Clinical Pharmacology in Drug Development
2020, 9(5) 573–581

DOI: 10.1002/cpdd.806

Bioequivalence and Bioavailability of an Orodispersible Tablet of Sildenafil Citrate in Healthy Chinese Male Subjects

Yuan Lv[1], Bin-yu Luo[2], Robert R. LaBadie[3], Hua Zhu[2], Yan Feng[4], Cynthia Ernst[5], Penelope H. Crownover[3], Yali Liang[3,*], and Qinying Zhao[3,*]

Abstract

Sildenafil citrate is approved to treat erectile dysfunction. An orally disintegrating tablet (ODT) of sildenafil citrate that does not require swallowing or administration with fluids has been developed. The bioequivalence and bioavailability of sildenafil citrate ODT (50 mg) without and with water were compared with conventional sildenafil citrate tablets (50 mg) in an open-label, randomized crossover study. Healthy Chinese male subjects (n = 36) were allocated to 1 of 6 sildenafil citrate treatment sequences under fasted conditions, and plasma samples for determination of sildenafil concentrations were collected predose through 14 hours postdose. Bioequivalence was demonstrated for sildenafil citrate ODT administered without water relative to the sildenafil citrate tablet administered with water; 90%CIs for the ratios of adjusted geometric means for sildenafil AUC_{last}, C_{max}, and AUC_{inf} (ratio, 101.41%; 90%CI, 95.49%-107.70%; ratio, 93.55%; 90%CI, 84.15%-104.00%; and ratio, 101.03%; 90%CI, 94.80%-107.66%; respectively) were wholly contained within the bioequivalence acceptance range of 80% to 125%, indicating bioequivalence criteria were met. Relative bioavailability of sildenafil citrate ODT administered with water to the sildenafil citrate tablet (50 mg) administered with water was 97.10%, 91.43%, and 97.09% with respect to sildenafil AUC_{last}, C_{max}, and AUC_{inf}, respectively (90%CI, 91.43%-03.12%, 82.25%-101.65%, and 90.90%-103.71%, respectively). Both sildenafil citrate formulations were generally well tolerated in healthy Chinese men. Sildenafil citrate ODT administered without or with water was bioequivalent to or met bioequivalence criteria compared with conventional sildenafil citrate tablets administered with water under fasted conditions in healthy Chinese men, thus offering a convenient alternative method of oral administration.

Keywords

sildenafil citrate, orally disintegrating tablet, erectile dysfunction, bioequivalence, bioavailability, pharmacokinetics

Erectile dysfunction (ED) affects millions of men globally, with 322 million cases predicted by 2025.[1] ED is common in men in China, affecting as many as 41% of those aged 40 years and older, as determined by a population-based study conducted from 2010 to 2013.[2] This percentage is in line with a large meta-analysis of approximately 48 000 Chinese men, of whom approximately 50% reported ED.[3] In Asian men, ED has been associated with a 2.2-fold increase in depression compared with men of a similar age without ED, with the incidence of depression highest within the first year of diagnosis.[4] Although not a life-threatening condition, ED is associated with anxiety and depression in men in China[4,5] as well as globally, resulting in a decreased quality of life and a health concern for men and their partners.[6,7]

[1]Peking University First Hospital, Institute of Clinical Pharmacology, Beijing, China
[2]Pfizer Inc, Shanghai, China
[3]Pfizer Inc, Groton, Connecticut, USA
[4]Pfizer Inc, Beijing, China
[5]ExecuPharm, King of Prussia, Pennsylvania, USA

Submitted for publication 13 February 2019; accepted 24 March 2020.

Corresponding Author:
Qinying Zhao, PhD, 27 Kelsey Springs Drive, Madison, CT 06443
(e-mail: qinyingzhao3@gmail.com)

*Employee of Pfizer at time of study.

Phosphodiesterase type 5 inhibitors are a first-line treatment for ED.[8,9] Sildenafil citrate (Viagra; Pfizer Inc, New York, New York) is a competitive and selective inhibitor of cyclic guanosine monophosphate–specific phosphodiesterase type 5 and is approved for the treatment of ED.[8,10] Sildenafil citrate tablets are approved at 25-, 50-, and 100-mg doses, although the recommended dose for most patients is 50 mg. The sildenafil citrate tablet is rapidly absorbed (approximately 1 hour in the fasted state) and has a terminal half-life of about 4 hours.[11] In healthy volunteers the mean plasma clearance of the sildenafil citrate tablet is 41 L/h, and the absolute bioavailability is 41%.[10,11] Oral sildenafil citrate undergoes first-pass metabolism in the gut wall and liver,[12] with N-desmethylation in the liver mediated by at least 4 cytochromes: CYP3A4, CYP2C9, CYP2C19, and CYP2D6, but primarily by CYP3A4,[13] which leads to the major circulating metabolite UK-103,320.[12,13] There is no impact of sildenafil citrate on the pharmacokinetics of the CYP2C9 substrates tolbutamide and warfarin and vice versa, but because of sildenafil being primarily metabolized by CYP3A4, inhibitors of this enzyme, such as HIV drugs ritonavir and indinavir, have been found to inhibit the metabolism of sildenafil citrate.[12,14,15]

