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Original Research

Food effect on pharmacokinetic profiles of sildenafil 100 mg oral films in healthy male volunteers: results from two randomized, single dose, crossover studies

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Abstract

Background: Decades after it was first put on the market, sildenafil is still a very successful treatment for erectile dysfunction. New formulations, such orodispersible films (ODFs), offer more convenience allowing more discreet use and enabling people who might have trouble swallowing tablets to take the drug.
Aim: To evaluate the impact of food and water on sildenafil ODF as compared to sildenafil film-coated tablet (FCT) and to assess the safety and palatability of the orodispersible formulation.
Methods: Two randomized, single-dose, three-period, crossover studies were conducted on healthy male volunteers. The first study, involving 45 subjects, was designed to compare ODF versus FCT under fasting conditions and to study the effect of high-fat, high-calorie meal on ODF pharmacokinetic (PK) profiles. The second study, involving 35 subjects, compared ODF versus FCT under fed conditions and the effect of water on ODF PK profiles. Blood samples were collected within 24 h post-dosing to measure plasma sildenafil and its metabolite, *N*-desmethyl-sildenafil.
Outcomes: Primary outcomes were maximum observed plasma concentration (C_{max}), the area under the concentration–time curve (AUC), and the time of maximum observed plasma concentration (T_{max}). Secondary outcomes included palatability and safety.
Results: Food delayed sildenafil 100 mg ODF T_{max} by 1.45 h and decreased C_{max} by 45% but did not affect the extent of systemic exposure to sildenafil (AUC). Bioequivalence was demonstrated for sildenafil ODF administered with and without water under fed conditions. C_{max} of plasma sildenafil was ∼13% and 17% lower for ODF (without and with water, respectively), and T_{max} was delayed by 1-1.5 h, compared to FCT under fed conditions, but both $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ met the bioequivalence limits. Palatability was acceptable with mild aftertastes. The ODF formulation was well-tolerated with no severe adverse events.
Clinical Implications: Sildenafil ODF is a bioequivalent alternative to traditional tablets. The food impact on sildenafil ODF taken with and without water is consistent with that associated with FCT, influencing C_{max} and T_{max} but not AUC.
Strengths and Limitations: The study population consisted exclusively of healthy subjects, and the study was limited to single-dose administration. Lastly, although bioequivalence of PKs implies therapeutic equivalence, future studies incorporating clinical endpoints would offer more conclusive evidence of interchangeability.
Conclusion: Sildenafil ODF has comparable PKs and added convenience for patients. Its versatility, ease of use, and discreetness make it ideal as safe and effective alternative to FCT.
ISRCTN registry numbers where the trial protocols can be accessed:
Study A: ISRCTN13297409 (https://doi.org/10.1186/ISRCTN13297409)
Study B: ISRCTN15394603 (https://doi.org/10.1186/ISRCTN15394603)

Keywords: sildenafil; orodispersible film; bioavailability; pharmacokinetic; food effect; PDE5i.

Introduction

Over 30 years have passed since the serendipitous discovery of the pro-erectile effects of the first phosphodiesterase type 5 inhibitor (PDE5i), sildenafil (Viagra®, Pfizer). The introduction of this drug marked a revolutionary milestone in the management of erectile dysfunction (ED) and paved the way for an ever-expanding field of research.[1]

Other molecules from the same class have been approved and marketed in subsequent years, including tadalafil, vardenafil, and avanafil.[2-4] While several studies have compared these four drugs, often recognizing similar subjective efficacy and safety profiles,[5] sildenafil still remains a preferred choice for many healthcare providers due to its robust evidence of clinical efficacy and favorable patient responses.[6,7] Moreover,

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its rapid onset and convenient duration of action align with patients' needs for a therapy that complements several aspects of the natural physiology and spontaneity of sexual activity.[6]

All PDE5i are available in film-coated tablet (FCT) forms designed for on-demand administration, typically about 30-120 min prior to sexual activity[4,8] or for daily administrations at low doses.[9] When taken under fasting conditions, conventional sildenafil tablets exhibit an oral bioavailability of 41% and reach maximum plasma concentration ~1 h post-administration, with a half-life of about 4 h.[10,11]

Sildenafil is primarily metabolized in the liver by cytochrome P450 (CYP)3A4 and, to a lesser extent, by CYP2C9.[12] Its major active metabolite, *N*-desmethyl-sildenafil, contributes ~20% of its pharmacological activity.[12] Food can delay the absorption of sildenafil FCT, reducing the maximum observed plasma concentration (C_{max}) and extending the time of maximum observed plasma concentration (T_{max}).[10] Nonetheless, sildenafil FCTs are approved for use regardless of meals, with no significant clinical implications beyond a delayed onset of action.

With the expiration of Pfizer's patent for sildenafil citrate, new pharmaceutical formulations have been developed and introduced to the market, aiming to improve the overall patient experience considering that ~31%-57% of men abandon PDE5i therapy despite successful intercourse because of the treatment and that one of the most common reasons for the discontinuation is "reluctant medication-dependent intercourse."[13] A substantial portion of research has focused on developing orally disintegrating formulations, such as orodispersible tablets (ODTs) and oral thin films, also referred to as orodispersible films (ODFs).

ODFs offer several advantages. They do not need to be swallowed or taken with water, making them particularly suitable for patients with dysphagia or patients requiring restricted water intake.[14,15] Unlike FCTs, which are highly recognizable and might be noticed by sexual partners, ODFs permit a much more discreet administration. Lack of discretion has been cited as a factor negatively impacting patient adherence and compliance to PDE5i therapy.[6,13]

Last but not least, the ODF formulation is, at present, the only one exempt from the risk of counterfeiting. As PDE5is are among the most counterfeited drugs worldwide,[16] this is an added benefit with potential beneficial effects on treatment compliance and safety.[17,18]

The pharmacokinetic (PK) properties of various orodispersible formulations of sildenafil have been evaluated in multiple studies, demonstrating substantial bioequivalence to equivalent doses of sildenafil in FCT form in fasting conditions.[19-25]

A maltodextrin-based ODF formulation of sildenafil has been developed by IBSA Institut Biochimique SA (IBSA) and is available in various dosages (25, 50, 75, 100 mg). This formulation has demonstrated safety and efficacy[7,26-29] and, from a PK perspective, has been shown to be bioequivalent to the conventional FCT.[22] However, the effect of food on the PK properties of this product has not yet been investigated.

