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Bioequivalence of Alprazolam Sublingual Tablet Formulation and Alprazolam Immediate Release Tablet in Healthy Volunteers

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Abstract

Alprazolam immediate release (IR) tablets are currently approved for the management of anxiety disorder or the short-term relief of symptoms of anxiety. A sublingual (SL) formulation of alprazolam, which disintegrates in the mouth without the need for additional fluids, has been developed. The aim of this study was to determine if the alprazolam SL 1 mg tablet was bioequivalent to the alprazolam IR 1 mg tablet in healthy volunteers.

In this randomized, open label, two-way crossover, single dose study, subjects were randomized to receive a single alprazolam 1 mg IR tablet during one dosing period and a single 1 mg SL tablet during the other dosing period. The primary pharmacokinetic endpoints were area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration $AUC_{(0-t)}$ and maximum plasma concentration (C_{max}). Adverse events (AEs) were monitored throughout the study. Bioequivalence was concluded if the 90% confidence intervals (CI) for the ratio of adjusted geometric means for both $AUC_{(0-t)}$ and C_{max} were wholly within 80%-125%.

Participants were mostly male (27/28 [96.4%]) and had a mean (standard deviation) age of 35.9 (8.2) years. For the alprazolam 1 mg SL tablet relative to the alprazolam 1 mg IR tablet, the ratio of adjusted geometric means (90% CI) for $AUC_{(0-t)}$ and C_{max} were 95.43% (91.74%, 99.27%) and 88.27% (83.68%, 93.11%), respectively. The incidence of AEs was similar during both treatment periods: 24 participants reported 39 AEs during the alprazolam 1 mg IR treatment period, and 23 participants reported 38 AEs during the alprazolam 1 mg SL treatment period.

Bioequivalence was demonstrated between the alprazolam IR and SL 1 mg tablets, suggesting that the clinical performance of the SL tablet will be similar to that of the IR tablet.

Keywords: Alprazolam; Anxiolytic; Sublingual; Bioequivalence

Introduction

The anxiolytic medication alprazolam, a 1,4 benzodiazepine compound, is indicated for the management of anxiety disorder or the short-term relief of symptoms of anxiety. Alprazolam is also indicated for the treatment of panic disorder, with or without agoraphobia [1].

Following oral administration of alprazolam immediate release (IR) tablets, alprazolam is readily absorbed, with peak concentrations in the plasma occurring between one and two hours following administration. Plasma levels are proportionate to the dose given: over the dose range of 0.5 to 3.0 mg, peak levels of 8.0 to 37 ng/mL were observed. The mean plasma elimination half-life ($t_{1/2}$) of alprazolam has been found to be about 11.2 hours (range of 6.3 to 26.9 hours) in healthy adults [2-4]. *In vitro*, approximately 80% of alprazolam is bound to human serum protein, primarily serum albumin.

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4, giving rise to two major pharmacologically inactive metabolites in the plasma: 4-hydroxyalprazolam and α-hydroxyalprazolam [3]. Pharmacokinetic (PK) studies of alprazolam under fasting [5] and fed [6] conditions following the administration of alprazolam IR 1 mg tablets showed no meaningful differences in the rate and extent of alprazolam absorption.

The alprazolam sublingual (SL) tablet was formulated to quickly disintegrate in the mouth when placed under the tongue and to provide a convenient and discreet pathway for administration without the need for administration with fluids. This additional pharmaceutical form would benefit not only those patients who have difficulty swallowing conventional solid oral pharmaceutical forms but also those who have a restriction on daily fluid intake.

Here, we report a study designed to determine if a new alprazolam SL 1 mg tablet formulation (Test formulation) was bioequivalent to an approved orally administered alprazolam IR 1 mg tablet (Reference formulation) in healthy volunteers.

Methods

Design

This was a randomized, open label, two-way crossover, single dose study conducted at a single site in the United States (clinicaltrials.gov: NCT01256151). The primary objective of the study was to determine if alprazolam SL 1 mg tablet formulation (Test formulation) was bioequivalent to an orally administered alprazolam IR 1 mg tablet (Reference formulation). Secondary objectives of the study were to evaluate the safety and tolerability of an alprazolam SL 1 mg tablet formulation and an approved alprazolam IR 1 mg tablet.

The study was conducted at a single site in the United States

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(Pfizer New Haven Clinical Research Unit, New Haven, CT, USA) in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. The final protocol, any amendments, and informed consent documentation were reviewed and approved by and in compliance with the institutional review board for the study site (Integ Review Ethical Review Board, Austin, Texas, USA).