Conventional sildenafil citrate tablets are typically ingested with a liquid such as water. To provide dosing alternatives for individuals who have difficulty swallowing or have restricted water intake, different oral formulations of sildenafil have been developed, including chewable tablets,[16] a sublingual formulation,[17] and a disintegrating film.[18] In addition, an orally disintegrating tablet (ODT), sildenafil citrate ODT, has been developed that does not require swallowing or coadministration with fluids.[19] As part of the registration requirement for sildenafil citrate ODT, the bioequivalence of this formulation was compared with conventional sildenafil citrate tablets in a study of healthy Asian male subjects 45 to 66 years of age in Singapore.[19] In that study, bioequivalence was met for sildenafil citrate ODT administered as a 50-mg dose without water compared with conventional sildenafil citrate tablets because all of the 90%CIs for the ratios of the geometric means of sildenafil maximum plasma concentration (C_{max}), the area under the plasma concentration-time profile from time 0 extrapolated to infinite time (AUC_{inf}), and the area under the plasma concentration-time profile from time 0 to the last quantifiable concentration (AUC_{last}) fell within the equivalence interval of 80% to 125%. For sildenafil citrate ODT administered with water under fasted conditions, the 90%CIs for sildenafil AUC_{inf} and AUC_{last} were contained within the range of 80% to 125%; however, the 90%CI (79.76%-92.78%) for sildenafil C_{max} was not within the lower bound of the equivalence interval. This reduction in C_{max} was less than the effect observed between fed/fasted conditions with commercial sildenafil, and therefore, this finding was considered unlikely to have clinically meaningful implications.[19]

The aim of the current study was to expand on the results of the bioequivalence study previously conducted in Singapore.[19] In the current study conducted in China, the bioequivalence and bioavailability of sildenafil citrate ODT administered with and without water were assessed relative to conventional sildenafil citrate in healthy Chinese male subjects aged 18 to 40 years. The study was conducted to support the registration of sildenafil citrate ODT in China. Because the highest manufactured dose strength of sildenafil citrate ODT is 50 mg, the study used this dose for both formulations. Safety and tolerability were also examined.

Methods

The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by the local ethics committee at Peking University First Hospital. All local regulatory requirements were followed. All subjects provided written informed consent. The study was conducted at a clinical research unit (CRU) in Peking University First Hospital, Beijing, China.

Study Subjects

Healthy Chinese male subjects with both parents of Chinese descent were eligible for the study if they were 18 to 40 years of age with no clinically relevant abnormalities, including those in blood pressure (BP), pulse rate measurements, and electrocardiogram, and had a body mass index (BMI) of 19.0 to 24.0 kg/m^2, a total body weight $\geq$ 50 kg, and a willingness to participate in the study. Subjects were excluded from the study if they had evidence or a history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease; prior or current hepatitis B or C, HIV, or syphilis infection; abnormal drug absorption; a positive drug screen; alcohol consumption exceeding 14 drinks per week; tobacco use in excess of 5 cigarettes per day; current use of nitrates or nitric oxide donors and cytochrome P450 3A4 inhibitors; use of investigational drugs within 90 days or 5 half-lives; and use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives or herbal supplements within 28 days.

Study Design

This phase 1 bioequivalence and bioavailability study conducted in 2016 was an open-label, randomized,

single-dose, 3-treatment, 3-period William's square crossover design. Chinese male subjects were enrolled and randomly assigned to 1 of 6 treatment sequences based on the following regimens: sildenafil citrate 50-mg film-coated tablet administered with 240 mL of water (reference treatment) under fasted conditions (overnight or ≥10 hours); sildenafil citrate ODT 50-mg tablet administered without water (test treatment; bioequivalence relative to reference treatment) under fasted conditions; and sildenafil citrate ODT 50-mg tablet administered with 240 mL of water (test treatment; bioavailability relative to reference treatment) under fasted conditions. There was a minimum 2-day washout period between doses. Subjects were not allowed to eat or drink beverages other than water during the first 4 hours after dosing on pharmacokinetic sampling days.

This study was designed to demonstrate bioequivalence of a single 50-mg dose of sildenafil citrate ODT administered fasted without water relative to a 50-mg dose of the commercial film-coated tablet of sildenafil citrate (Viagra; Pfizer Inc, Dalian, China) administered fasted with water. The bioavailability of a single 50-mg dose of sildenafil citrate ODT administered fasted with water relative to a 50-mg dose of the commercial film-coated tablet of sildenafil citrate administered fasted with water was also estimated to determine the worst-case scenario should patients inadvertently consume water. Safety and tolerability of sildenafil citrate ODT administered fasted with or without water were also assessed during the study.

