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RESEARCH**

APPLICATION NUMBER:

218527Orig1s000

CLINICAL PHARMACOLOGY
REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 218527	Submission Date(s): 08/30/2023
Proposed Brand Name	(b) (4)
Generic Name	Tadalafil
Clinical Pharmacology Reviewer	Mohammad (Ahsan) Akbar, PhD
Clinical Pharmacology Secondary Reviewer	Yanhui Lu, PhD
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology (DCEP)
OND Division	Division of Urology, Obstetrics and Gynecology (DUOG)
Sponsor	B Better, LLC
Submission Type	Original-1
Formulation; Strength(s)	Chewable tablet, 5 mg, 10 mg, and 20 mg
Indication	For the treatment of • Erectile dysfunction (ED) • The signs and symptoms of benign prostatic hyperplasia (BPH) • ED and the signs and symptoms of BPH (ED/BPH)

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1. EXECUTIVE SUMMARY

B Better LLC, referred to in this review as the applicant, has developed tadalafil chewable tablets in strengths of 5 mg, 10 mg, and 20 mg. The applicant submitted this NDA via the 505(b)(2) regulatory pathway and proposed to rely on the FDA's previous findings of safety and efficacy for Cialis® (tadalafil) tablets, an FDA-approved drug indicated for the treatment of erectile dysfunction (ED), signs and symptoms of benign prostatic hyperplasia (BPH), and ED and the signs and symptoms of BPH. The approved strengths of Cialis (the listed drug) are 2.5 mg, 5 mg, 10 mg, and 20 mg.

This NDA includes a pivotal relative bioavailability (BA)/bioequivalence (BE) study (TADA-22-051) and a pilot study (TADA-22-008) comparing the proposed drug and the listed drug Cialis® at the highest dose of 20 mg to establish a scientific bridge to the listed drug. The pivotal study also assessed food effect on the pharmacokinetics (PK) of the proposed tadalafil chewable tablet at 20 mg. Additionally, the applicant conducted a study (TADA-23-023) to assess the impact of water on the BA of the tadalafil chewable tablet, 20 mg.

The applicant submitted a biowaiver request for the lower strengths of the proposed product, 5 mg and 10 mg. We defer to the Biopharmaceutics Review Team for the acceptability of the biowaiver request.

1.1. RECOMMENDATIONS

The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology (DCEP) has reviewed the clinical pharmacology information submitted for NDA 218527 (tadalafil chewable tablets 5, 10 and 20 mg). We find that the current application is acceptable for approval from the clinical pharmacology standpoints.

1.2. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The key clinical pharmacology review assessments are summarized in **Table 1**.

Table 1. The key clinical pharmacology review issue and assessments

Review issues	Key assessments
Pharmacokinetics (PK) bioavailability (BA)/bioequivalence (BE)	The applicant conducted a randomized, single-dose, open-label, two-treatment, three-sequence, three-period, crossover pivotal relative BA/BE study (Study TADA-22-051) in healthy adult male subjects to assess BE between the proposed product, tadalafil chewable tablets 20 mg, and the reference product, Cialis® tablets 20 mg, under fasting condition. The proposed product was chewed and swallowed with water while the reference product was swallowed whole with water. The proposed product (test) was bioequivalent (BE) to the

	reference product. The test-to-reference geometric mean ratios (GMRs) (90% confidence interval) for C_{max} [97.04% (91.93% – 102.44%)] and $AUC_{0-\infty}$ [96.84% (91.32% – 102.69%)] of tadalafil were all within the acceptance BE range of 80% to 125%.
Food effect assessment	In the pivotal BA/BE Study TADA-22-051, the applicant assessed the effect of food on the BA of the proposed product. A high-fat, high-calorie meal was served 30 minutes prior to dosing for the fed condition. The GMRs (90% CIs) of fed to fasted conditions for C_{max} [87.19% (80.01% – 95.02%)] and $AUC_{0-\infty}$ [111.63% (105.97% – 117.59%)] of tadalafil were all within the accept BE range of 80% to 125%. These results indicate that food intake does not have clinically meaningful impact on the PK of the proposed product.
Water impact assessment	The applicant conducted a dedicated randomized, single-dose, open-label, one-treatment, two-sequence, two-period, crossover study, TADA-23-023, to assess the PK of the proposed product, tadalafil chewable tablets 20 mg, when administered without the aid of water (treatment A) compared with that when administered with the aid of water (treatment B) in healthy male subjects, each under fasting conditions. The treatment A-to-treatment B GMRs (90% CIs) for C_{max} [95.13% (88.9% – 101.81%)] and $AUC_{0-\infty}$ [98.63% (91.81% – 105.96%)] of tadalafil were all within the acceptable BE range of 80% to 125%. These results indicate that water intake during drug administration does not have a clinically meaningful impact on the PK of the proposed product.