Participants

Eligible participants were healthy males or females aged 18 to 55 years with a body mass index (BMI) of 17.5 to 30.5 kg/m^2 and a total body weight >50 kg (110 lbs). Participants were deemed healthy if there were no clinically-relevant abnormalities identified by a detailed medical history, full physical examination (including blood pressure and pulse rate measurement), 12-lead electrocardiogram, or clinical laboratory tests. Women of childbearing potential were included provided they were not pregnant or nursing and had agreed to use an acceptable method of non-hormonal contraception from at least 14 days prior to the first dose of study treatment. Participants were required to provide informed consent and be willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion criteria included any evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease; hypersensitivity to alprazolam and other benzodiazepine derivatives; treatment with an investigational drug within 30 days or five half-lives prior to the first dose of study treatment.

Screening assessments occurred within 28 days prior to the first dose of Period 1. Subjects were admitted to the Clinical Research Unit (CRU) at least 12 hours prior to Day 1 dosing. For each Period, subjects received study treatment on Day 1 and remained at the CRU until the morning of Day 4.

Study treatments

Participants received each study treatment according to a computer-generated randomization schedule. Subjects were randomized to receive a single dose of alprazolam 1 mg IR tablet (Reference formulation) during one dosing period and a single 1 mg SL tablet (Test formulation) during the other dosing period, with an interval of five days between the dosing periods (washout period). Following a 10-hour fast, subjects received study treatment at approximately 0800 hours during each dosing period. The alprazolam IR tablet was administered with 240 mL of ambient temperature water and participants were to swallow the tablet whole, without chewing prior to swallowing. The alprazolam SL formulation tablet was administered by placing the tablet under the tongue where it was to be held for at least two minutes and participants were then allowed to swallow as long as any remaining tablet was not swallowed. Participants were permitted to consume water as desired without restriction one hour after dosing. In order to standardize the conditions on PK sampling days, all subjects were asked to refrain from lying down, eating, and drinking beverages other than water during the first four hours after dosing.

Pharmacokinetics

During both study periods, blood samples (6 mL) were collected to provide a minimum of 2.5 mL of plasma in tubes containing sodium heparin. Blood samples were collected for each period at the following time points: pre-dose and at 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, 36, 48, and 72 hours post-dose. After sample collection, plasma was separated from whole blood by centrifugation at approximately 1700 x g for about 10 minutes at 4°C, and the separated plasma was stored in screw-capped polypropylene tubes at approximately -70°C within 1 hour of collection. Samples were stored frozen until analyses. In-process sample stability and frozen sample stability was confirmed.

Plasma samples were analyzed for alprazolam concentrations at PPD's Bioanalytical (Richmond, VA, USA) using a validated high-performance liquid chromatography tandem mass spectrometric (HPLC/MS/MS) method following liquid-liquid extraction. Alprazolam and internal standard (alprazolam-d_5) were separated using an YMC ODS-AQ column (2.0×50 mm, 5 µm particle size; Waters) and detected using an API-3000 (Applied Biosystems Sciex) with electrospray ionization. The mass spectrometer was operated in positive ion mode using a multiple reaction monitoring (MRM) scan. The following MRM transitions were monitored: *m/z* 309.1→281.0 for alprazolam and *m/z* 314.2→286.2 for the internal standard. The mobile phase used was methanol/water/0.79 M ammonium formate buffer (70:29:1, v:v:v). Calibration standard responses were linear over the range of 0.250 to 40.0 ng/mL using a weighted (1/concentration) linear regression. Those samples with concentrations above the upper limit of quantification were adequately diluted into calibration range. The lower limit of quantification (LLOQ) for alprazolam was 0.250 ng/mL. Samples with concentrations below the LLOQ were reported as below the limit of quantification (BLQ). The between-day assay accuracy (expressed as the percent relative error) of the quality control samples used during sample analysis ranged from -3.51% to 3.07% (excluding an outlier; -3.51% to 24.4% with outlier) and the between-day assay precision (expressed as the percent coefficient of variation) was 7.31% (excluding an outlier; 84.8% with outlier). Incurred sample reproducibility was tested on at least 10% of the study samples and results met the acceptance criteria, two-thirds of the samples had a percent difference, relative to the average of the original value and the re-assayed value, within ± 20%.

The primary PK endpoints were area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration $AUC_{(0-t)}$ and maximum plasma concentration (C_{max}). Secondary PK endpoints were area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}), time to maximum plasma concentration (T_{max}), and $t_{1/2}$.