For each of the 3 treatment periods, subjects were admitted to the CRU on the day before dosing (day 0). Subjects received their allocated dose on day 1 under fasted conditions and remained at the CRU until the completion of all study activities on day 1 for treatment periods 1 and 2. During treatment period 3, which was the final treatment period in the study, subjects remained at the CRU on day 2 for a physical examination, vital sign measurements, and laboratory safety evaluation and were discharged later that day. Subjects could remain at the CRU between treatment periods if successive doses were no more than 3 days apart.

Study Medications

Sildenafil citrate ODT (50 mg) and sildenafil citrate film-coated tablets (50 mg) were labeled as investigational products in accordance with current guidelines and applicable local and legal regulatory requirements.

Pharmacokinetics

Blood samples (n = 15) were taken from predose to 14 hours postdose for each subject as follows: predose (immediately before dosing); 5, 15, 30, and 45 minutes postdose; and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 14 hours postdose. Blood samples were centrifuged at approximately 1700*g* for about 10 minutes at 4°C. All plasma samples were stored at −20°C within 1 hour of collection until analysis. Plasma samples were analyzed at Covance Bioanalytical Services (Shanghai, China) for sildenafil concentrations using a validated high-performance liquid chromatography-tandem mass spectrometric method as described in detail by Eerkes et al[20] with some minor modifications for assay improvement. The calibration range of the assay was 1.00 to 500 ng/mL using a weighted ($1/\text{concentration}^2$) linear regression. The lower limit of quantification (LLOQ) for sildenafil was 1.00 ng/mL, and samples with concentrations below this range were reported as <1.00 ng/mL. Samples with concentrations above the upper limit of quantification were diluted into calibration range.

The accuracy of the sildenafil assay, expressed as percent relative error, ranged from -4.0% to 4.3% for the low, medium, high, and diluted quality control samples. Assay precision, expressed as the between-day percent coefficients of variation of the mean estimated concentrations of quality control samples, was ≤5.3% for low (3.00 ng/mL), medium (30.0 ng/mL), high (350 ng/mL), and diluted (700 ng/mL) concentrations.

Pharmacokinetic parameters were determined for each subject and each treatment regimen using noncompartmental analysis. Samples below LLOQ were set to 0 for analysis. AUC_{last} (primary end point) and AUC_{inf} were determined using the linear-log trapezoidal method; C_{max} (primary end point) and time to C_{max} (t_{max}) were based on observed data. Terminal half-life ($t_{1/2}$) was calculated using $\log_e(2)/k_{el}$, where k_{el} is the terminal-phase elimination rate constant calculated by a linear regression of the log-linear concentration-time curve. Apparent clearance (CL/F) was calculated as dose/AUC_{inf}. Pharmacokinetic parameter values were calculated using an internally validated software system, eNCA, version 2.2.4. The AUC_{inf}, $t_{1/2}$, and CL/F parameters were reported only when a well-characterized terminal phase was observed, which was defined as one with at least 3 data points, a goodness-of-fit statistic for the log-linear regression (r^2) ≥ 0.9, and a percent of AUC_{inf} extrapolated ($AUC_{extrap}\%$) ≤ 20%.

Safety Evaluations

All subjects who received ≥1 dose of study medication were included in the safety analyses. Throughout the study duration, all adverse events (AEs) regardless of treatment or suspected causal relationship to sildenafil citrate were reported; any nonserious AE that was determined by the sponsor to be serious was reported by the sponsor as a serious AE (SAE). Laboratory evaluations were performed at screening, on day 0, day 1, and

Table 1. Subject Demographics

Demographic	All Male Subjects, n = 36
Age, y	
18-25	12
26-35	22
36-45	2
Mean (SD)	27.8 (4.0)
Range	21–38
Race, Asian	36
Racial designation, Chinese	36
Weight, kg	
Mean (SD)	63.6 (5.8)
Range	50.7–74.1
BMI, kg/m^2	
Mean (SD)	21.9 (1.4)
Range	19.3–24.0
Height, cm	
Mean (SD)	170.5 (4.7)
Range	162.0–179.0

BMI, body mass index.

day 2, and at any time during the study to assess any perceived safety concerns. Other safety measures included physical examinations, including BP, pulse rate, temperature, and electrocardiogram.