2. QUESTION BASED REVIEW

2.1. GENERAL ATTRIBUTES

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of tadalafil chewable tablets formulation?

The applicant initially developed a formulation and conducted a randomized, single-dose, open-label, two-treatment, three-sequence, three-period, crossover study (TADA-21-079) in 18 healthy male subjects to evaluate: (i) the relative BA/BE of the earlier formulation containing 20 mg tadalafil compared to 20 mg Cialis® tablets (reference) in a fasted state; and (ii) the impact of food on the BA of the earlier formulation. The

study found that the earlier formulation was not BE to the listed drug in the fasted state and that the formulation was affected by food intake.

Subsequently, the applicant reformulated to the proposed product and conducted a pilot study (Study TADA-22-08), which was a randomized, single-dose, open-label, two-treatment, two-sequence, two-period, two-way crossover study in a fasted state in 14 healthy male subjects. This study demonstrated BE between the test and reference products under fasted conditions.

Following that, the applicant conducted two studies (TADA-22-051 and TADA-23-023) which are considered as the key studies supporting this NDA.

TADA-22-051 was a pivotal randomized, single-dose, open-label, two-treatment, three-sequence, three-period, crossover study conducted in 42 healthy male subjects to determine: (i) the bioequivalence of the tadalafil chewable tablets to Cialis® tablets at 20 mg in the fasted state; and (ii) the food effect on the bioavailability of the tadalafil chewable tablets.

TADA-23-023 was a randomized, single-dose, open-label, one-treatment, two-sequence, two-period, crossover study conducted in 24 healthy male subjects under fasting conditions to evaluate the oral BA of 20 mg tadalafil chewable tablets administered with and without the aid of water.

2.2. GENERAL CLINICAL PHARMACOLOGY

2.2.1 Is the tadalafil chewable tablets 20 mg formulation appropriately bridged to the Cialis® tablets 20 mg according to the pivotal clinical pharmacology Study TADA-22-051 data?

Results from Study TADA-22-051 support an adequate bridge between the proposed product, tadalafil chewable tablets 20 mg, and the listed drug, Cialis® tablets 20 mg. A single dose of the proposed product resulted in similar systemic exposure to the listed drug in healthy adult male subjects under fasting conditions at the highest proposed therapeutic dose of 20 mg.

In this study, subjects were randomized to the following treatments as shown in **Table 2**.

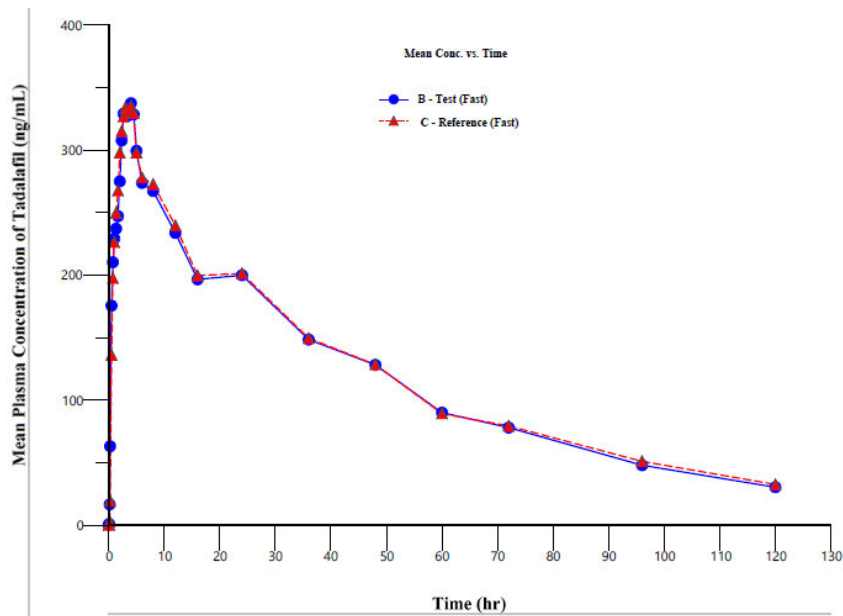
Table 2. Treatments administered in the pivotal Study TADA-22-051.