Safety assessments

Adverse events (AEs) were monitored throughout the study. For AEs deemed by the Investigator to have a causal relationship to treatment, follow-up was required until resolution or stabilization occurred. AEs were encoded according to the *Medical Dictionary for Regulatory Activities* (MedDRA; Version 14.0) preferred term and system organ class.

Statistical analysis

Alprazolam 1 mg IR tablet was the Reference treatment while the new alprazolam 1 mg SL tablet was the Test treatment. $AUC_{(0-t)}$, AUC_{inf}, C_{max}, T_{max}, and $t_{1/2}$ were summarized descriptively by treatment. Natural log transformed AUC_{0-t}, AUC_{inf}, and C_{max} of alprazolam were analyzed using a mixed effect model with sequence, period, and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference)

and corresponding 90% confidence interval (CI) were obtained from the model. The adjusted mean differences and 90% CI for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Bioequivalence of the two treatments was concluded if the 90% CI for the ratio of adjusted geometric means for both $AUC_{(0-t)}$ and C_{max} fell wholly within (80%, 125%).

A sample size of 28 subjects was required to provide: a) 98% power that the 90% CI for the ratio of Test to Reference treatment for area under the plasma concentration versus time curve (AUC) would lie within the acceptance region of (80%, 125%); and, b) 93% power that the 90% CI for the ratio of Test to Reference treatment for C_{max} would lie within the acceptance region of (80%, 125%). Consequently, this study had at least 91% power overall to demonstrate bioequivalence of the Test treatment to the Reference treatment [i.e., equivalence in both AUC 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: a) the true ratio between Test and Reference treatments for both AUC and C_{max} was 0.9; and, b) within-subject standard deviations for $\log_e$ AUC and $\log_e C_{max}$ were 0.111 and 0.134, respectively, as obtained from the average of 10 previous Pfizer-sponsored studies (Pfizer data on file).

Results

Study population

Twenty eight (28) participants were assigned and received study treatment. All 28 subjects completed the study and were included in the pharmacokinetic and safety analyses. Participants were mostly male (27/28 [96.4%]) and had an overall mean (SD) age of 35.9 (8.2) years. Thirteen (13) participants were Black, nine were White, two were Asian, and for four participants race was not specified. Mean (SD) participant BMI was 26.4 (2.9) kg/m^2.

Pharmacokinetics

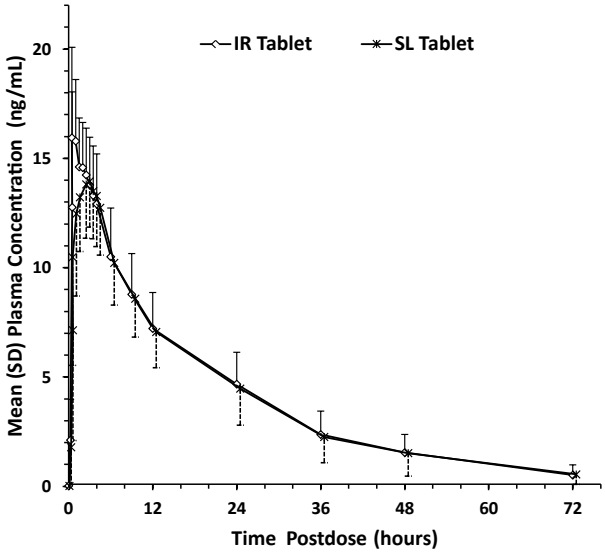
Median plasma alprazolam concentration-time profiles for both formulations are presented in Figure 1. This graph indicates that the concentration-time profiles are overlapping for both formulations. Bioequivalence criteria were met for the alprazolam 1 mg SL formulation relative to the alprazolam 1 mg IR formulation as the corresponding 90% CIs for the adjusted geometric mean AUC_{inf}, $AUC_{(0-t)}$, and C_{max} ratios were all contained within the 80% to 125% range. The ratio of adjusted geometric means (90% CI) of alprazolam AUC_{inf}, $AUC_{(0-t)}$, and C_{max} were 95.75% (91.96%, 99.69%), 95.43% (91.74%, 99.27%) and 88.27% (83.68%, 93.11%), respectively (Table 1), following administration of the alprazolam 1 mg SL formulation relative to alprazolam 1 mg IR formulation.

The median T_{max} for alprazolam IR tablet was shorter than the SL tablet with median T_{max} values of 0.892 and 2.00 hours, respectively. Apparent $t_{½}$ was similar for both formulations, with a mean value of approximately 15 hours.