This article will describe two different PK studies performed on healthy male volunteers to assess: (1) The bioequivalence between sildenafil IBSA 100 mg ODF (Test) and sildenafil 100 mg FCT (Reference) in both fasting and fed conditions; (2) The influence of food and water on the PKs of the ODF; and (3) The safety and palatability of the studied pharmaceutical formulations.

Methods

The first study (hereafter referred to as Study A) was conducted to confirm the bioequivalence of sildenafil IBSA ODF and marketed sildenafil FCT under fasting conditions, as well as to compare the PKs and bioavailability of sildenafil IBSA ODF taken under fed and fasting conditions; the second (hereafter referred to as Study B) was conducted to compare the PKs and bioavailability of sildenafil IBSA ODF and marketed sildenafil FCT under fed conditions, as well as to compare the PKs and bioavailability of sildenafil IBSA ODF taken with and without water under fed conditions.

Study population

A total of 80 healthy male volunteers were enrolled in two randomized control trials, 45 subjects aged 18-45 years for Study A and 35 subjects aged 18-55 years for Study B.

Inclusion criteria required participants to have a body mass index (BMI) of 18.5-30 kg/m^2 and have no clinically significant diseases based on medical history or evidence of clinically significant findings from physical examinations, clinical laboratory evaluations (hematology, general biochemistry, lipid profile, and urinalysis), and instrumental evaluation (12-lead ECG) performed during the pre-trial phase.

Exclusion criteria included a history of hypersensitivity to sildenafil or any related products such as PDE5is, severe hypersensitivity reactions to any drugs, recent use of sildenafil, nitrates, medications that could interfere with sildenafil metabolism or situations that induce or inhibit hepatic enzyme activity within 28 days, anatomical deformation of the penis, recent participation in another clinical trial, or recent blood donation.

Additional exclusions for Study A included smokers or ex-smokers who had quit for <6 months, as well as individuals with a current or recent history of tongue piercings. Additional exclusions for Study B included a history of drug, alcohol, caffeine, or tobacco abuse and abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study.

Study design

Study A was carried out at Algorithme Pharma, Phase I Unit, Canada. Study B was carried out at CROSS Research S.A., Phase I Unit, Switzerland. They were both single-center, randomized, single-dose, laboratory-blinded, three-period, crossover trials.

Participants in Study A were given one of the following treatments during each study period separated by a minimum of a 7-day washout period to minimize carryover effects: sildenafil 100 mg ODF without water under fed conditions; sildenafil 100 mg ODF without water under fasting conditions; sildenafil 100 mg FCT with water under fasting conditions.

Participants in Study B were given one of the following treatments during each study period separated by a minimum of a 5-day washout period: sildenafil 100 mg ODF without water under fed conditions; sildenafil 100 mg ODF with water under fed conditions; sildenafil 100 mg FCT with water under fed conditions.

The order of investigational product administration was sequentially assigned from a computer-generated randomization list in both studies. All volunteers underwent a supervised 10-h overnight fast before each drug administration. For fed conditions, a standardized high-fat (ca. 50% of total caloric

content of the meal), high-calorie (800-1000 cal) breakfast was consumed 30 min before dosing. According to the FDA guidance, it consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and eight ounces of whole milk.

Qualified clinical staff members directly placed the ODF on the subjects' tongues without water; the film was not allowed to be swallowed, chewed, or broken in the mouth. The dissolution time was recorded. For treatment with sildenafil 100 mg ODF with water under fed conditions in Study B, after complete film dissolution, the subjects were given 240 mL of water. The sildenafil FCT was swallowed (without chewing or breaking it) with 240 mL of water.

Post-dose fasting was maintained for at least 4 h and water was allowed ad libitum until 1 h before dosing and resumed 1 h after drug administration.

Blood samples for PK analysis were collected pre-dose and at 22 post-dose intervals for Study A (0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, and 24.00 h) and 16 post-dose intervals for Study B (0.1, 0.25, 0.50, 0.75, 1.00, 1.25, 1.5, 2.00, 2.5, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, and 24.00 h).

As part of Study A, a palatability appreciation questionnaire was administered immediately after the ODF dissolved completely and ~30 min after dosing. Subjects would state whether they strongly/somewhat agree/disagree or be neutral with the statements I have a favorable overall opinion about the treatment. I can handle this kind of therapy every day, and There is no after-taste left in my mouth after intake. The remaining two statements, The formulation is easy to consume/swallow (does not cause discomfort during the administration), and How do you like the taste of the drug? Would you say that the taste is, were rated as unpleasant/very unpleasant, acceptable, or good/very good.

Ethical conduct

All subjects provided written informed consent before study participation. Study A was performed after approval by IRB Services, Canada (approval code: Pro00021969, June 13, 2017). Study B was performed after approval by Canton Ticino Ethics committee, Switzerland; (approval code: 2020-01698/CE-3698, July 14, 2020). The studies were conducted following the ethical principles outlined in the Declaration of Helsinki.

PK analysis

Blood samples were centrifuged at 4°C, and plasma was separated within 90 min, stored at −20°C, and transported on dry ice to the bioanalytical facility for analysis. Plasma concentrations of sildenafil and its active metabolite, *N*-desmethyl-sildenafil, were measured using a validated high-performance liquid chromatography method coupled with tandem mass spectrometry. The assay's quantitation limits ranged from 1 to 1000 ng/mL for sildenafil and 1 to 300 ng/mL for its metabolite.

The PK parameters were estimated for sildenafil and its metabolite using a standard non-compartmental analysis. The determination of C_{max} and T_{max} was based on observed data. The linear trapezoidal method was used to estimate the area under the plasma concentration–time curve from zero to the last quantifiable time ($AUC_{0\text{-}T}$), while the area under the plasma concentration–time curve extrapolated to infinity ($AUC_{0\text{-}\infty}$) was derived by extrapolating the terminal phase using the terminal elimination rate constant (λ_z), which was in turn estimated from the log-linear portion of the plasma concentration-time curve.

The relative bioavailability of the ODF compared to the FCT was assessed using C_{max} and AUC parameters. The food effect was evaluated by comparing C_{max}, AUC parameters, and T_{max} under fed and fasting conditions.

Safety assessments

Safety was evaluated by monitoring treatment-emergent adverse events (TEAEs), clinical laboratory results, vital signs, and physical examinations.