Treatment A (test fed)	Tadalafil chewable tablets 20 mg chewed and swallowed with water, 30 minutes after the start of a high-fat-high-calorie meal.
Treatment B (test fasted)	Tadalafil chewable tablets 20 mg chewed and swallowed with water under overnight fasting condition of at least 10 hours.

Treatment C (reference fasted)	Cialis® tablets 20 mg swallowed whole with water under overnight fasting condition of at least 10 hours.

The plasma concentration versus time profiles of tadalafil following the administration of treatments B and C (treatments for BE determination) are displayed in **Figure 1**, and descriptive statistics for PK parameters are shown in **Table 3**.

Figure 1. Mean tadalafil plasma concentration versus time profile following administration of Treatment B (test, fasted), and Treatment C (reference, fasted) in linear scale.



Source: The applicant's submitted clinical summary, figure 8.

Table 3. Descriptive statistics for pharmacokinetic parameters

Parameters (Units)	Tadalafil (Mean ± SD)		
	Treatment (A) (Test Fed)	Treatment (B) (Test Fasted)	Treatment (C) (Reference Fasted)
C _{max} (ng/mL)	313.011 ± 64.4890	368.714 ± 101.5119	377.540 ± 87.8398
AUC _{0-t} (ng*hr/mL)	15328.463 ± 4122.5815	14077.480 ± 4485.0696	14272.512 ± 4134.0367
AUC _{0-∞} (ng*hr/mL)	17497.082 ± 5529.0061	16153.046 ± 5953.4773	16537.536 ± 5943.9809
T _{max} (hr) [#]	5.00 (4.00 – 24.07)	2.67 (0.50 – 4.50)	2.67 (0.75 – 4.50)
T _{lag} (hr) [#]	0.17 (0.00 – 0.75)	0.17 (0.00 – 0.27)	0.25 (0.00 – 1.33)
t _{1/2} (hr)	34.049 ± 12.4359	34.739 ± 14.7915	36.125 ± 14.5542
K _{el} (1/hr)	0.0231 ± 0.00889	0.0232 ± 0.00936	0.0223 ± 0.00878
AUC _{Extrap_obs} (%)	10.79 ± 7.24	10.97 ± 7.64	11.51 ± 8.21

[#] T_{max} and T_{lag} are presented as median (minimum and maximum)

Source: The applicant's report for supplemental PK analysis, table 1

Relative bioavailability/bioequivalence determination

The applicant assessed treatment B (test fasted) and treatment C (reference fasted) for BE testing. The PK results showed that the test fasted-to-reference fasted GMRs and corresponding 90% CIs for C_{max} and AUC_{0-∞} of tadalafil were all within the acceptable BE range of 80% to 125% (**Table 4**).

Table 4. Summary of relative BA/BE results for test fasted vs reference fasted in Study TADA-22-051

Parameter (units)	Geometric Mean		Power (%)	ISCV (%)
	Test fasted	Reference fasted		
C _{max} (ng/mL)	356.01	366.85	100.0	14.22
AUC _{0-t} (ng*hr/mL)	13321.89	13666.19	100	14.15
AUC _{0-∞} (ng*hr/mL)	15022.79	15513.51	99.99	15.43
Parameters (units)	Ratio (%)	90% CI (Test fasted vs reference fasted)	BE Criteria	Outcome
	Test fasted/Reference fasted			
C _{max} (ng/mL)	97.04	91.93% to 102.44%	80% - 125%	BE
AUC _{0-t} (ng*hr/mL)	97.48	92.37% to 102.84%	80% - 125%	
AUC _{0-∞} (ng*hr/mL)	96.84	91.32% to 102.69%	80% - 125%	

ISCV: Intra-subject Coefficient of Variation

Source: The applicant's report for supplemental PK analysis, table 2

A total of 42 subjects were enrolled in this study. Of these, 39 successfully completed both the test fasted and reference fasted conditions. Three subjects, identified as Subject IDs (b) (6), failed to complete either period 2 or period 3. Consequently, 39 subjects were included in the PK and statistical analyses for BE testing. It is noteworthy that none of the exclusions from the PK and statistical analyses were due to atypical PK data (outliers).