Variability for AUC and C_{max}, based on percent coefficients of variation (%CV), was generally similar for both formulations (approximately 33% and 18%, respectively).

Adverse events

The incidence of AEs was similar across both treatments; 24 participants reported a total of 39 AEs during the alprazolam 1 mg IR treatment period and 23 participants reported a total of 38 AEs during the alprazolam 1 mg SL treatment period. The majority of AEs were considered related to study treatment by the Investigator (24 participants/37 AEs during the alprazolam 1 mg IR treatment and 23 participants/36 AEs during the alprazolam 1 mg SL treatment). The most frequently reported treatment emergent AEs were somnolence (alprazolam 1 mg IR, 39.2%; alprazolam 1 mg SL, 28.6%), fatigue (alprazolam 1 mg IR, 25.0%; alprazolam 1 mg SL, 32.1%), dizziness (alprazolam 1 mg IR, 21.4%; alprazolam 1 mg SL, 14.3%), and euphoric mood (alprazolam 1 mg IR, 7.1%; alprazolam 1 mg SL, 14.3%). There were no deaths, no serious AEs, and no permanent or temporary discontinuations due to AEs during the study. The majority of AEs were mild to moderate in intensity. One AE of severe intensity (fatigue) was reported across each treatment in the same subject and the Investigator considered both of these events related to study treatment.



Note: The time axis has been intentionally shifted to the right for SL tablet to avoid the two treatments being superimposible.
IR: immediate release; SL: sublingual.
Figure 1: Mean (SD) plasma alprazolam concentration-time profiles following single oral doses.

Discussion

Bioequivalence criteria were met for the alprazolam 1 mg SL formulation with respect to both C_{max} and AUC relative to the currently approved alprazolam 1 mg IR formulation. The median T_{max} for the alprazolam SL tablet (2.00 hours) was longer than that for the IR tablet (0.892 hours). The increased T_{max} is presumably due to administration of alprazolam SL tablet without water. The subjects were asked to place the alprazolam SL tablet under the tongue until it disintegrated and were then asked to swallow. As water was not permitted until one hour after administration of the alprazolam SL tablet, only the limited amount of gastrointestinal fluid was available for drug dissolution and further absorption. In contrast, the conventional alprazolam IR tablet was administered with 240 mL of water which aided in drug dissolution and resulted in faster absorption compared to the SL tablet. A similar trend was also noted by Scavone et al. [6] with another SL formulation of alprazolam where T_{max} for the SL tablet was delayed compared to that of the oral tablet. Furthermore, it should be noted that the sustained release formulation of alprazolam (Xanax XR) results in T_{max} values

Parameter (Units)	Alprazolam 1 mg SL (Test Treatment) N=28	Alprazolam 1 mg IR (Reference Treatment) N=28
AUC_{inf} (ng*hour/mL)		
Geometric Mean (%CV)	274.1 (38)	286.3 (31)
Ratio of Adjusted Means (90% CI)	95.75 (91.96, 99.69)	
Arithmetic Mean (SD)	289.7 (110.6)	299.1 (92.6)
$AUC_{(0-t)}$ (ng*hour/mL)		
Geometric Mean (%CV)	259.5 (33)	271.9 (29)
Ratio of Adjusted Means (90% CI)	95.43 (91.74, 99.27)	
Arithmetic Mean (SD)	271.1 (88.1)	282.9 (81.3)
C_{max} (ng/mL)		
Geometric Mean (%CV)	15.2 (18)	17.2 (19)
Ratio of Adjusted Means (90% CI)	88.27 (83.68, 93.11)	
Arithmetic Mean (SD)	15.4 (2.8)	17.5 (3.4)
T_{max} (hour)		
Median (range)	2.00 (0.500-3.50)	0.892 (0.500-2.50)
$t_{1/2}$ (hour)		
Arithmetic mean (SD)	15.3 (4.6)	15.2 (3.5)
%CV: Percent Coefficients of Variation; IR: Immediate Release; SL: Sublingual; CI: Confidence Interval		

Table 1: Summary of pharmacokinetic parameters of plasma alprazolam following single oral doses.