Statistical Analyses

Sample Size. A sample size of 36 subjects was required to provide 99% power that the 90%CI for the ratio of test to reference treatment for sildenafil AUC_{last} lay within the acceptance region of 80% to 125%, and 91% power that the 90%CI for the ratio of test to reference treatment for sildenafil C_{max} lay within the acceptance region of 80% to 125%. Consequently, this study had at least 90% power overall to demonstrate bioequivalence of the test treatment (ODT without water) to the reference treatment (ie, equivalence in AUC_{last} and C_{max}), where overall study power was based on the product of the individual powers of the parameters of interest. This estimate was based on the assumption that the true ratio between test and reference treatments for both AUC_{last} and C_{max} was 0.90 and 0.95, respectively, and also assumed within-subject standard deviations of 0.124 and 0.236 for $\log_e AUC_{last}$ and $\log_e C_{max}$, respectively.

Pharmacokinetic Parameters. Natural log-transformed AUC_{last}, AUC_{inf}, and C_{max} of sildenafil were analyzed using a mixed-effects model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (test-reference) and the corresponding 90%CIs were obtained from the model. The adjusted mean differences and the 90%CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and the 90%CIs for the ratios.

The bioequivalence of sildenafil citrate ODT administered without water relative to the sildenafil citrate tablet administered with water was demonstrated if the 90%CIs for the ratio of adjusted geometric means of sildenafil citrate ODT administered without water relative to the commercial sildenafil citrate tablet for sildenafil AUC_{last} and C_{max} were within 80% to 125%. The relative bioavailability was estimated as the ratio of adjusted geometric means for sildenafil citrate ODT administered with water relative to the sildenafil citrate tablet administered with water for sildenafil AUC_{last} and C_{max}.

The pharmacokinetic parameters AUC_{inf}, AUC_{last}, C_{max}, t_{max}, $t_{1/2}$, and CL/F of sildenafil were summarized descriptively by treatment. For sildenafil AUC_{last}, AUC_{inf}, and C_{max}, individual subject parameters were plotted by treatment. Mean sildenafil plasma concentration-time data were plotted against treatment and were presented on log-linear scales. All statistical analyses were performed using SAS version 9.2 (TS2M3; SAS Institute Inc, Cary, North Carolina).

Results

Study Subjects

In total, 36 healthy male Chinese subjects were enrolled and randomized; all subjects received all allocated study treatments, completed the study, and were assessed for pharmacokinetics and safety. Subjects ranged in age from 21 to 38 years and had a mean age ± SD of 27.8 ± 4.0 years. Mean ± SD weight and BMI were 63.6 ± 5.8 kg and 21.9 ± 1.4 kg/m^2, respectively (Table 1).

Pharmacokinetics

Following a single oral dose of 50-mg sildenafil citrate, all 3 treatments had similar and well-overlapping mean sildenafil plasma concentration-time profiles (Figure 1). The geometric mean values for sildenafil AUC_{inf}, AUC_{last}, and C_{max} were also similar (Figure 2), and variability estimates between subjects ranged from 39% to 55% (Table 2). The median t_{max} for sildenafil was comparable across all 3 treatments, with 0.75 hours for sildenafil citrate ODT administered without water and the sildenafil citrate tablet administered with water and 0.5 hours for sildenafil citrate ODT administered with water. Mean $t_{1/2}$ (terminal-phase half-life) values for sildenafil were approximately 3 hours for all 3 treatments (Table 2).

Bioequivalence criteria were met for sildenafil citrate ODT administered without water relative to the sildenafil citrate tablet administered with water, both under fasted conditions. For the comparisons of