The applicant reported protocol deviations related to blood sample collection for PK analysis. A total of eight deviations were noted in certain subjects' sampling time points during the study, and all deviations were considered minor. These minor deviations in the timing of blood sample collection were judged to have no impact on the PK analysis results, and the actual time of collection was used for the calculation of PK parameters.

The applicant reported that the tadalafil chewable tablets were well-tolerated for all treatments. For safety evaluations, please refer to the clinical review.

In the study, all the samples were analyzed with a validated bioanalytical method (refer to Section 2.3. Analytical Section) with acceptable accuracy and precision.

Considering the above findings, the proposed drug tadalafil chewable tablets 20 mg and the listed drug, Cialis® tablets 20 mg, are bioequivalent. Therefore, the applicant has established an adequate scientific bridge for reliance on the Agency's previous findings of safety and efficacy for Cialis®.

Reviewer's comments:

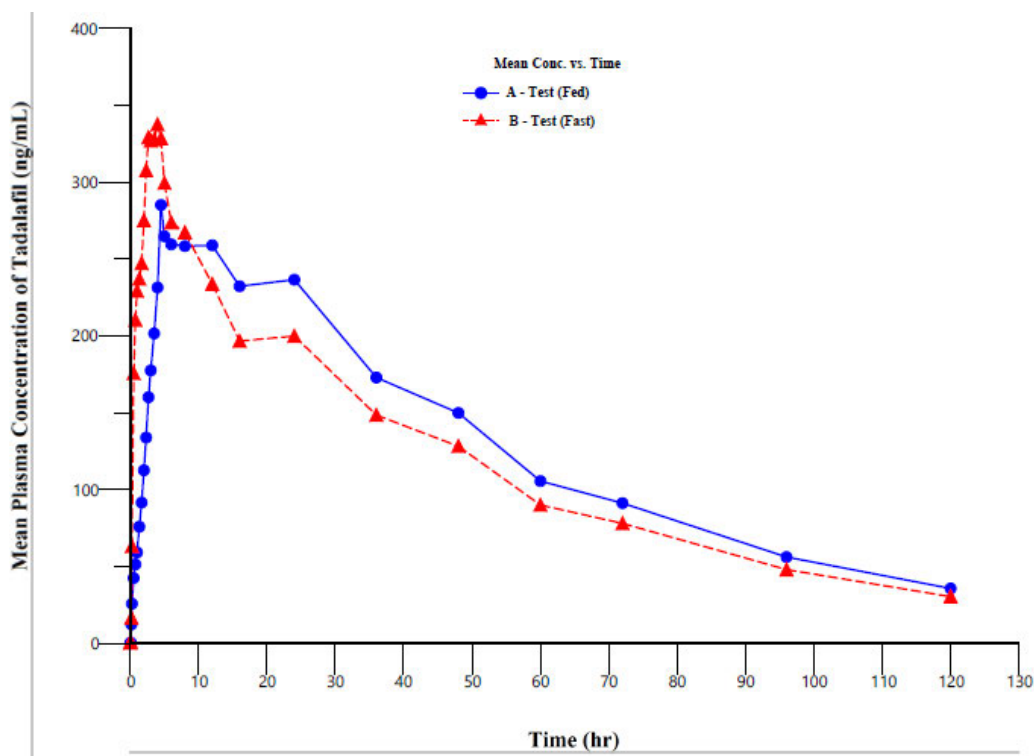
In the study described above (TADA-22-051), the mean half-life ($t_{1/2}$) of tadalafil following administration of the proposed product and Cialis® (the listed drug) under fasting conditions was estimated to be approximately 35 hours and 36 hours, respectively (Table 3). These values are longer than the half-life of 17.5 hours presented in the approved labeling of Cialis®. The difference may be attributed to factors such as differences in the bioanalytical assay used for tadalafil concentration measurement, PK sampling timepoints used for half-life estimation, and/or study design (e.g., the characteristics of study subjects). Such a difference in half-life values based on a cross-study comparison is not considered clinically meaningful considering that the BE criteria for AUC and C_{max} were met and the half-life values of tadalafil were similar between the proposed product and Cialis® (the listed drug) in the same study.