TEAEs were classified by severity as mild (no limitation of usual activities with slight discomfort), moderate (some limitations of usual activities with annoying discomfort), or severe (inability to perform usual activities with intolerable discomfort or pain). Furthermore, the relationship of each TEAE to the investigational product was categorized as certain, probable, possible, unlikely, or not related.

Statistical analysis

For Study A, the sample size was determined on the basis of an intra-subject variation of ~31% for C_{max} and 17% for $AUC_{0\text{-}T}$ following a single dose of sildenafil 100 mg. Assuming the geometric LSmeans ratio between ODF and FCT formulations would fall within the range of 95%-105%, it was calculated that a minimum of 39 subjects would be required to achieve the 80%-125% bioequivalence range with a statistical power of at least 80%.

For Study B, the sample size was not statistically determined due to the lack of previous informative data on the sildenafil bioavailability following the administration of sildenafil 100 mg FCT in fed conditions.

The PK analysis and the statistical analysis of PK parameters were performed using Phoenix® WinNonlin® version 6.3 (Study A) and 8.3.5 (Study B) (Pharsight Corporation, Mountain View, CA, USA), and SAS® version 9.3 (TS1M1).

Sildenafil and *N*-desmethyl-sildenafil rate (C_{max}) and extent (AUC) of absorption were compared between test and reference using analysis of variance for a crossover design on log-transformed data. Period, treatment, sequence, and subject within sequence were taken into account as sources of variation. The acceptance criterion for bioequivalence was to have all 90% confidence interval (CI) for the ratio of geometric least square (LS) means of C_{max}, $AUC_{0\text{-}T}$, and $AUC_{0\text{-}\infty}$ falling within the 80.00%-125.00% range as required by regulatory guidelines.

Results

Study subjects

Between June 15, 2017, and August 1, 2017, 45 participants in Study A were recruited and completed the trial. All subjects were included in the PK analyses for bioequivalence and food effects, as well as for safety profiles. The subjects included were Caucasian (93.4%), Black or African American (2.2%), Asian (2.2%), and other races (2.2%). The mean (SD) age was 35.0 (8.0) years, and the mean BMI was 25.9 (2.9) (range, 18.8-29.7 kg/m^2).

One of the 35 participants in Study B who were enrolled between December 1, 2020, and January 28, 2021, withdrew the trial before receiving any medication for personal reasons.

Table 1. Descriptive summary of plasma sildenafil and *N*-desmethyl-sildenafil pharmacokinetic parameters after a single oral dose of sildenafil 100 mg film-coated tablet (FCT) or sildenafil 100 mg orodispersible film (ODF) in different conditions (Study A).

	Sildenafil ODF, fed (T1) ($n = 45$)	Sildenafil ODF, fast (T2) ($n = 45$)	Sildenafil FCT, fast (T3) ($n = 45$)	Point estimate[a] (%) *P*-value[b]	
				T2/T3	T1/T2
Sildenafil					
C_{max} (ng/mL)	277.73 (46.4)	503.47 (37.7)	466.29 (42.1)	108.55% (99.19-118.79) .1399	54.68% (49.96-59.84) <.0001
$AUC_{0\text{-}T}$ (ng h/mL)	1691.77 (33.5)	1876.41 (36.1)	1585.95 (34.0)	116.68% (111.09-122.55) <.0001	91.07% (86.70-95.65) .0028
$AUC_{0\text{-}\infty}$ (ng h/mL)	1725.79 (33.8)	1902.41 (36.3)	1609.85 (34.2)	116.52% (110.97-122.34) <.0001	91.57% (87.22-96.15) .0044
λ_z (h^{-1})	0.1777 (19.4)	0.1707 (18.5)	0.1694 (24.6)		
T_{max} (h)	3.00 (0.50-8.00)	1.33 (0.33-5.00)	1.00 (0.33-4.00)	.9229	<.0001
T_{half} (h)	4.05 (20.4)	4.20 (19.5)	4.32 (23.3)		
***N*-Desmethyl-sildenafil**					
C_{max} (ng/mL)	116.56 (45.1)	233.80 (37.9)	242.65 (38.9)	96.71% (88.65-105.50) .5237	48.83% (44.76-53.27) <.0001
$AUC_{0\text{-}T}$ (ng h/mL)	747.55 (43.4)	960.21 (42.8)	895.85 (41.1)	106.02% (101.89-110.33) .0165	78.08% (75.03-81.24) <.0001
$AUC_{0\text{-}\infty}$ (ng h/mL)	768.51 (43.9)	981.76 (43.1)	915.12 (41.4)	106.12% (102.00-110.40) .0145	78.45% (75.40-81.62) <.0001
λ_z (h^{-1})	0.1731 (20.7)	0.1751 (12.8)	0.1732 (13.1)		
T_{max} (h)	2.67 (0.83-8.00)	1.33 (0.50-5.00)	1.00 (0.50-4.00)	.5817	<.0001
T_{half} (h)	4.18 (21.6)	4.02 (12.0)	4.07 (12.5)		

Values are presented as arithmetic mean (% coefficient of variation) except for T_{max}, which is presented as the median with the range (Min–Max). Abbreviations: $AUC_{0\text{-}T}$: cumulative area under the plasma concentration–time curve calculated from time zero to the last observed quantifiable plasma concentration; $AUC_{0\text{-}\infty}$: area under the plasma concentration-time curve extrapolated to infinity; C_{max}: maximum observed plasma concentration; λ_z: apparent elimination rate constant; T_{max}: time of maximum observed plasma concentration; T_{half}: terminal elimination half-life time. [a]Ratio of geometric least-squares means (90% CI). [b]Overall test of fixed treatment effect.

During the study period, two subjects withdrew due to adverse events and one subject due to personal reasons. As a result, 34 subjects were included in the safety analysis, while PKs analysis comparing sildenafil FCT (fed) versus sildenafil ODF (fed, without water), sildenafil FCT (fed) versus sildenafil ODF (fed, with water), and sildenafil ODF (fed, with water) versus sildenafil ODF (fed, without water) involved 32, 30, 30 subjects, respectively. The subjects included were Caucasian (97.1%) and Black or African American (2.9%). The mean (SD) age was 36.1 (10.5) years, and the mean BMI was 25.4 (3.2) (range, 18.6-30.0 kg/m^2).