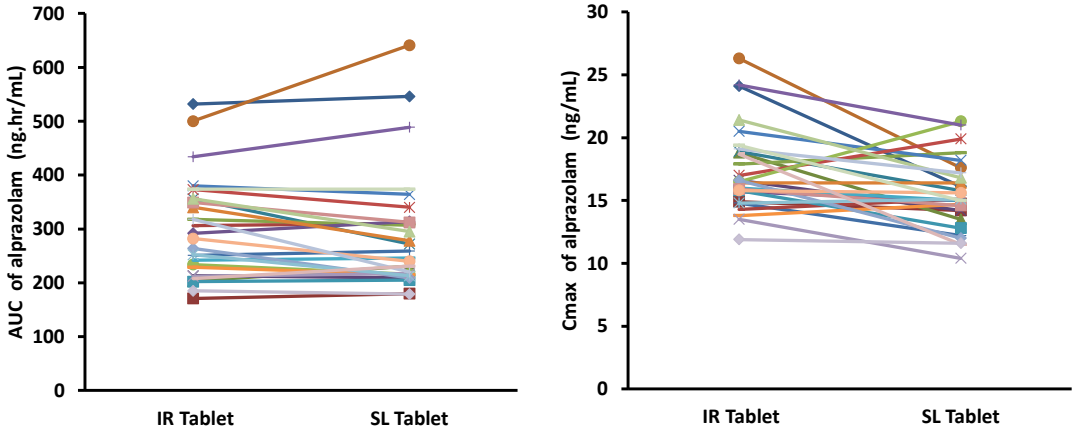


Figure 2: C_{max} (top panel) and AUC (bottom panel) values by treatment.

occurring approximately six to eight hours post-dose [7]. Overall, the slight delay in T_{max} with the SL tablet is not clinically relevant.

Alprazolam is rapidly absorbed following oral administration of the IR tablets; peak concentrations in plasma generally occur one to two hours after dosing. The average absolute oral bioavailability of alprazolam is approximately 92% [1]. Considering these pharmacokinetic properties of alprazolam, the SL formulation was not designed to provide a faster absorption rate and/or faster onset of action or to enhance the bioavailability by circumventing first pass metabolism, but to make drug administration more convenient. Alprazolam SL tablets are intended to be administered by placing under the tongue without the need for water. The SL tablets will disintegrate completely when held under the tongue for a sufficient period of time. However, to allow for sufficient time for complete disintegration to occur, subjects in this study were asked to hold the SL tablet under the tongue for up to two minutes. Importantly, subjects were asked not to swallow the whole tablet but to allow it to be completely disintegrated under the tongue before swallowing, thus allowing for convenient drug administration without the need for water.

This study was designed to demonstrate bioequivalence of alprazolam SL tablet versus the commercial IR tablets; it was not designed to assess the amount of drug that is absorbed from the oral cavity versus that absorbed from the gastrointestinal tract. However, the data collected does provide some insight into the manner in which alprazolam may be absorbed. The study demonstrates that alprazolam SL tablets are bioequivalent to the IR tablets with respect to both C_{max}

and AUC values. The slightly delayed T_{max} for the SL tablet is likely due to the fact that it was administered without water versus the IR tablet which was taken with water. Buccal absorption is typically characterized by a faster increase in plasma concentration compared to absorption via the gastrointestinal tract which can then be reflected in the T_{max} values. The T_{max} values for the SL and IR tablets suggest that while some SL absorption cannot be ruled out, clinically meaningful absorption of alprazolam would not occur in the oral cavity following administration of the SL tablet. In other words, a majority of the drug appears to be absorbed following ingestion of the disintegrated SL tablet. Although administered without water, saliva in the mouth helps in disintegration of the SL tablet, and gastric fluids aid in dissolution and eventual absorption of the drug. Since the drug is intended for systemic effect, and considering SL tablets are bioequivalent to the IR tablets, the site of drug absorption does not have a clinically meaningful impact on systemic drug exposure (Figure 2).

In addition to the alprazolam SL 1 mg tablet, a 0.5 mg orally disintegrating tablet is also under development. It should be noted that the PK of alprazolam are linear over this dose range. The 1 and 0.5 mg SL tablets are manufactured from proportional blend using similar equipment and methods. Furthermore, the *in-vitro* dissolution profile between the 0.5 and 1 mg SL tablets has been demonstrated to be similar. Considering this, the bioequivalence results from the alprazolam SL 1 mg tablet can be extrapolated to the 0.5 mg strength tablet.

In summary, the alprazolam 1 mg SL tablets were well tolerated in healthy male and female subjects and had a similar safety profile to the alprazolam 1 mg IR tablets. Bioequivalence was demonstrated between the currently approved alprazolam IR tablets and the SL tablets, which suggests that the clinical performance of the SL tablet will be similar to that of the IR tablet.

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