2.2.2 Does food affect the pharmacokinetics of the proposed product, tadalafil chewable tablets?

In the pivotal BA/BE Study TADA-22-051, the applicant assessed the effect of food on the BA of tadalafil chewable tablets 20 mg by comparing treatment A (test fed) vs treatment B (test fasted). Plasma concentration-time data from 37 subjects who completed both the test fed and test fasted conditions were included in the PK and statistical analysis for food effect evaluation.

The plasma concentration versus time profiles of tadalafil following the two treatments are displayed in **Figure 2**. The descriptive statistics for PK parameters of these two treatments are shown in **Table 3** above.

Figure 2. Mean tadalafil plasma concentration versus time profile following administration of Treatment A (test, fed), and Treatment B (test, fasted) in linear scale.



Source: The applicant's submitted clinical summary, figure 9

The PK results showed that the test fed-to-test fasted GMRs and corresponding 90% CIs for C_{max} and AUC_{0-∞} of tadalafil were all within no effect range of 80% to 125% (Table 5).

Table 5. Summary of relative BA results for test fed vs test fasted in Study TADA-22-051

Parameter (units)	Geometric Mean		Power (%)	ISCV (%)
	Test fed	Test fasted		
C _{max} (ng/mL)	306.75	351.82	98.42	22.06
AUC _{0-t} (ng*hr/mL)	14751.66	13205.97	100.0	13.73
AUC _{0-∞} (ng*hr/mL)	16588.15	14860.18	100.0	13.25
Parameters (units)	Ratio (%)		BE Criteria	Outcome
	Test fed/test fasted	90% CI (Test fed vs test fasted)		
C _{max} (ng/mL)	87.19	80.01% to 95.02%	80% - 125%	BE
AUC _{0-t} (ng*hr/mL)	111.70	105.84% to 117.89%	80% - 125%	
AUC _{0-∞} (ng*hr/mL)	111.63	105.97% to 117.59%	80% - 125%	

ISCV: Intra-subject Coefficient of Variation

Source: The applicant's report for supplemental PK analysis, table 3

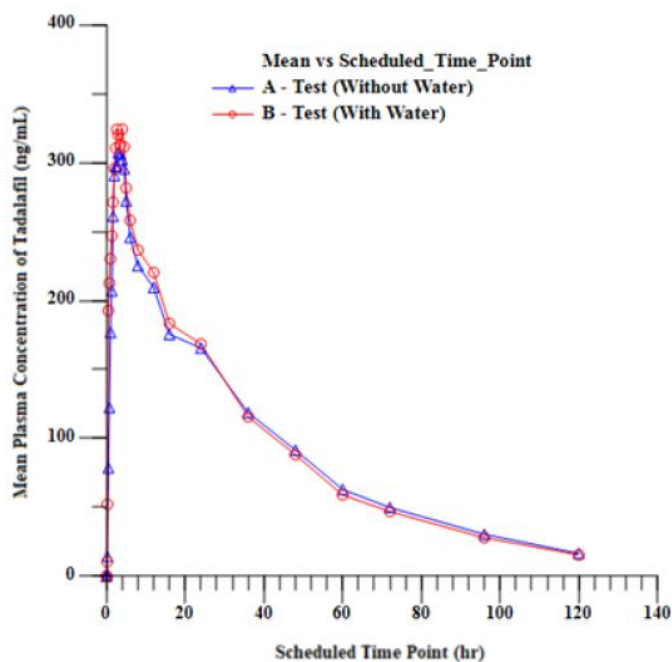
The results showed that the ingestion of a high-fat high-caloric meal 30 minutes before the administration of tadalafil chewable tablets 20 mg had no clinically meaningful effect on the BA of tadalafil exposure. Therefore, the applicant's proposal of administering the proposed product with or without food is acceptable.

2.2.3 Does water intake affect the pharmacokinetics of the proposed product, tadalafil chewable tablets?

The applicant conducted a dedicated study (TADA-23-023) to evaluate the effect of water intake on the PK of tadalafil chewable tablets. The study assessed the relative oral bioavailability of the proposed product, tadalafil chewable tablets 20 mg, administered without water (Treatment A) compared with the same dosage of the tablets administered with water (Treatment B) in healthy adult male subjects following an overnight fast of at least 10 hours prior to dosing.