No subjects in either study had a history of exposure to other medications during the screening period. Plasma levels of sildenafil in all samples collected before dosing were below the limit of quantitation (1.00 ng/mL), indicating appropriate wash-out interval times.

Pharmacokinetics

Tables 1 and 2 summarize the PK parameters of sildenafil and *N*-desmethyl-sildenafil for Study A and Study B, respectively. The mean plasma concentration–time profiles within 24 h after a single dose of sildenafil 100 mg FCT (fast) and sildenafil 100 mg ODF (fast and fed) In Study A are displayed in Figure 1 for sildenafil and in Figure 2 for *N*-desmethyl-sildenafil. Figures 3 and 4 illustrate the change in mean plasma concentration of sildenafil and *N*-desmethyl-sildenafil following sildenafil 100 mg FCT (fed) and sildenafil 100 mg ODF (fed, with and without water) in Study B.

Bioequivalence under fasting conditions

Under fasting conditions, no statistically significant difference was found between sildenafil 100 mg ODF and FCT in terms of C_{max}, T_{max}, and terminal elimination half-life time (T_{half}) of plasma sildenafil. However, the $AUC_{0\text{-}T}$ and $AUC_{0\text{-}\infty}$ of plasma sildenafil were significantly higher with the ODF formulation compared to sildenafil FCT ($P < .001$ for both). The same conclusion applies to the PK parameters of *N*-desmethyl-sildenafil.

Table 1 compares the bioavailability of sildenafil 100 mg ODF and FCT under fasting conditions. The geometric LSmeanratios between the two formulations for C_{max}, $AUC_{0\text{-}T}$, and $AUC_{0\text{-}\infty}$ of plasma sildenafil were 108.55% [90% CI, 99.19-118.79], 116.68% [90% CI, 111.09-122.55], and 116.52% [90% CI, 110.97-122.34], respectively. In the case of *N*-desmethyl-sildenafil, these ratios were 96.71% [90% CI, 88.65-105.50] for C_{max}, 106.02% [90% CI, 101.89-110.33] for $AUC_{0\text{-}T}$, and 106.12% [90% CI, 102.00-110.40] for $AUC_{0\text{-}\infty}$.

The geometric LSmean ratios and 90% CIs for all the aforementioned PK parameters were entirely within the 80% to 125% equivalence interval.

Food effect assessment

When comparing sildenafil 100 mg ODF under fasting and fed conditions (Table 1), statistically significant differences in plasma sildenafil were found for most PK parameters, including C_{max} ($P < .001$), T_{max} ($P < .001$), $AUC_{0\text{-}T}$ ($P = .003$), and $AUC_{0\text{-}\infty}$ ($P = .004$). Food intake delayed the T_{max} from a median of 1.33 under fasting conditions to 3.00 h. The C_{max} of sildenafil also significantly decreased under fed conditions with a geometric LSmean ratio (fed/fast) of 54.68% [90% CI, 49.96-59.84]. The geometric LS mean ratios (fed/fast) of $AUC_{0\text{-}T}$ and $AUC_{0\text{-}\infty}$ for sildenafil were 91.07% [90% CI, 86.70-95.65] and 91.57% [90% CI, 87.22-96.15], respectively, both meeting the 80%-125% bioequivalence

Table 2. Descriptive summary of plasma sildenafil and *N*-desmethyl-sildenafil pharmacokinetic parameters after a single oral dose of sildenafil 100 mg film-coated tablet (FCT) or sildenafil 100 mg orodispersible film (ODF) in different conditions (Study B).

	Sildenafil ODF, fed without water (T1) ($n = 32$)	Sildenafil ODF, fed with water (T2) ($n = 30$)	Sildenafil FCT, fed (*R*) ($n = 32$)	Point estimate [a] (%) *P*-values[b]		
				T1/R	T2/R	T1/T2
Sildenafil						
C_{max} (ng/mL)	317.48 (33.2)	295.54 (32.2)	393.44 (57.5)	86.86 (77.50-97.35) .045	83.37 (73.75-94.24) .018	105.28 (96.75-114.57) .309
$AUC_{0\text{-}T}$ (ng h/mL)	1708.91 (34.6)	1671.91 (35.1)	1624.08 (45.2)	107.67 (100.45-115.41) .081	108.24 (101.90-114.96) .034	101.67 (95.50-108.25) .655
$AUC_{0\text{-}\infty}$ (ng h/mL)	1752.54 (34.0)	1698.36 (35.1)	1646.67 (44.8)	107.62 (100.22-115.56) .091	108.39 (102.01-115.16) .032	101.66 (95.25-108.51) .669
λ_z (h^{-1})	0.17 (15.9)	0.18 (23.1)	0.19 (22.4)			
T_{max} (h)	3.00 (0.50-4.00)	2.50 (0.25-4.00)	1.50 (0.50-6.00)	.102	.627	.549
T_{half} (h)	4.07 (16.0)	4.04 (24.4)	3.87 (23.3)			
***N*-Desmethyl-sildenafil**						
C_{max} (ng/mL)	103.56 (35.1)	91.08 (31.5)	130.04 (56.8)	85.71 (77.99-94.19) .009	77.78 (70.34-86.01) .0002	109.48 (102.96-116.41) .018
$AUC_{0\text{-}T}$ (ng h/mL)	568.21 (33.4)	546.18 (32.7)	557.11 (40.7)	103.25 (98.51-108.22) .256	102.18 (97.32-107.28) .458	101.51 (97.17-106.04) .564
$AUC_{0\text{-}\infty}$ (ng h/mL)	588.23 (33.3)	562.92 (32.7)	575.18 (40.7)	103.63 (98.82-108.68) .213	101.95 (97.07-107.08) .509	101.97 (97.60-106.54) .455
λ_z (h^{-1})	0.13 (33.6)	0.16 (37.9)	0.14 (38.9)			
T_{max} (h)	3.00 (1.00-4.00)	2.75 (0.75-4.00)	1.50 (0.75-4.00)	.048	.2254	.658
T_{half} (h)	5.73 (28.9)	5.09 (35.3)	5.65 (29.8)			

Values are presented as arithmetic mean (% coefficient of variation) except for T_{max}, which is presented as the median with the range (Min–Max). Abbreviations: $AUC_{0\text{-}T}$: cumulative area under the plasma concentration-time curve calculated from time zero to the last observed quantifiable plasma concentration; $AUC_{0\text{-}\infty}$: area under the plasma concentration-time curve extrapolated to infinity; C_{max}: maximum observed plasma concentration; λ_z: apparent elimination rate constant; T_{max}: time of maximum observed plasma concentration; T_{half}: terminal elimination half-life time. [a]Ratio of geometric least-squares means (90% CI). [b]Overall test of fixed treatment effect.