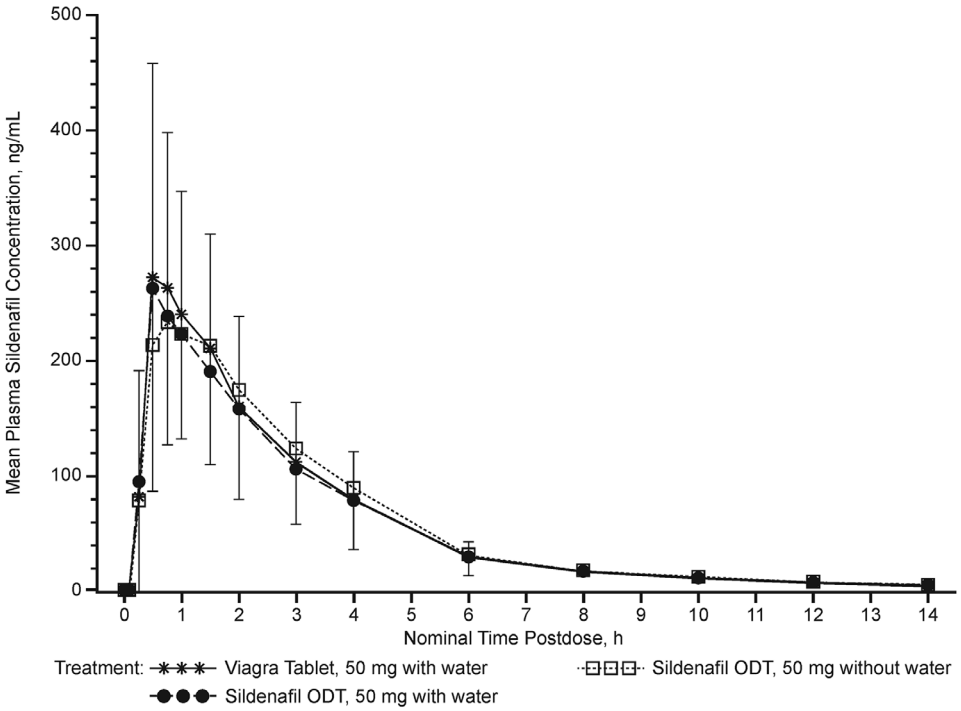


Figure 1. Mean plasma sildenafil citrate concentration-time profile following a single oral dose of 50-mg sildenafil. Error bars are the SD for Viagra tablet, 50 mg with water. ODT, orally disintegrating tablet.

sildenafil citrate ODT without water versus the sildenafil citrate tablet with water, the ratios of adjusted geometric means (test/reference) for sildenafil AUC_{last} and C_{max} were 101.41% (90%CI, 95.49%-107.70%) and 93.55% (90%CI, 84.15%-104.00%), respectively; sildenafil AUC_{inf} was 101.03% (90%CI, 94.80%-107.66%; Table 3). The 90%CIs for the ratios of adjusted geometric means for all 3 parameters were wholly contained within the acceptance range of 80% to 125% for bioequivalence (Table 3).

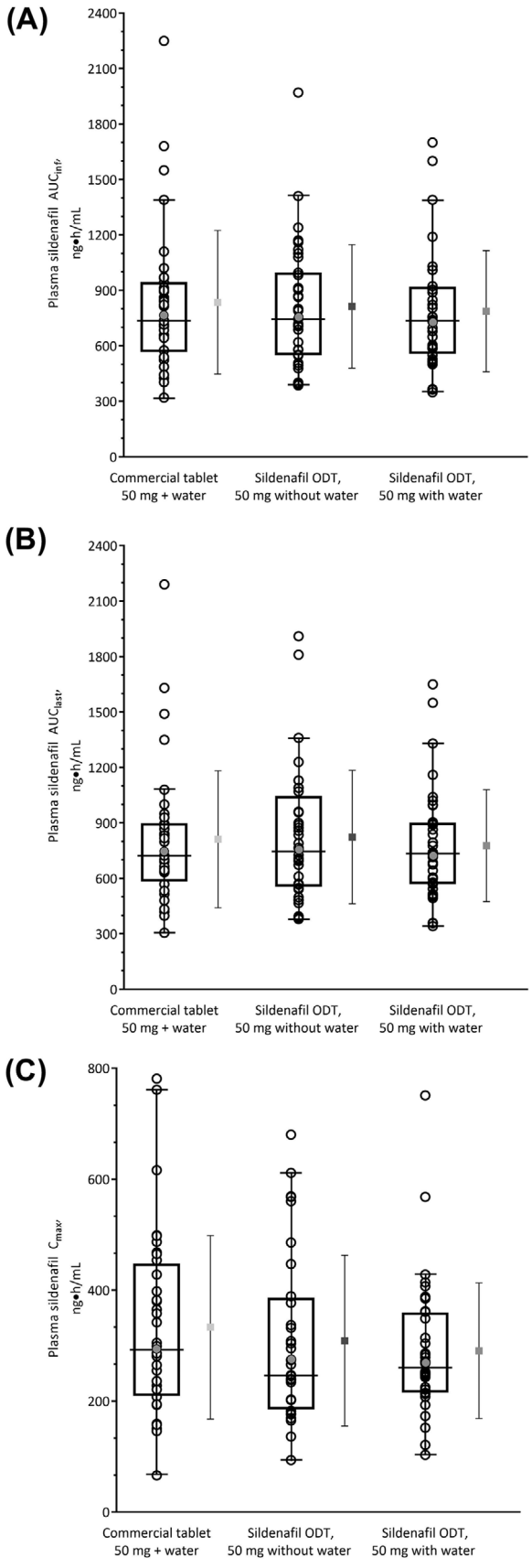
Bioavailability was estimated as the ratio of adjusted geometric means for sildenafil AUC_{last} and C_{max} for sildenafil citrate ODT administered with water relative to the sildenafil citrate tablet administered with water, both under fasted conditions. The ratios of adjusted geometric means (test/reference) for sildenafil AUC_{last} and C_{max} were 97.10% (90%CI, 91.43%-103.12%) and 91.43% (90%CI, 82.25%-101.65%), respectively; the ratio for sildenafil AUC_{inf} was 97.09% (90%CI, 90.90%-103.71%). The 90%CIs for the ratios of adjusted geometric means for all 3 parameters were wholly contained within the acceptance range of 80% to 125% (Table 3).