The plasma concentration versus time profiles of tadalafil following administration of Treatments A and B, are displayed in **Figure 3**, and the descriptive statistics for PK parameters are shown in **Table 6**.

Figure 3. Mean tadalafil plasma concentration versus time profile following administration of Treatment A and B in linear scale.



Source: The applicant's clinical study report for Study TADA-23-023, figure 3.

Table 6. Descriptive statistics for pharmacokinetic parameters

Parameters (Units)	Tadalafil (Mean ± SD)	
	Treatment A (N=21)	Treatment B (N=21)
C _{max} (ng/mL)	330.222 ± 75.7878	347.260 ± 71.9933
AUC _{0-t} (hr*ng/mL)	10916.854 ± 3367.8937	11030.931 ± 2903.8310
AUC _{0-∞} (hr*ng/mL)	12127.330 ± 4360.1408	12236.253 ± 4029.6379
T _{max} (hr) #	2.70 (1.00 – 4.50)	2.67 (0.50 – 4.53)
t _½ (hr)	29.397 ± 14.3702	29.232 ± 15.8176
t _{lag} (hr)	0.25 (0.11 – 0.75)	0.17 (0.08 ± 0.25)
K _{e1} (1/hr)	0.0284 ± 0.01199	0.0288 ± 0.01183
AUC _{%Extrap_obs} (%)	8.47 ± 6.40	8.13 ± 7.93

(#) T_{max} and T_{lag} are presented as median (minimum and maximum)

Source: The applicant's report for supplemental PK analysis, table 4

The results (see the **Table 7**) showed that treatment A-to-treatment B GMR and corresponding 90% CI for C_{max} and AUC_{0-∞} of tadalafil were all within the acceptable BE range of 80.00% to 125.00%.

Table 7. Summary of relative BA results for Treatment A (fasted; without water) vs Treatment B (fasted; with water) in Study TADA-23-023

Parameters (Units)	Geometric Mean (N=21)		Power (%)	ISCV (%)
	Test (Treatment A)	Test (Treatment B)		
C _{max} (ng/mL)	322.9502	339.4779	99.84%	12.74%
AUC _{0-t} (hr*ng/mL)	10477.926	10647.328	99.85%	12.69%
AUC _{0-∞} (ng*hr/mL) [§]	11495.440	11655.356	99.70%	13.48%
Parameters	Ratio (%)	90% CI (A vs. B)	BE Criteria	Outcome
	A/B			
C _{max}	95.13%	88.9% to 101.81%	80.00% - 125.00%	BE
AUC _{0-t}	98.41%	91.98% to 105.28%	80.00% - 125.00%	
AUC _{0-∞} [§]	98.63%	91.81% to 105.96%	80.00% - 125.00%	

[§]AUC_{0-∞} data was not included in the original NDA. It was computed at FDA request (Filing Review, November 7, 2023). Treatment A = Tadalafil Chewable 20 mg Tablets (Test, Fasted, Without Water); Treatment B = Tadalafil Chewable 20 mg Tablets (Test, Fasted, With Water)

ISCV: Intra-subject Coefficient of Variation

Source: The applicant's report for supplemental PK analysis, table 5

A total of 24 subjects were enrolled in this study. Of these, 21 completed both study periods. Three subjects, identified as Subject IDs [REDACTED] (b) (6), failed to complete either period 1 or period 2. Consequently, 21 subjects were included in the PK and statistical analyses. None of the exclusions from the PK and statistical analyses were due to atypical PK data (outliers).

The applicant reported protocol deviations related to blood sample collection for PK analysis. A total of 13 deviations were noted in 11 subjects' (subject ID: [REDACTED] (b) (6) [REDACTED] (b) (6)) sampling time points during the study. These deviations in the timing of blood sample collection were judged to have no impact on the study outcome.

The applicant reported that the tadalafil chewable tablets were well-tolerated for all treatment periods. For safety evaluations, please refer to the clinical review.

In the study, all the samples were analyzed with a validated bioanalytical method (refer to Section 2.3. Analytical Section) with acceptable accuracy and precision.

Based on the results of this study, the clinical pharmacology review team agrees with the applicant's proposal that the proposed product can be taken with or without water. For further details, refer to Section 3 for labeling recommendations.