range. When considering the PK results of *N*-desmethyl-sildenafil under fasting and fed conditions, the geometric LSmean ratios (fed/fast) of C_{max}, $AUC_{0\text{-}T}$, and $AUC_{0\text{-}\infty}$ were 48.83% [90% CI, 44.76-53.27], 78.08% [90% CI, 75.03-81.24], and 78.45% [90% CI, 75.40-81.62], respectively. Even if the 90% CI of C_{max} ratio fell outside the acceptable range, the 90% CIs of $AUC_{0\text{-}T}$ and $AUC_{0\text{-}\infty}$ were partly contained by the 80%-125% range. Under fed conditions, *N*-desmethyl-sildenafil C_{max} was decreased by 51.07%, exposure (AUC) was reduced by ∼22%, while T_{max} was delayed from a median of 1.33 to a median of 2.67 h.

Comparison under fed conditions

Under fed conditions, there was a significant inter-subject variability (CV% > 30%) in C_{max}, $AUC_{0\text{-}T}$, $AUC_{0\text{-}\infty}$, and T_{max} for all treatments, in particular in C_{max} and T_{max} for sildenafil 100 mg FCT (CV% = 57.5% and 65.6%, respectively) in Study B (Table 2). In comparison with sildenafil 100 mg FCT (fed), C_{max} of plasma sildenafil and *N*-desmethyl-sildenafil were statistically lower after dosing sildenafil 100 mg ODF (fed, without water) ($P = .045$ and $P = .009$, respectively) or sildenafil 100 mg ODF (fed, with water) ($P = .018$ and $P < .001$, respectively). The T_{max} of sildenafil and *N*-desmethyl-sildenafil were not significantly different in any paired comparison (all $P > .05$). Moreover, the extent of drug exposure (AUC) for plasma sildenafil and *N*-desmethyl-sildenafil was also not significantly different when comparing sildenafil 100 mg FCT (fed) with sildenafil 100 mg ODF (fed, without water) (all $P > .05$). However, $AUC_{0\text{-}T}$ and $AUC_{0\text{-}\infty}$ of plasma sildenafil were greater after administration of sildenafil 100 mg ODF (fed, with water) compared to sildenafil 100 mg FCT (fed) ($P = .034$ and $P = .032$, respectively), while no difference was found regarding plasma *N*-desmethyl-sildenafil ($P = .458$ and $P = .509$, respectively).

As shown in Table 2, the C_{max} geometric LSmean ratios and 90% CIs for both plasma sildenafil and *N*-desmethyl-sildenafil between sildenafil 100 mg FCT (fed) versus ODF (fed, with/without water) fell out of the 80%-125% range for bioequivalence. Findings indicated an ∼13% and 17% lower rate of sildenafil absorption and ∼14% and 22% lower rate of *N*-desmethyl-sildenafil absorption for ODF without water and with water, respectively, compared to the conventional FCT product. The $AUC_{0\text{-}T}$ and $AUC_{0\text{-}\infty}$ geometric LSmeans ratios and 90% CIs for plasma sildenafil and *N*-desmethyl-sildenafil between sildenafil 100 mg FCT (fed) versus ODF (fed, with/without water) both met the bioequivalence criteria.

When comparing the administration of sildenafil 100 mg ODF with and without water under fed conditions, no significant differences were found for T_{max}, $AUC_{0\text{-}T}$, and $AUC_{0\text{-}\infty}$ of plasma sildenafil and *N*-desmethyl-sildenafil (all $P > .05$) except for the C_{max} of *N*-desmethyl-sildenafil ($P = .018$). The geometric LSmeans ratios and 90% CIs of C_{max}, $AUC_{0\text{-}T}$, and $AUC_{0\text{-}\infty}$ presented in Table 2 support the bioequivalence between sildenafil ODF under fed conditions taken with and without water.

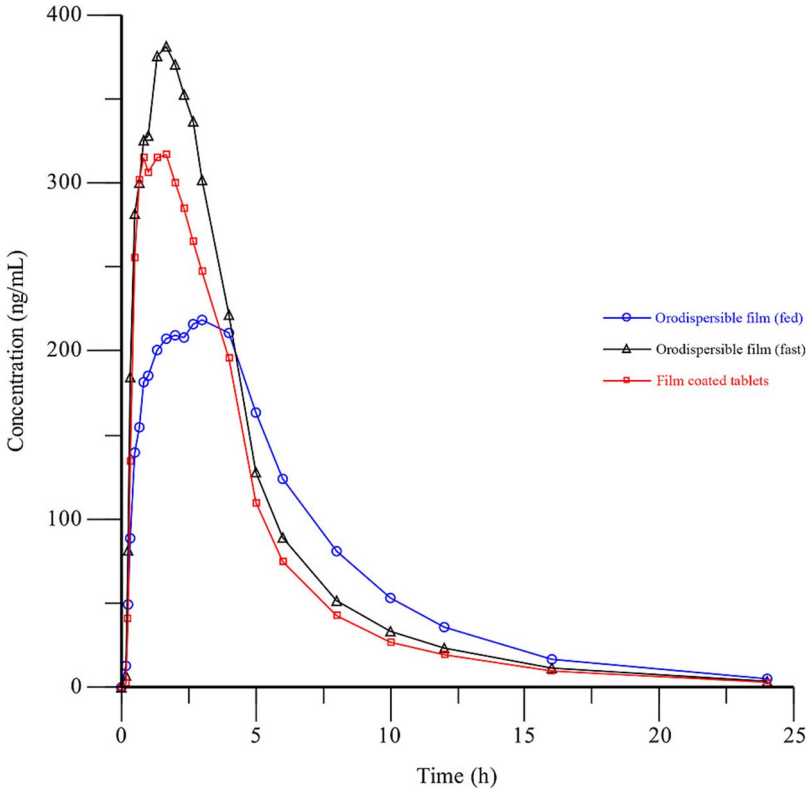

Figure 1. Linear profile of mean plasma concentrations versus time for sildenafil after single dose of sildenafil 100 mg film-coated tablet (fast), sildenafil 100 mg orodispersible film (fast), and sildenafil 100 mg orodispersible film (fed) ($n = 45$).