Safety

Sildenafil citrate ODT administered with or without water and the sildenafil citrate tablet were generally well tolerated in healthy male subjects. No deaths, SAEs, temporary or permanent discontinuations, or dose reductions because of an AE were reported during the study. Of the 9 treatment-emergent AEs reported, 1 AE was reported with the commercial sildenafil citrate tablet with water (decrease in blood potassium), 2 AEs with sildenafil citrate ODT without water (dizziness, headache), and 6 AEs with sildenafil citrate ODT with water (nausea, decrease in blood potassium, hypoglycemia, dizziness, headache, flushing); all were considered mild in severity. The majority of treatment-emergent AEs (6 of 9) were considered treatment related by the investigator (Table 4). Treatment-emergent AEs (n = 3) that were not considered related to treatment included a decrease in blood potassium in 2 subjects, 1 after receiving sildenafil citrate ODT with water and 1 after receiving sildenafil citrate tablet with water, and hypoglycemia in 1 subject receiving sildenafil citrate ODT with water.

Discussion

When the sildenafil citrate ODT formulation was administered without or with water, the total exposure was comparable to the conventional sildenafil citrate tablet. The 90%CIs of the ratios of adjusted geometric means for sildenafil citrate ODT without or with water compared with the sildenafil citrate tablet administered with water for sildenafil AUC_{last}, C_{max}, and AUC_{inf} were completely contained within the bioequivalence range of 80% to 125%; thus, bioequivalence for sildenafil citrate ODT without water was demonstrated.



When both formulations were administered with water, the bioavailability of sildenafil citrate ODT relative to the sildenafil tablet was above 90% with respect to the ratio of adjusted geometric means for pharmacokinetic parameters (sildenafil AUC_{last}, C_{max}, and AUC_{inf}), and the 90%CIs of the ratios were within the range of 80% to 125%, indicating that bioequivalence criteria were met. For both formulations, the median t_{max} of sildenafil was within 0.5 to 0.75 hours, and the mean $t_{1/2}$ of sildenafil was approximately 3 hours, indicating that the blood sampling time points for determination of sildenafil concentrations were appropriate for this bioequivalence and bioavailability study.

The comparable bioequivalence of sildenafil citrate ODT administered with water relative to the sildenafil citrate tablet administered with water demonstrated in this study contrasts slightly with the previous pharmacokinetic study of these formulations in Asian men.[19] Specifically, the previous study suggested that the C_{max} of sildenafil citrate ODT with water did not meet the criteria for bioequivalence compared with the sildenafil citrate tablet with water in Asian men (aged 45-66 years).[19] However, it should be noted that the reduction in sildenafil C_{max} observed in the previous study was small and did not likely have a clinically meaningful effect.[19] Based on results of the current study, bioequivalence of sildenafil citrate ODT administered without or with water relative to the sildenafil citrate tablet administered with water is fully supported by sildenafil AUC_{last}, AUC_{inf}, and C_{max}.

Both formulations of sildenafil citrate were generally well tolerated in healthy Chinese men. Of the 9 treatment-emergent AEs reported by study subjects across the 3 treatment periods, 6 AEs (nausea, dizziness [2 subjects], headache [2 subjects], and flushing) were considered treatment related by the study investigator; 3 AEs (decrease in blood potassium [2 subjects] and hypoglycemia) were considered unrelated. There were slightly more AEs in subjects who received sildenafil citrate ODT with water (n = 6) compared with those receiving sildenafil citrate ODT without water (n = 2) and the conventional sildenafil citrate tablet (n = 1). All AEs

Figure 2. Individual and geometric mean plasma sildenafil AUC_{inf} (A), AUC_{last} (B), and C_{max} (C) values by treatment. Circles represent individual values, and gray-filled dots represent geometric means. The box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times the interquartile range. Arithmetic means (SDs) are also provided as separate data points, where squares represent arithmetic means, whereas error bars are the SDs. AUC_{inf}, area under the plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last}, area under the plasma concentration-time profile from time 0 to the last quantifiable concentration; C_{max}, maximum plasma concentration; ODT, orally disintegrating tablet.

Table 2. Descriptive Summary of Plasma Sildenafil Pharmacokinetic Parameters After a Single Oral Dose of 50 mg Sildenafil Citrate