2.3. ANALYTICAL SECTION

Analytical method validation:

The concentrations of tadalafil in human plasma samples from clinical Studies TADA-22-051 and TADA-23-023 were determined using a validated ultra performance liquid chromatography tandem-mass spectrometry (UPLC-MS/MS) detection method TD-AM (Rev.01 and Rev.02). A summary of the validation results is shown in **Table 8**. The study results met the analytical method acceptance criteria according to "Guidance for Industry: Bioanalytical Method Validation, May 2018".

Table 8. Summary of validation results for the bioanalytical method used to measure human plasma tadalafil concentrations#.

Information Requested	Parameter
Analyte	Tadalafil
Internal standard (IS)	Tadalafil D3
Method description	LC/MS.MS
Limit of quantitation	10.005 ng/mL
Average recovery of drug (%)	95.2367

Average recovery of IS (%)	97.2900
Standard curve concentrations (ng/mL)	10.005 to 1202.288
QC concentrations (ng/mL)	LLOQQC: 10.017 LQC: 29.548 MQC1:78.171 MQC: 390.853 HQC: 880.299
QC Intra-run precision range (% CV)	LLOQQC: 2.23 to 3.29 LQC:1.91 to 3.39 MQC1: 0.72 to 1.89 MQC: 0.72 to 3.07 HQC: 0.43 to 1.49
QC Intra-run accuracy range (% Deviation)	LLOQQC: -0.04 to 3.57 LQC: -2.06 to 0.47 MQC1: -2.83 to -0.57 MQC: -2.70 to 1.34 HQC: -0.56 to -0.03
QC Inter-run precision range (% CV)	1.02 to 3.09
QC Inter-run accuracy range (% Deviation)	-1.58 to 1.42
Bench-top stability (hr)	24.0 hours @ room temperature.
Processed stability (hr)	27.0 hours @ room temperature 57.5 hours @ autosampler/ refrigerated conditions (5 ± 5°C)
Freeze-thaw stability of (cycles)	5 cycles
Long-term freezer storage stability (days)	126 days @ -20°C set point freezer 126 days @ -70°C set point freezer
Master stock stability (room temperature) STSS (hr)	7.0 hours @ room temperature for Tadalafil 14.5 hours @ room temperature for Tadalafil D3
Master stock stability (refrigerated) LTSS (days)	07 days @ refrigerated conditions (2 to 8°C) for Tadalafil 07 days @ refrigerated conditions (2 to 8°C) for Tadalafil D3
Selectivity	Known metabolites, endogenous plasma Components, Concomitant medication do not significantly interfere with the analytical assay and precision and accuracy for LLOQ, Accuracy of LLOQ (% Deviation): -0.56; Precision of LLOQ (% CV): 3.54

Validation SOP: (b) (4) (TADA-22-051 & TADA-23-023).

Source: Applicant's clinical summary report, table 28, cross reference to applicant's method validation report (b) (4).

Analytical method performance:

Study TADA-22-051

The performance results of the bioanalytical method for tadalafil concentration measurement for Study TADA-22-051 are summarized in **Table 9** and **Table 10**.

Table 9. Summary of plasma assay performance for calibration standard in Study TADA-22-051

Parameter	Standard Curve Samples								
	01	02	03	04	05	06	07	08	09
Concentration (ng/mL)	10.006	20.012	60.223	120.445	240.891	481.782	721.230	961.640	1202.050
Inter-run precision (%CV)	0.94	1.75	1.33	1.75	2.16	1.62	1.70	1.34	2.30
Inter-run accuracy (% Actual)	99.99	99.71	100.81	100.52	99.51	100.97	99.76	99.71	99.04
Linearity	0.995606 to 0.9999969								
Linearity range (ng/mL)	10.006 to 1202.50								
Sensitivity/LLOQ (ng/mL)	10.006								

Source: Applicant's bioanalytic report for Study TADA-22-051 (report number: TADA-22-051, version number 01), table 4.