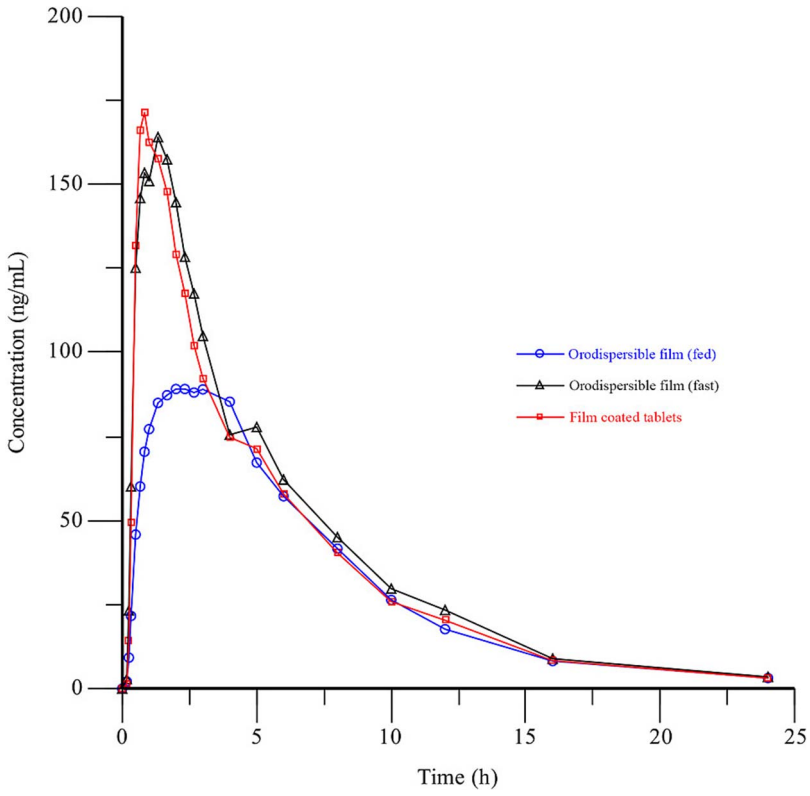

Figure 2. Linear profile of mean plasma concentrations versus time for *N*-desmethyl-sildenafil after single dose of sildenafil 100 mg film-coated tablet (fast), sildenafil 100 mg orodispersible film (fast), and sildenafil 100 mg orodispersible film (fed) ($n = 45$).

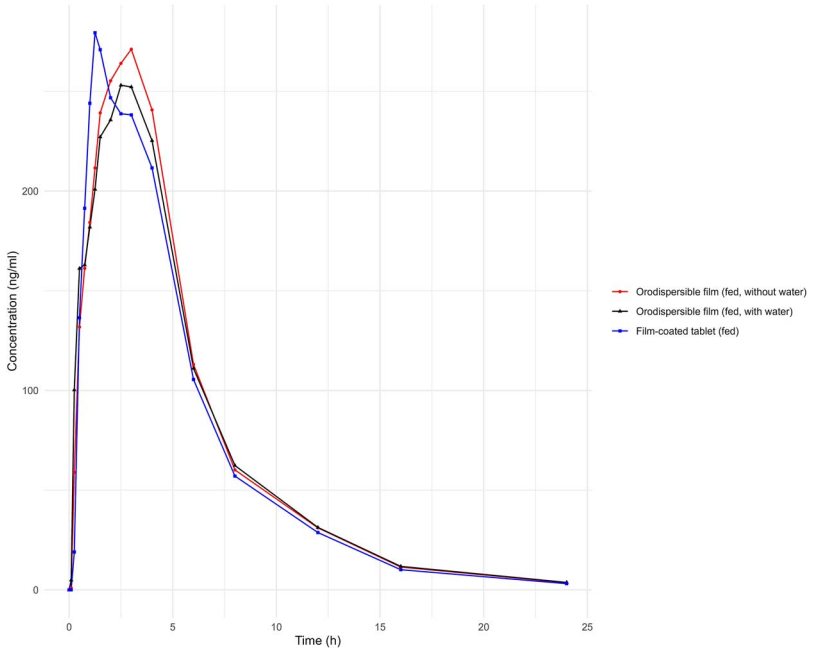

Figure 3. Linear profile of mean plasma concentrations versus time for sildenafil after single dose of sildenafil 100 mg film-coated tablet (fed, $n = 33$), sildenafil 100 mg Orodispersible film (fed, without water, $n = 32$), and sildenafil 100 mg Orodispersible film (fed, with water, $n = 31$).

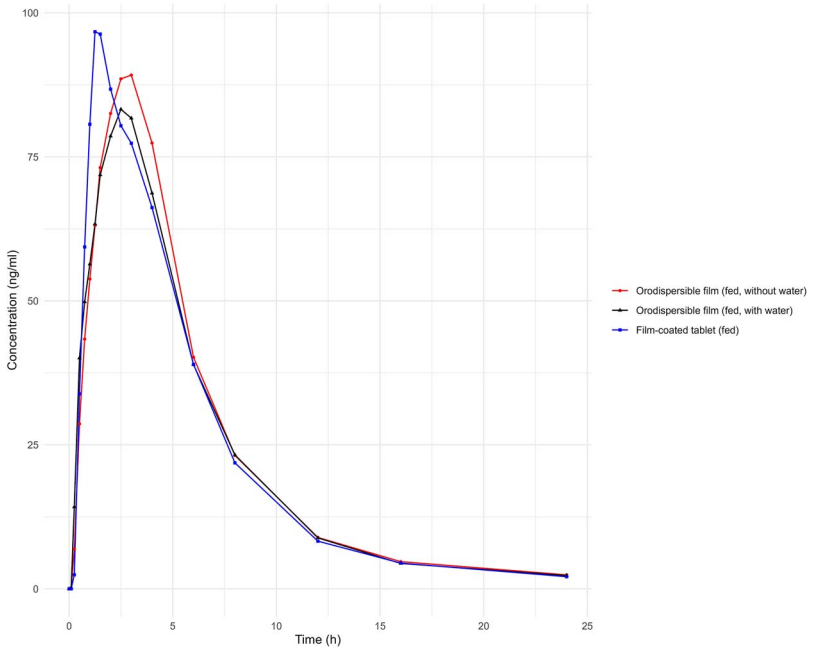

Figure 4. Linear profile of mean plasma concentrations versus time for *N*-desmethyl-sildenafil after single dose of sildenafil 100 mg film-coated tablet (fed, $n = 33$), sildenafil 100 mg orodispersible film (fed, without water, $n = 32$), and sildenafil 100 mg orodispersible film (fed, with water, $n = 31$).