Pharmacokinetic Parameter, Unit	Sildenafil Citrate Tablet With Water n/N = 35/36	Sildenafil Citrate ODT Without Water n/N = 35/36	Sildenafil Citrate ODT With Water n/N = 32/36
AUC_{inf}, ng·h/mL[a]	766.6 (43)	754.6 (40)	729.3 (41)
AUC_{inf}, ng·h/mL[b]	835.5 ± 388.5	813.0 ± 334.2	787.0 ± 327.7
AUC_{last}, ng·h/mL[a]	747.2 (42)	757.7 (43)	725.5 (39)
AUC_{last}, ng·h/mL[b]	811.6 ± 370.7	823.5 ± 361.0	777.1 ± 303.0
CL/F, L/h[a]	65.23 (43)	66.25 (40)	68.56 (41)
CL/F, L/h[b]	70.5 ± 28.3	71.1 ± 26.9	73.7 ± 28.7
C_{max}, ng/mL[a]	295.2 (55)	276.1 (50)	269.9 (40)
C_{max}, ng/mL[b]	333.0 ± 165.4	308.8 ± 153.9	290.7 ± 122.3
t_{max}, h[c]	0.750 (0.250–3.00)	0.750 (0.250–2.00)	0.500 (0.250–2.00)
$t_{½}$, h[b]	2.8 ± 0.5	2.8 ± 0.4	2.8 ± 0.4

AUC_{inf}, area under the plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last}, area under the plasma concentration-time profile from time 0 to the last quantifiable concentration; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; n, subjects with reportable AUC_{inf}, CL/F, and $t_{½}$; N, subjects in treatment group; ODT, orally disintegrating tablet; $t_{½}$, terminal half-life; t_{max}, time to C_{max}.
[a]Geometric mean (% CV).
[b]Arithmetic mean ± SD.
[c]Median (range).

Table 3. Statistical Summary of Treatment Comparisons for Plasma Sildenafil Pharmacokinetic Parameters

Parameter, Units	Adjusted (Least-Squares) Geometric Means		Ratio[a]	90%CI[a]
	Sildenafil Citrate ODT Without Water	Sildenafil Citrate Tablet With Water		
AUC_{inf}, ng·h/mL	773.4	765.5	101.03	94.80–107.66
AUC_{last}, ng·h/mL	757.7	747.2	101.41	95.49–107.70
C_{max}, ng/mL	276.1	295.2	93.55	84.15–104.00
	Sildenafil Citrate ODT With Water	Sildenafil Citrate Tablet With Water		
AUC_{inf}, ng·h/mL	743.3	765.5	97.09	90.90–103.71
AUC_{last}, ng·h/mL	725.5	747.2	97.10	91.43–103.12
C_{max}, ng/mL	269.9	295.2	91.43	82.25–101.65

AUC_{inf}, area under the plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last}, area under the plasma concentration-time profile from time 0 to the last quantifiable concentration; C_{max}, maximum plasma concentration; ODT, orally disintegrating tablet.
[a]Ratio of test to reference of adjusted geometric means and 90%CIs are percentages.

were mild in severity, and no subjects discontinued from the study.

Based on data from this study, sildenafil citrate ODT and the sildenafil citrate tablet are considered interchangeable. Given that dysphagia is a common ailment in adults,[21] with an estimated prevalence of up to 22% in adults aged ≥ 50 years,[22] this dosage form of sildenafil will provide a useful alternative to conventional tablets.

Conclusions

As a 50-mg dose, sildenafil citrate ODT taken either without or with water is bioequivalent to or meets bioequivalence criteria compared with the commercial sildenafil citrate film-coated tablet taken with water, thus offering a convenient alternative method of oral administration. Both formulations were safe and generally well tolerated in healthy Chinese men.

Acknowledgments

Medical writing support was provided by Jill E. Kolesar, PhD, and Susan E. DeRocco, PhD, of Complete Healthcare Communications, LLC, and was funded by Pfizer.

Conflicts of Interest

B. Luo, R. R. LaBadie, H. Zhu, Y. Feng, and P. H. Crownover are employees of Pfizer and may hold stock and/or stock

Table 4. Incidence of All-Causality (Treatment-Related) Treatment-Emergent Adverse Events

	Subjects, n = 36		
Adverse Event	Sildenafil Citrate Tablet With Water, n (n[a])	Sildenafil Citrate ODT Without Water, n (n[a])	Sildenafil Citrate ODT With Water, n (n[a])
Gastrointestinal disorders	0	0	1 (1)
Nausea	0	0	1 (1)
Investigations	1 (0)	0	1 (0)
Blood potassium decreased	1 (0)	0	1 (0)
Metabolism and nutrition disorders	0	0	1 (0)
Hypoglycemia	0	0	1 (0)
Nervous system disorders	0	2 (2)	2 (2)
Dizziness	0	1 (1)	1 (1)
Headache	0	1 (1)	1 (1)
Vascular disorders	0	0	1 (1)
Flushing	0	0	1 (1)
Total	1 (0)	2 (2)	6 (4)

ODT, orally disintegrating tablet.
n, number of subjects with all-causality treatment-emergent AEs.
n[a], number of subjects with treatment-related treatment-emergent AEs.

options. Y. Liang and Q. Zhao were employees of Pfizer during the time the study was conducted. C. Ernst is a contractor with Pfizer and may hold stock. Y. Lv has served as an investigator for Pfizer Inc and has no other conflicts to disclose.

Funding

This study was sponsored by Pfizer.

