermore, the PK difference between Han Chinese and Korean subjects may be influenced by different drug' manufacturers. The original drug compared in this study is produced by Celgene Corporation, while the manufacturer of apremilast in Korean studies did not state.[14]

Regarding safety, a large number of clinical trials reported that the most common ADR with apremilast were the gastrointestinal symptoms (such as nausea, vomiting, and diarrhea)[16] and upper respiratory tract infections.[17,18] The symptoms of nausea and vomiting induced by apremilast were felt to be due to increased activity at the chemoreceptor trigger zone and effects on central neurokinin receptors,[19] and the mechanism of upper respiratory tract infection has not been elucidated completely, which may be related to the fact that apremilast does not have any significant PDE4 subtype selectivity.[20] Our studies reported similar ADRs to apremilast; however, the ADR were all mild or moderate, and spontaneously resolved without any specific treatment, which indicated that the apremilast was generally well tolerated in vivo.

This study had some limitations. First, this study merely demonstrates that the generic apremilast tablet is similar to the original reference in terms of PK parameters. Thus, the therapeutic bioequivalence between the generic and the original drug needs further trials to verify. Although the sample size is up to the requirements of a bioequivalence trial, it is still another limitation of the study. We were unable to conduct a comprehensive assessment for the safety of these two drugs due to sample size limitations. Finally, this study collects data from single-dose administration in healthy populations, as patients are most likely to take the drug for a long time, and its cumulative effects in humans need to be explored in the future.

Conclusion

Based on the results of the current study, generic apremilast tablets are bioequivalent to the reference formulation (OTEZLA®) in terms of the extent and rate of absorption under fasting and postprandial state, and the bioavailability of the test and reference formulation is similar. Both formulations were generally well tolerated in the healthy Chinese population and can be used interchangeably in the clinic.

Data Sharing Statement

Individual identified subject data is not going to be shared because of confidentiality.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. WB, XS, XZ, and ZD had involved in drafting the manuscript or revising it critically for important intellectual content.

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Disclosure

The authors declare that there are no conflicts of interest in this study.

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