Palatability

According to Study A, 80% of healthy volunteers taking the sildenafil ODF for the first time felt after-tastes left in their mouths at the point of complete dissolution, while 51.1% still felt something after 30 min of administration. The taste was considered acceptable or good/very good by the 42.2% and the 51.1% of the subjects immediately and after 30 min from complete dissolution in the mouth, respectively. No differences were found between using sildenafil 100 mg ODF under fed or fasting conditions.

Safety

Overall, the administration of sildenafil 100 mg ODF and sildenafil 100 mg FCT was safe and well tolerated by most subjects in both studies. Two subjects discontinued participation in Study B due to adverse events: one due to moderate syncope and dizziness related to the first administration of sildenafil 100 mg ODF under fed conditions with water, and the other due to moderate nausea occurring before the last dose in the sequence and categorized as not related to the investigational product. Most subjects showed no clinically

significant changes in physical examinations or laboratory evaluations during the study, except for a 45-year-old man in Study B who presented with an abnormal ALT level (170 U/L), which was subsequently categorized as an adverse event.

A total number of 50 and 18 TEAEs were reported in 51% (23/45) and 29.4% (10/34) subjects participating in Study A and B, most of which (66% in Study A and 61.1% in Study B) were considered related to drug administration. The most commonly experienced TEAEs were dizziness in Study A and headache in Study B. Most of the TEAEs were deemed mild (94% in Study A and 61.1% in Study B) and moderate (6% in Study A and 38.9% in Study B) in intensity. There were no deaths or severe adverse events that required withdrawal for safety reasons. The number of subjects reporting at least one TEAE or drug-related TEAEs were not statistically different among treatments in Study A ($P = .212$ and $P = .186$, respectively) and in Study B ($P = .450$ and $P = .181$, respectively).

Discussion

The two present phase I studies were conducted to assess the PK properties of sildenafil 100 mg ODF under different conditions and to compare it with the conventional marketed sildenafil 100 mg FCT.

In the bioequivalence study under fasting conditions, the 90% CIs of the geometric LSmeans ratios for C_{max}, $AUC_{0\text{-}T}$, and $AUC_{0\text{-}\infty}$ of both sildenafil and its metabolite between the two formulations were entirely within the 80%-125% range. As a result, sildenafil 100 mg ODF is bioequivalent to reference FCT formulation under fasting conditions, which is consistent with a previous study.[22] Additional time-related PK parameters of absorption (T_{max}) and elimination (T_{half}) were statistically similar between the two formulations. Interestingly, compared with the FCT, the ODF provided extended drug exposure with significantly higher $AUC_{0\text{-}T}$ and $AUC_{0\text{-}\infty}$ of sildenafil and its active metabolite. This feature may have potential clinical relevance: although ODF and FCT formulations share similar T_{max}, T_{half}, and C_{max} values, the higher AUC suggests that tissue exposure to the drug may be prolonged.

Since erection involves complex interactions among various individual factors, the correlation between the plasma concentrations of sildenafil and its metabolites with the time to onset of erection and duration of rigidity has not been well-established.[12] Indeed, the C_{max} and AUC of plasma sildenafil increase by 2.08- and 2.23-fold, respectively, for every two-fold increase in dose from 25 to 100 mg.[10] The literature on the effectiveness of sildenafil FCT also highlights its dose-dependent efficacy.[11,30] Guidelines suggest starting with an intermediate dose, such as 50 mg for sildenafil, with the option to up- or down-titrate to the optimal dose for achieving efficacy, satisfaction, and tolerability.[8] The issue of erection duration is important and should be addressed, especially in patients who do not respond to lower doses and require the maximum recommended dose of 100 mg.[11,31-33] Furthermore, with sildenafil 100 mg FCT, the average times of maintaining an erection during visual sexual stimulation are ~19 min after 2 h and 14 min after 4 h post-dose.[32] It remains to be demonstrated that the superior drug exposure with sildenafil 100 mg ODF may result in a longer or better clinical efficacy. Although this issue remains speculative due to the absence of clinical data and the lack of direct comparison between the two formulations at the 100 mg dose, a previous study in men with ED comparing sildenafil 100 mg FCT and sildenafil 75 mg ODF showed a higher overall sexual satisfaction score, as measured by the International Index of Erectile Function, for the latter formulation, despite the lower dose and without differences in the safety profile.[28] The safety profile exhibited by the two formulations was also similar in our study, with all reported TEAEs being mild, indicating good tolerability of the ODF comparable to that of the FCT.

The sildenafil ODF developed by IBSA uses maltodextrin as the film-forming agent and glycerin as the plasticizer, allowing it to dissolve completely in the oral cavity within <1 min through saliva.[22] Its ability to disperse without water makes it more convenient than conventional tablets and more suitable for individuals with dysphagia or neurological disorders affecting swallowing.[14] ODF is also the best choice in cases requiring water input restriction, such as congestive heart failure or renal impairment.[4,6,14] While the film is instructed to be placed on the tongue, findings from a previous study indicate the PK bioequivalence between supra- and sublingual routes of administration.[34] Despite orodispersible products are designed for use without water, a recent study shown that an ODF formulation different from the one used in the present study can be taken with or without water because water does not affect sildenafil absorption under fasting conditions.[24] The present study demonstrated that ODF developed by IBSA can be used both with and without water also under fed conditions. Thus, even if patients do not remember the usage instructions, the product can still dissolve in the oral cavity and maintain its effectiveness.