Author Contributions

This research was designed by R. R. LaBadie and Q. Zhao and performed by Y. Lv, B. Luo, R. R. LaBadie, H. Zhu, Y. Feng, C. Ernst, and Q. Zhao. The data were analyzed by Y. Lv, B. Luo, R. R. LaBadie, H. Zhu, C. Ernst, P. H. Crownover, Y. Liang, and Q. Zhao. All authors drafted the article.

Data-Sharing Statement

On request and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requesters must enter into a data access agreement with Pfizer.

References

1. Aytac IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int*. 1999;84(1):50-56.
2. Zhang X, Yang B, Li N, Li H. Prevalence and risk factors for erectile dysfunction in Chinese adult males. *J Sex Med*. 2017;14(10):1201-1208.
3. Wang W, Fan J, Huang G, et al. Meta-analysis of prevalence of erectile dysfunction in mainland China: evidence based on epidemiological surveys. *Sex Med*. 2017;5(1):e19-e30.
4. Chou PS, Chou WP, Chen MC, et al. Newly diagnosed erectile dysfunction and risk of depression: a population-based 5-year follow-up study in Taiwan. *J Sex Med*. 2015;12(3):804-812.
5. Mo MQ, Long LL, Xie WL, et al. Sexual dysfunctions and psychological disorders associated with type IIIa chronic prostatitis: a clinical survey in China. *Int Urol Nephrol*. 2014;46(12):2255-2261.
6. Althof SE, O'Leary MP, Cappelleri JC, et al. Sildenafil citrate improves self-esteem, confidence, and relationships in men with erectile dysfunction: results from an international, multi-center, double-blind, placebo-controlled trial. *J Sex Med*. 2006;3(3):521-529.
7. Litwin MS. Health related quality of life in older men without prostate cancer. *J Urol*. 1999;161(4):1180-1184.

8. European Association of Urology. Guidelines on Male Sexual Dysfunction: Erectile Dysfunction and Premature Ejaculation. http://uroweb.org/wp-content/uploads/14-Male-Sexual-Dysfunction_LR1.pdf. Accessed April 12, 2020.
9. Hackett G, Kell P, Ralph D, et al. British Society for Sexual Medicine guidelines on the management of erectile dysfunction. *J Sex Med*. 2008;5(8):1841-1865.
10. Boolell M, Allen MJ, Ballard SA, et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res*. 1996;8(2):47-52.
11. Nichols DJ, Muirhead GJ, Harness JA. Pharmacokinetics of sildenafil citrate after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br J Clin Pharmacol*. 2002;53(suppl 1):5S-12S.
12. Hyland R, Roe EG, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the *N*-demethylation of sildenafil. *Br J Clin Pharmacol*. 2001;51(3):239-248.
13. Warrington JS, Shader RI, von Moltke LL, Greenblatt DJ. In vitro biotransformation of sildenafil (Viagra): identification of human cytochromes and potential drug interactions. *Drug Metab Dispos*. 2000;28(4):392-397.
14. Merry C, Barry MG, Ryan M, et al. Interaction of sildenafil and indinavir when co-administered to HIV-positive patients. *AIDS*. 1999;13(15):F101-F107.
15. Muirhead GJ, Wulff MB, Fielding A, Kleinermans D, Buss N. Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. *Br J Clin Pharmacol*. 2000;50(2):99-107.
16. Valenzuela F, Davila G, Ibañez Y, et al. Relative bioavailability of chewable and conventional film-coated tablet formulations of sildenafil 100 mg in healthy volunteers under fasting conditions. *J Bioequiv Availab*. 2011;3(9):207-210.
17. Deveci S, Peskircioglu L, Aygun C, et al. Sublingual sildenafil in the treatment of erectile dysfunction: faster onset of action with less dose. *Int J Urol*. 2004;11(11):989-992.
18. Roh H, Son H, Lee D, et al. Pharmacokinetic comparison of an orally disintegrating film formulation with a film-coated tablet formulation of sildenafil in healthy Korean subjects: a randomized, open-label, single-dose, 2-period crossover study. *Clin Ther*. 2013;35(3):205-214.
19. Damle B, Duczynski G, Jeffers BW, et al. Pharmacokinetics of a novel orodispersible tablet of sildenafil in healthy subjects. *Clin Ther*. 2014;36(2):236-244.
20. Eerkes A, Addison T, Naidong W. Simultaneous assay of sildenafil and desmethylsildenafil in human plasma using liquid chromatography-tandem mass spectrometry on silica column with aqueous-organic mobile phase. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2002;768(2):277-284.
21. Bhattacharyya N. The prevalence of dysphagia among adults in the United States. *Otolaryngol Head Neck Surg*. 2014;151(5):765-769.
22. Howden CW. Management of acid-related disorders in patients with dysphagia. *Am J Med*. 2004;117(suppl 5A):44S-48S.