Table 10. Summary of plasma assay performance for quality controls in Study TADA-22-051

BA/BE Study TADA-22-051 (Analyte: Tadalafil)				
Parameter	Quality Control Samples			
	LQC	MQC 1	MQC	HQC
QC ID				
Concentration (ng/mL)	29.543	78.156	390.781	880.137
Inter run Precision (%CV)	7.42	2.25	2.38	6.55
Inter run Accuracy (%Actual)	99.44	99.04	98.52	98.64

LQC: Low Quality Control; MQC1: Mid-low Quality Control; MQC: Mid Quality Control; HQC: High Quality Control

Source: Applicant's clinical summary report, table 32, cross reference to applicant's bioanalytic report for Study TADA-22-051 (report number: TADA-22-051, version number 01), table 5.

In Study TADA-22-051, a total of 220 valid incurred samples (6.72%) were selected from the total number of samples analyzed (3,274 samples). All the samples were considered for the Incurred Sample Reanalysis (ISR) calculation, and 216 samples (i.e., 98.18%) met the ISR criteria which is acceptable.

The long-term stability of the samples, maintained at -20°C (± 15°C) in plasma, was validated at 126 days (see Table 7). The time span from the first sample collection to the last sample analysis was 40 days, which falls within the validated long-term stability period of 126 days.

Study TADA-23-023

The performance results of the bioanalytical method for tadalafil concentration measurement for Study TADA-23-023 are summarized in **Table 11** and **Table 12**.

Table 11. Summary of plasma assay performance for calibration standards in Study TADA-23-023

BA/BE Study TADA-23-023 (Analyte: Tadalafil)									
Parameter	Standard Curve Samples								
Standard ID	01	02	03	04	05	06	07	08	09
Concentration (ng/mL)	10.006	20.012	60.223	120.445	240.891	481.782	721.230	961.640	1202.050
Inter-run Precision (%CV)	1.28	2.38	2.02	1.43	1.80	2.17	2.16	1.55	4.38
Inter-run Accuracy (%Actual)	100.36	98.68	101.97	99.87	99.23	101.59	99.45	100.33	98.55
Linearity	0.994799 to 0.999870								
Linearity Range (ng/mL)	10.006 to 1202.050								
Sensitivity/LLOQ (ng/mL)	10.006								

Source: Applicant's clinical summary report, table 33, cross reference to applicant's bioanalytic report for Study TADA-23-023 (report number: TADA-23-023, version number 01), table 4.

Table 12. Summary of plasma assay performance in Study TADA-23-023

BA/BE Study TADA-23-023 (Analyte: Tadalafil)				
Parameter	Quality Control Samples			
	LQC	MQC 1	MQC	HQC
QC ID				
Concentration (ng/mL)	29.543	78.156	390.781	880.137
Inter run Precision (%CV)	3.03	2.12	2.31	2.30
Inter run Accuracy (%Actual)	99.30	100.44	99.54	99.27

LOC: Low Quality Control; MQC1: Mid-low Quality Control; MQC: Mid Quality Control; HQC: High Quality Control

Source: Applicant's clinical summary report, table 34, cross reference to applicant's bioanalytic report for Study TADA-23-023 (report number: TADA-23-023, version number 01), table 5.

In Study TADA-23-023, a total of 112 valid incurred samples were selected (9.41%) from the total number of samples analyzed (1190 samples). All the samples were considered for ISR calculation and all the samples (i.e., 100.00%) met the ISR criteria, which is acceptable.

The time span from the first sample collection to the last sample analysis was 24 days which falls within the validated long-term stability period of 126 days.

In a consultation request, the clinical pharmacology review team requested the Office of Study Integrity and Surveillance (OSIS) to inspect both the analytical and clinical sites for Studies TADA-22-051 and TADA-23-023. OSIS declined to conduct on-site inspections, deeming them unnecessary. They noted that the analytical site had already been inspected in (b) (4). Furthermore, OSIS explained that an inspection of the clinical laboratory was not required, as basic clinical chemistry analyses are not subject to regular review under the current regulatory program of OSIS. Consequently, OSIS advised that no further action was required for either site.

In conclusion, after reviewing the analytical method validation and performance results, the clinical pharmacology review team determined that the bioanalytical method used to measure the plasma concentration of tadalafil in study samples for both Studies TADA-22-051 and TADA-23-023 are acceptable.

3. LABELING RECOMMENDATIONS

Recommendations (Pending discussion):

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology has the following labeling recommendations for revisions to the Applicant's proposed language.

[Note: The blue text is the recommended revision and strikethrough text in red color is the deletion]

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/s/

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