Moreover, IBSA incorporated polyvinyl acetate to enhance the product's flexibility and tensile strength, making sildenafil ODF easy to carry in a wallet and discreet to use without the sexual partner noticing.[14,22] It should be noted that many patients do not disclose their use of PDE5is to their partners[35] and this lack of communication can potentially cause relationship distress, leading to treatment discontinuation.[36] Due to the characteristics of the ODF, acceptance and satisfaction rates are very high, with over 80% of participants in both clinical trials and observational studies reporting positive outcomes, consistent with our findings.[26-28] In a study by Droupy and Colson, 84.2% of patients who used other PDE5is before were more satisfied with the ODF formulation than previous treatments.[26]

The sildenafil ODF developed by IBSA contains sucrose and lemon/grapefruit flavor as taste-masking agents which can mask the bitter taste of sildenafil citrate; however, the feeling of an unpleasant aftertaste immediately following oral dissolution persists as a frequent complaint among first-time users of the medication as the heathy volunteers involved in phase I studies. Nonetheless, the majority of patients are inclined to persist in utilizing and endorsing this product to others.[27,28] Furthermore, since water does not affect the rate or extent of sildenafil ODF absorption regardless of whether it is taken on an empty[24] or full stomach, patients may drink water after the film has dissolved if necessary (eg, to eliminate the bitter taste of sildenafil citrate from the mouth).

The effects of fluid on orodispersible products have been previously investigated only under fasting conditions.[23,24] In the case of sildenafil ODT, while bioequivalence to conventional FCT was evident when administered without water, the administration with water can slightly affect the C_{max} of plasma sildenafil.[23] On the other hand, a recent study on the

bioequivalence of sildenafil 50 mg ODF versus FCT showed that water does not impact the film absorption or other PKs compared with reference treatment.[24] Our findings showed that, also under fed conditions, the co-administration of water with ODF does not influence its bioavailability.

In the food-effect experiment, the standardized high-fat, high-calorie meal significantly influenced the PKs of sildenafil 100 mg ODF. Under the fed condition, the maximum observed plasma concentration of plasma sildenafil was reduced by ~45%, and T_{max} was delayed by 1.45 h compared to the fast condition. However, interestingly, the extent of sildenafil exposure was not affected by food with geometric LSmean ratios of $AUC_{0\text{-}T}$ and $AUC_{T\text{-}\infty}$ of plasma sildenafil included in the reference range for bioequivalence.

The effect of food on the absorption rate in our study was higher than that reported for sildenafil FCT, with a mean reduction in C_{max} of 29% and a delay in T_{max} of 1.1 h.[10] However, the food effect was less pronounced on IBSA ODF formulation than that observed for the ODT formulation, showing a mean reduction in C_{max} and AUC of 59% and 12%, respectively, a delay in median T_{max} of more than 3 h compared to administration under fasting conditions, recommending the use of ODT on an empty stomach.[23,37] Interestingly, like for conventional FCT[10] and differently for ODT,[23,37] no significant effect of food on the extent of sildenafil exposure was observed for IBSA ODF formulation.

Thus, for all available formulations of sildenafil—both the traditional ones designed to disintegrate in the stomach and the more innovative ones designed to disintegrate in the oral cavity—the fed state influences the drug's absorption parameters, potentially delaying the onset of action, and this aspect should be clearly communicated to patients.

The fact that there is an effect on the rate of absorption but not on the extent of absorption suggests that the primary mechanism is most likely related to delay gastric emptying in the presence of food.[38]

Despite the use of common mathematical models that consider gastric chyme as a homogeneous mix to explain drug absorption under fed conditions, deeper insights can be gained by using models that account for the stomach contents being divided into compartments with distinct physical characteristics. In particular, one proposed model considers stomach contents divided into two compartments: one along the greater curvature, richer in food and more viscous, which empties more slowly, and another, fluid-rich compartment along the lesser curvature that serves as a faster pathway for drug transport.[39] The differing dissolution rates between formulations may result in varying distributions of the active ingredient between these two gastric compartments, ultimately leading to differences in the relative concentration of the active pharmaceutical ingredient in different phases of the chyme. Danielak and colleagues employed a similar model to compare the effects of a high-fat meal on an FCT and an ODT. Their findings showed that the latter tends to mix to a greater extent with the more viscous, food-rich compartment, causing slower transfer to the small intestine and, ultimately, a reduced absorption rate.[40]

Due to the lack of evidence on the bioequivalence between ODF and FCT under fed conditions, in Study B, for the first time, we directly compared the PKs of sildenafil IBSA 100 mg ODF and FCT following a high-fat, high-calorie meal. The findings revealed ~13% and 17% reductions in C_{max} for ODF compared to the conventional FCT, without and with water, respectively. However, both products exhibited similar T_{max} under fed conditions. In terms of drug exposure, sildenafil ODF and FCT were found to be bioequivalent and using ODF with water even resulted in a higher AUC for plasma sildenafil compared to FCT. It is important to note that substantial inter-subject variability was observed across all PK analyses, highlighting the complex mechanisms of food effects at the individual level, thus suggesting including more subjects in the bioequivalence studies in fed condition for sildenafil formulations. Considering the slight reduction in the rate but not the extent of absorption under fed conditions, sildenafil ODF developed by IBSA is a valuable alternative to the conventional FCT also in fed conditions.

Conclusion

Sildenafil IBSA ODF is a bioequivalent alternative to conventional FCT under fasting conditions, offering the convenience of administration without water. While food slows the rate of absorption, it has no effect on the extent of drug exposure. Under fed conditions, the rate of absorption is slightly reduced compared to FCT, but other PK parameters remain unaffected. Moreover, ODF administration with or without water under fed conditions results in a similar PK profile.

Given its comparable PK and safety profiles, sildenafil IBSA ODF represents an effective and versatile option for managing ED, with the potential to improve patient adherence and satisfaction. In addition to the fact that food has a less significant effect on the IBSA ODF than other orodispersible formulations with a proven efficacy in real-life clinical settings without any restriction related to food intake,[26-29] and that all sildenafil formulations may take longer to start working if taken with a heavy meal, patients should be properly informed of the appropriate usage instructions prior to the sexual attempt, just like with other sildenafil formulations.[33,41]

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Author contributions

V.F.: Conception and Design. V.F.: Acquisition of Data. Q.M.P., D.Y.: Analysis and Interpretation of Data. Q.M.P., D.Y., A.S.: Drafting the Article. J.R-O., P.V., V.F., E.A.J.: Revising it for Intellectual Content. J.R-O., P.V., V.F., E.A.J.: Final Approval of the Completed Article.

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Conflicts of interest

E.A.J. is a paid consultant and/or speaker for several pharmaceutical companies, including Bayer, IBSA, Menarini, Otsuka, Pfizer, Recordati, Viatris.

V.F. is an employee of IBSA, sponsor, and funder of the studies described in the manuscript.

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